Chaires internationales

de recherche Blaise Pascal

Financée par l'État et la Région d'Ile de France, gérée par la Fondation de l'École Normale Supérieure The Seventh Blaise Pascal Lecture Wednesday May 19, 2010 Ecole Polytechnique Amphi Faurre

Acceleration

Toshiki Tajima Blaise Pascal Chair, Fondation Ecole Normale Supérieure Institut de Lumière Extrême and LMU,MPQ, Garching

Acknowledgments for Advice and Collaboration: G. Mourou, M. Molls, F. Nuesslin, M. Abe, M. Murakami, V. Malka, J. Fuchs, C. Labaune, P. Mora, F. Krausz, D. Habs, T. Esirkepov, S. Bulanov, S. Kawanishi, M. Hegelich, Y. Kishimoto, D. Jung, D. Kiefer, X. Yan, A. Henig, R. Hoerlein, S. Steinke, W. Sandner, Y. Fukuda, A. Faenov, M. Tampo, P. Bolton, N. Rostoker, F. Mako, L. Yin, T. Pikuz, A. Pirozhkov, M. Borghesi, M. Gross, M. Zepf, Y. Gauduel



DUM DOM www.attoworld.de

Cancer causing human genome mutations: scary! (Time Magazine)

fundamental to biology



5-year survival rates after curative treatment in early cancer stages



M. Molls/ Japan Apr 09

	Radiotherapy alone	Surgery alone	Chemotherapy alone
Prostate	79 % (5 y) 66 – 79 % (10 y)	75 – 85 %	Ø
Lung	6 – 50 % (Stereotact. RT: > 50 %)	30 – 80 %	Ø
Cervix	63 – 91 %	74 – 91 %	Ø
Skin	up to 100 %	up to 100 %	Ø
Anus	60 – 80 % (T1, T2) 33 – 58 % (T3, T4)	comparable with results after RT	Ø
Rectum	~ 65 %	78 – 82 %	Ø

Ø: no data in the literature: CHEMOTHERAPY has no curative potential in solid tumors (exception: testic@lar cancer)

In the last decades: no improvement of survival in metastatic cancer diseases (macroscopic metastases)



M. Molls/ Japan Apr 09



Data from "Tumor Center München"

M. Molls/ Japan Apr 09





Chemotherapy (medical cancer treatment) has no curative potential in solid tumors!

WHY?

M. Molls/ Japan Apr 09

Radiation

Chemotherapy



Homogeneous dose distribution

The tumor cell kill depends on intrinsic radiation sensitivity, DNA repair capacity, repopulation, oxygenation status etc.. However, the entire tumor can be irradiated homogeneously with that dose, which is necessary to kill all clonogenic tumor cells, even the most resistant ones.

Inhomogeneous dose distribution

The tumor cell kill depends on the transport of the substance to the clonogenic cells and molecular targets, DNA repair capacity, repopulation, pO2, pH, MDR, etc.. In macroscopic tumors not all the subvolumes of the tumor, clonogenic cells and relevant molecular targets are reached by those doses of the medical substance which are needed for cell kill.





Macroscopic Tumor: \geq 5mm (more than 10⁷ cells) Microscopic Tumor: < 5mm (1 – 10⁷ cells)

Cell kill after Chemotherapy: only about 3 logarithmic steps (ordinate)

Prof. Molls (TUM/MAP) says: M. Molls/ Japan Apr 09



"Solid tumors which consist in more than about 1000 cells apparently <u>can not be cured by medical</u> <u>treatment</u>. This holds true especially for macroscopic tumors which consist in more than 1 to 10 million cells (exception: testicular cancer)

The main problem:

The <u>medical substances don't reach all dividing</u> <u>tumor cells</u> and respective molecular targets in a concentration which is high enough to kill the cells. After medical treatment there remain dividing cells from which <u>tumor regrowth is starting</u>."

Breast Cancer: Improvement of survival by better diagnosite and earlier detection of the tumor

(Patients with breast carcinoma in Brisbane, Australia; Webb et al, The Breast 2004)

	Diagnosis 1981 - 84	Diagnosis 1990 – 94
Patients	469	520
Average age	56 J	53 J
Tumor < 1cm	11%	22%
Tumor > 2cm	44%	34%
Lymph node metast.	50%	38%
Stage 1	32%	46%
Stage 2	61%	47%
Stage 3	7%	7%
5 y survival	74%	84%

Brilliant X-rays M. Molls/ Japan Apr 09 iffraction enhanced imaging: breast, ex vivo 1 CT ex vivo, 2 Brilliant X-ray image ex vivo, 3 Histology skin-muscle collagen strands Ca in collagen fat 3

2: DEI 33 keV

3: Histology

Bravin et al. Phys Med Biol 52:2197-211, 2007

Small-angle X-ray scattering (SAXS)





vision: direct cancer diagnosis without biopsy

M. Molls/ Japan Apr 09

The Economist

DaimlerChrysler's long turnaround PAGES 12 AND 63-65

Reform fatigue in Turkey PAGE 27

Pressure on China's currency PAGES 11 AND 67

An editor's valedictory thoughts PAGE 13

Science and technology 73

The Economist April 1st 2006

APRIL 15T-7TH 2006

· ger in patent) by signing contracts with manufacturers in India and South Africa. that guarantee large order-volumes and rehable payment. As a result of this and similar initiatives, the price of a course of these drugs has, in some cases, fallen below \$150 per person per year-down from over \$1,000 at the turn of the century. Progress, then, is being made. And par-

haps the most telling sign of that is what has not happened. The AIDS-activists' organisations, normally sensitive to the least failure to honour a pledge, have, by and large, kept quiet. Dr De Cock will not he drawn into predictions about what progress to expect over the next few years, but Mr Climton (admittedly not an epidemiologist) says he will be both disappointed and surprised if the ym figure is not reached by the end of this year. With an epidemic the size of Arps, that means a lot of extra deaths. But, realistically, it is not that great an overrun.

Imaging technology

A discerning view

A new way of processing X-rays gives much clearer images

X BAYS are the mysterious phenome-non for which Wilhelm Rönigen was awarded the first Nobel prize in physics, in 1901. Since then, they have shed their mystery and found widespread use in medicine and industry, where they are used to reveal the inner properties of solid bodies.

Some properties, however, are more easily discorned than others. Conven tional x-ray imaging relies on the fact that different materials absorb the radiation to different degrees. In a medical context, for example, hones absorb x-new readily, and so show up white on an x-radiograph, which is a photographic negative. But x-rays are less good at discriminating between different forms of soft tissue, such as muscles, tendons, fat and blood vessels. That, however, could score change. For Franz Pfeiffer of the Paul Scherrer Institute m Villigen, Switzerland, and his colleagues report, in the April adition of Nature Plasics, that they have manipulated standard a may imaging techniques to show many more details of the inner budy.

The trick needed to discern this fine day tail, according to Dr Pfeiffer, is a simple one. The researchers took advantage not only of how tissues absorb x-rary but also of how much they slow their passage. This slowing can be seen as changes in the phase of the radiation that emerges-in other words of the relative positions of the neaks and troughs of the waves of which

x-rays are composed. Subtle changes in phase are easily nicked up, so doctors can detect even small variations in the composition of the tissue under investigation, such as might be caused by the early stages of breast cancer. Indeed, this trick-known as phase-contrast imaging-is already used mutinely in optical microscopy and transmission elec-tron microscopy. Until now, however, no one had thought to use it for medical x-ra-

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diography. To perform their trick, the researchers used a series of three devices called transmission gratings. They placed one berowen the source of the x-rays and the body under examination, and two between the body and the x-my detector that forms the image. The first grating gathers information on the phases of the x-rays passing through it. The second and third work together to produce the detailed phase-contrasted image. The approach generates two separate images-the classic x-ray image and the phase-contrasted im-age-which can then be combined to produce a high-resolution picture

The msearchers tested their technique on a Cardinal tetra, 4 tiny iridescent fish commonly found in fish tanks and aquariums. The conventional x-ray image showed the bones and the gut of the fish. while the phase-contrasted image showed details of the fins, the ear and the eve-

Dr Pfeiffer's technique would thus appear to offer a way to get much greater desail for the same amount of radiation exposure. Moreover, since it uses standard hospital equipment, it should be easy to introduce into medical practice, x-rays may no longer be the stuff of Nobel prizes, but their usefulness may just have inreased significantly.



Before and after

Encyclopedias Battle of Britannica

War has broken out between Encyclopaedia Britannica and Nature

AT FIRST, it was an innocuerus test of acwondered how scientific entries in Wikipedia-a free web encyclopedia that any one can edit-compared with those in "Encyclopaedia Britannica". They compiled a list of subjects, downloaded rele vant entries from each website, and sent the results to experts.

The findings were published in December and Britannica won-a blow had been struck by the gold-standard encyclopedia compiled by experts over the collective knowledge of a bunch of hobbyists and amateurs. Except that the results held a surprise. Britannica contained a lot of ermes, and it was only 30% more accurate than the free encyclopedia.

This was all too much for Britannica. So, five weeks ago, it launched a 30 strong team of rebuttal editors and experts to pick apart the Nature study. The team's 20-page report concluded that "almost everything about the journal's investigation was wrong and misleading". Oh, and it demanded that Nature retract its study. Noture hit back with its own rebuttal and re fused to retract anything. On March 27th Britannica fired another salvo, with advertisements in the Times and the New York Tisses. Nature returned fire with a rebuttal editorial.

Some of Britannica's criticisms are bbles, it didn't like Namre's headline, and Ted Pappas, Britannica's executive editor, says Nature didn't allow Bettannica to see any of the evidence on which the study was based until a week after it was published. That was a bit unsporting. In the media binge after the study's release. No tare's journalists talked widely about their findings, while Britannica's editors felt they could not defend themselves.

Besides these quibbles, there are a courele of more serious issues. One is the over all accuracy of Britannica, the other is its relative accuracy compared with Wikipe dia. On the first, Nature identified 123 etrors in 42 Britannica articles. These comprise factual errors, misloading statements and critical emissions.

However, many of these "errors" are really the opinion of the reviewers. For example, a Native reviewer says of the Britanesica entry on the Cambrian period that the "evolution of hard parts at the baginning of the Cambrian involved much more than development of calcium carbonate." Britannica replies: "the article #

应用普通X射线源 进行相位对比度成像

前沿

前言

FOREFRONT

在医学诊断领域,放射诊断是建立 在X射线吸收对比度成像基础上的。然 而对于人体软组织及一些生物组织样本 而言,由于它们对X射线吸收能力较弱, X射线吸收对比度成像的应用受到了限 制。这一缺陷可通过采用同步加速器高 亮度同步辐射或者微焦X射线源等设备 应用相位对比度成像方法加以解决(见 IMD Vol.10 No.3 及IMD Vol.12 No.6)。可是, 要将产生高亮度同步辐射 的装置——大型同步加速器安装在临床 医院中是不切实际的。在本文中,我们 介绍的是在应用普通X射线发生器的情 况下,利用一种由3个透射光栅(Transmission Grating)组成的装置来产生 定量微分相位对比图像(Differential Phase-Contrast, DPC),



来的吸收对比 放射线片就很 难将某些病变 组织从非病变 组织中区分开 亲。

相位移动来产生放射成像对比度的方法。 这些方法可归类为干涉计法、分析仪法 以及自由空间传输法等。这些方法在信 号记录、实验装置和对辐射亮度的要求 等方面有很大的不同。干涉计法和分析 仪法需采用光学晶体,这两种方法需要 高度平行的单色×射线束。自由空间传 输法可放松对时间相干性的要求,但该 种方法要求用微焦X射线源或者同步加 速器发射的射线才能达到。以上种种限 制的存在,使得迄今为止研究者们依然 不能使相位对比度成像成为医疗或工业 应用的标准方法。

在本文中,我们将展示一套基于光 栅的 DPC装置,采用该方法可以在使用 低亮度多色×射线源的情况下有效地对 定量相位图像进行恢复。

下文会描述如何应用3个光栅就低 亮度X射线源进行物体成像。三光栅 DPC 成像装置由光源光栅 Go、相位光 栅 G₁和带有分析器的吸收光栅 G₂组成

Franz Pfeiffer 等 Franz Pfeiffer先生、博士、瑞士 Paul Scherrer 研究所组长: Timm Weitkamp 先生, 博士、德国 Forschungszentrun Karisruyhe 研究所成员: Oliver Bunk 先生, 瑞士 Paul Scherrer 研究所成员。Christian David 先生。 瑞士 Paul Scherrer 研究所成员。 刘红霞 编译 2006年8月30日收到。

关键词: 普通 X 射线源 相位对比度成像



由于光源光栅 Go包括大量的独立 狭缝,每个狭缝都可产生充分相干光 线,因此一个源面积大于1 mm²的普通 X射线发生器就足够用。本文所用X射 线发生器为40 kV/25 mA, Mo靶, 焦点 为8mm(水平)×0.4mm(垂直),由于 靶相对于光轴倾斜 6°,有效源面积为 0.8 mm × 0.4 mm。为了确保由 Go产生 的每一条射线都能够在图像形成过程中 发挥作用,这个光栅装置的几何学设计 必须满足以下条件(图 1b):

 $p_0 = p_2 \times \frac{1}{d}$

需要注意的事是:总源面积 w 决定 了最后成像的分辨率。即 wd/l。在 G1和 G2两个光栅之间完成的 DPC 图像形成 过程类似于 Schlieren 成像或衍射增强 成像(Diffraction Enhanced Imaging, DEI)。其成像的本质是当一目标物体放 置于 X 射线束经过通路时, 透过物体进 行传输的光束发生了轻微的折射。DPC 成像基本原理依赖于所探测到的局部偏 转角(图 1b)。偏转角α的大小同物体的 局部相位移动梯度成正比,定量表示

这一缺陷, 目 前许多人研究 了利用X射线 穿透样品时的

为了克服

Phase contrast imaging: F. Pfeiffer

本文作者 Franz Pfeiffer 先生







F. Pfeiffer et al., Phys. Med. Biol. 52, 6923

phase tomograms

absorption tomograms

State-of-the-art 3D phase-contrast tomography at highly brilliant synchrotron radiation sources (@ESRF Grenoble/ France)









white & gray brain matter

(2mm size)

contact: franz.pfeiffer@psi.ch & www: http://people.epfl.ch/fran z.pfeiffer

F. Pfeiffer et al., Phys. Med. Biol. 52, 6923 (2007)



Small tumor detection

Early tumor detection:

- Less chance of metastasis
- Higher Quality-of-Life (QoL)
- Fit for laser acceleration approach (compact laser accelerator: not good for large dose)

Sharpness of Dose of Proton Therapy

X-ray IMRT

Proton IMRT



T Surgical sharpness of dose compared with X-ray Intensity Modulated Radio Therapy (X-ray IMRT)

Artist's view of the Heavy Ion Therapy Center (HIT) in Heidelberg





Suggested Strategy for Laser Ion Accelerator



- Detect early and small (laser-driven brilliant coherent X-rays): <u>micro</u> tumors
- <u>Small spot</u> irradiation(including scanning): ideal for laser acceleration of ions, as ion therapy is <u>nearly surgically sharp</u>
- <u>Feedback</u> necessary: irradiate→verify→irradiate→verify→....
- <u>Shallow</u> tumors and other shallow treatments (e.g. ARMD) first
- Other industrial applications

Toward Compact Laser-Driven Ion Therapy



PET or γ ray image of autoradioactivation



治療計画(診断と照射)

Laser particle therapy (image-guided diagnosis→irradiation→dose verification) targeting at smaller pre-metastasis tumors with more accuracy



- 1kg tumor (10cm x10cm x 10cm): 70J proton energy @ 70Gy
- 1g tumor (1cm x 1cm x 1cm): 70mJ
- 1mg tumor (1mm x 1mm x 1mm): 70μJ takes about 10⁸ protons at ~100MeV (only 10% of the beam assumed to be used to inject, and in turn 10% of which stops at tumor; with 10% laser to proton efficiency, laser energy of 70mJ); takes 10⁵ protons per laser shot (if 2minutes therapy at 10Hz)

Within grasp!







Spot-Scanning Simulation of Laser Proton Radiotherapy





Spot-scanning simulation of laser proton radiotherapy for eye melanoma (a,b) and ARMD (c,d).

Particle-in-cell simulation (PIC) software which calculates the properties of laser-accelerated protons, Monte-Carlo simulation software, and visualization tools for the dose evaluation were used. Iso-dose curve:Blue: 25%, Sky blue: 22 50%, Yellow: 75%, Orange: 90%, Red: 110%. Miyajima(JAEA)2005







X. Yan et al., 2009



CAIL

Rev. Accel. Sci. Tech. (Tajima, Habs, Yan, 2009)

Optimal Thickness Scaling



Optimal acceleration of ions

Normalized thickness $\sigma \sim a_0$ (normalized intensity)



Recent Experimental Breakthroughs

Leadership by Dieter Habs

LMU, MPQ, Max-Born Institute, LANL, RAL, PMRC



Nanometer target: DLC Sharp contrast laser double plasma mirrors

More coherent electron dynamics in $\sigma \sim a_0$

Recent experiments in CAIL Regime

CAIL Regime: Overcomes old TNSA regime

Ultrathin film : $\sigma = a_0$, where $\sigma = d n /\lambda n_c (\xi = \sigma/a_0)$ High laser contrast: not to destroy ultrathin target



MAP + MBI

(Henig et al, 2009; Steinke et al.)

Conversion efficiency of laser to ion energy I

Two orders of magnitude higher efficiency in CAIL







Circularly polarized laser irradiation

more adiabatic acceleration→ more monoenergy



Carbon spectrum for three consecutive shots using circular polarized light at 5 *10^19 W/cm2 and a DLC foil target thickness of 5.9 nm



Henig et al, PRL (2009)

Energy Gain in Laser Ion acceleration: CAIL (Coherent Acceleration of Ions by Laser) regime

 When electron dynamics by laser drive is sufficiently coherent, with <u>coherence parameter α</u> of electrons, the ion energy in terms of electron energy is :

$$\varepsilon_{\max,i} = (2\alpha + 1) Q \varepsilon_0$$

Ion energy

(the more coherent the electron motion, the higher the ion energy)

$$\varepsilon_0 = mc^2 \left(\sqrt{1 + a_0^2} - 1 \right)$$

Electron energy = ponderomotive energy

$$\varepsilon_{\max,i} = (2\alpha + 1) Q \bar{\varepsilon}_0(t_1) \left((1 + \omega_L t_1)^{1/2\alpha + 1} - 1 \right)$$

α maximizes at $\xi = 1$

CAIL Theory Prediction



CAIL (Coherent Acceleration of lons by Laser) theory has definitive prediction of max energies



experiment prediction (relative long pulse with nm targets)



CP laser drives ions out of ultrathin (nm) foil adiabatically Monoenergy peak emerges



(X. Yan et al: 2009)

Ponderomotive force drives electrons, Electrostatic force nearly cancels Slowly accelerating bucket formed



The more **adiabatic**, the longer accelerated, the higher energy Energy by **CP** tends to increase as $\frac{a_0^2}{a_0^2}$



Concave Ultrathin Target Enhances Energy

Concave target focuses laser energy, doubling the ion energy



(Wang et al. 2010)



⁷IG. 4: (color online). (a)Proton energy evolution for LP and CP laser. (b)Maximum proton energy versus radius of sulge-out target for LP and CP laser.

Wang et al. 2010



Ultrathin (2nm) foil (CP) irradiation drives monoenergetic electrons







Graded, thin (nm), or clustered target and/or circular polarization

 $v_{tr, ion} \sim c \sqrt{a_0(m/M)} \sim c$ (ultrarelativistic $a_0 \sim M/m$)



Manostructured target



(Habs, 2009)

Toward Adiabatic Acceleration (ca. 1999)

ГЛU

Energy conversion and acceleration of particles is strongly dependent on the state of the thin foil surface.

$a_0 = 30$ 1 PW Laser Intensity;	target type $a_{o_s} = 69$	Al [™] (56nm) solid H⁺ (28nm) solid	Al ¹⁰ *(2240nm) gas H⁺ (28nm) solid	Al ¹⁰⁺ (112nm) culster H ⁺ (28nm) solid
electron density Al soild ; 6*10 ²³ cm ³ (416n _c) gas ;1.5*10 ²² cm ³ (10.4n _c)	energy conversion ion; electron;	24% 8% 16%	50% 4% 46%	31% 14% 17%
culster;3*10 ²³ cm ⁻³ (208nc) H soild ; 4.6*10 ²² cm ⁻³ (31.8nc)	peak (average) energy H*;	0,4GeV (95MeV)	0.2GeV (58MeV)	0.8GeV (115MeV)
n _c : cut off density 1.4*10 ²¹ cm ⁻³	Al ^{ie} ; electron;	2GeV (500MeV) 15MeV	1GeV (130MeV) 25MeV	2GeV (500MeV) 20MeV

Patent (Tajima) : submitted from LLNL (2002); granted (2005)



Cluster target: order of magnitude



With a modest (140mJ) laser, to go beyond 15MeV/nucleon by cluster target



FIG. 3 (color online). The ion energy spectrum obtained by the TOF method. The inset shows TOF spectrum obtained in one laser shot which registers 15 MeV/u ion signal. A saturated signal around the flight time t = 5 is caused by hard x rays emitted from the laser-cluster interaction region.

Clustered target allows another leap in energy of ions

Fukuda et al. (PRL 2009)





Fig.11



Maximum energy vs. laser intensity



Cluster target scaling

Consistent to the Theory by Yan et al. (2009), though it is based on thin film case

$$\varepsilon_{\rm max} = (2\alpha + 1)Q\sqrt{1 + a_0^2}$$

Kishimoto, 2009

Ion Energy spectrum r=125µm



Ion Energy vs. Cluster Radius

Cluster target scaling: ion energy ~ 1/(cluster radius)





Conclusions



- Cancer: unsolved problem, as fundamental to biology
- Ion beam radiotherapy: superior cure to chemotherapy, though expensive today
- Detection and cure of small unmetastasized tumor = future (fundamental cure, better quality of life, better fit for compact laser accelerator)
- Compact laser ion acceleration: niche for small tumors
- Breakthroughs in laser ion acceleration: overcomes the previous paradigm (TNSA) with the new conditions
- Higher energies, higher efficiency, and less energy spread
- With compact laser (10²⁰W/cm²) 100MeV protons possible
- Feedback therapy essential for small tumors
- Laser-driven compact coherent X-ray source : detect small tumors
- A lot more medical applications on the horizon

Merci Beaucoup et a la Prochaine Fois