Laser-driven Medicine: A prelude

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In memory of and dedication to the late Profs. \textsuperscript{+}J. M. Dawson and \textsuperscript{+}N. Rostoker
abstract

1. History of laser accelerator, which drove the laser technology and vice versa
2. Elements of laser acceleration: a novel path toward tiny radiobeams (electrons, ions, X-rays (gamma-rays), neutrons, and radio-isotopic beams)
3. Convergence with nanotechnology, biotechnology
4. Potentiality: portability, intra-operative, endoscopic, theranostics, ....
History of laser accelerator: Elements of innovation
COHERENT PRINCIPLE OF ACCELERATION OF CHARGED PARTICLES

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Electrophysical Laboratory, Academy of Sciences, Moscow

This paper will include a very brief description of a new principle regarding the acceleration of charged particles.

In all existing accelerators of charged particles, the constant and varying electric field accelerating them is created by a powerful external source, and hence the strength of the field is independent in the first approximation, of the number of particles which are being accelerated.

In resonance accelerators, the electromagnetic field has to be synchronized with the movement of the particles (this is of particular importance in linear accelerators). Finally, none of the existing methods permits the acceleration of neutral bunches of particles.

A new principle of particle acceleration is set forth below. Its distinctive feature lies in the fact that the particle-accelerating electric field is produced by the interaction of a geometrically small group of accelerated particles with another group of charged, plasma or an electromagnetic wave. This method has a number of important features. It appears, in the first place, that the magnitude of the accelerating field produced by this interaction and acting on each particle depends on the number of theoretical studies of various aspects of the coherent acceleration method have been made by M. S. Rabinovich, A. A. Kolomenski, B. M. Boloovski, L. V. Kovrizhnik and I. V. Iankov, as well as by A. I. Akhiezer, Ia. Fainberg and their collaborators. The calculations made by these theoretical workers shed light on a number of complicated problems connected with the development of the different variants of this new acceleration principle, and it therefore seems appropriate to describe the new method despite the fact that a great many problems involved still await solution.

1. Acceleration of charged bunches by means of the medium

It was pointed out in a paper by Tamm that the loss of energy by particles due to Čerenkov radiation could be reversed, i.e., the medium travelling at a great velocity past charged particles should be able to convey energy to the latter. Up to now, however, no attention has been paid to the possibility of developing an acceleration process of this kind by using a high density electron beam (plasma) as the moving medium. Of course, if a single charge e is
Prehistoric activities (1973-75, 78)

Collective acceleration suggested:
Veksler (1956)
(ion energy)~ (M/m)(electron energy)

Many experimental attempts (~’70s):
led to no such amplification
(ion energy)~ (several)x(electron)
Mako-Tajima found its reason (1978)

Introduction of wakefields (Tajima-Dawson, 1979)
→ electron acceleration possible
with trapping (with Tajima-Dawson field. 1979), more tolerant
for sudden process

However, requires relativistically strong laser (see next development)
**Laser wakefield (Tajima-Dawson, 1979 @UCLA)**

Thousand-fold Compactification over conventional accelerators

Laser pulse

\[ E_{\text{max}} \approx 32 \text{MV/m} \]

(gas tube)

\[ E_{\text{max}} \approx 100,000 \text{MV/m} \]
At ICTP Summer School (1981), Prof. Salam summoned me and discussed about laser wakefield acceleration.

Salam: ‘Scientists like me began feeling that we had less means to test our theory. However, with your laser acceleration, I am encouraged’. (1981)

He organized the Oxford Workshop on laser wakefield accelerator in 1982.

Effort: many scientists over many years to realize his vision / dream
High field science: spawned. (* 1979 Nobel Prize in physics)
The superconducting RF proton linac at the SNS at Oak Ridge National Laboratory is providing valuable experience for a future ADS accelerator.

Image credit: ORNL.
Laser technology invented (1985)

Chirped pulse amplification (CPA) invented:
to overcome the gain medium nonlinearities in spatially expanded amplification to temporal expansion:
smaller, shorter pulse, more intense, higher reprise, all simultaneous.
→ relativistically strong laser realized (1990’s)
→ many table-top TW and PW lasers world-wide
first Chair, ICUIL (International Committee for Ultra Intense Lasers)
toward EW laser (Extreme Light Infrastructure)

→ First LWFA experiments
→ drives High Field Science

Professor Gerard Mourou*

* 2018 Nobel in Physics
Laser accelerators demanded more laser inventions

CAN fiber laser (2013)
← tiny laser (like a hair $\mu$m individually), efficiency, large rep-rate, yet, large average power (by bundles)

Thin Film Compression (2014)
← even shorter pulse ($fs$)

Mourou*, Brockelesby, Tajima, Limpert (2013)

Mourou* et al, (2014)
Elements of laser acceleration
Laser Wakefield (LWFA):

Wake phase velocity $>>$ thermal speed ($v_{ph} >> v_{th}$) maintains coherent and smooth structure

Tsunami phase velocity becomes $\sim 0$, causes wavebreak and turbulence

"Onigokko (hide 'n seek)" state

Strong beam (of laser / particles) drives plasma waves to saturation amplitude: $E = m_0 n_{ph} / e$

No wave breaks and wake peaks at $v \approx c$

Wave breaks at $v < c$

$\leftarrow$ relativity regularizes (relativistic coherence)

Relativistic coherence enhances beyond the Tajima-Dawson field $E = m_0 \omega_p c / e$ ($\sim$ GeV/cm)
Adiabatic (Gradual) Acceleration of Ions

from #1 lesson of Mako-Tajima problem

Accelerating structure (Shinkansen Nozomi model)

Inefficient if suddenly accelerated

Efficient when gradually accelerated

Lesson #1: gradual acceleration → Relevant for ions
Laser-Thin Foil Interaction

X. Yan et al., 2009
Radiation (Laser) Pressure Acceleration

Double layer target (metal layer with smaller hydrogen (or light Z metarial))

Esirkepov et al. (2002)
Radiation (Laser) Pressure Acceleration

Radiation dominant regime

Esirkepov et al. (2004)
Nanometric target
Adiabatic acceleration (2)

Thick metal target

Most experimental configurations of laser proton acceleration (2000-2009)

Innovation (“Adiabatic Acceleration”) by laser (2009-)

= Method to make the electrons within ion trapping width

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

-laser
-protons, electrons
-slow
-c

Target thickness scales with $a_0$

Coherent Acceleration of Ions by Laser (CAIL)

Deuteron energy vs. thickness of foil

$E_{\text{max}} [\text{MeV}]$

$\sigma \approx a_0$

target thickness [normalized to laser intensity]

Our simulation

Optimum parameters (sweet-spot) for ion acceleration at $\sigma \approx a_0$

Experiment: Steinke,..Tajima (2010)

Necas, Tajima (2018)
Nanostructured target

(Habs, 2009)
Why is Laser-Cluster Interaction Strong?

"clusterd phase" vs. "gas", "plasma", "solid phase"

Transverse polarization manifest

- "Small particle system" and enhanced fluctuation
  - free energy originated from the surface is NOT neglected.
  - energy and structural deformation/fluctuation

- Freedom of transverse polarization through "surface"
  - different nature in linear and non-linear dispersion

(Y. Kishimoto)

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.
Ion Energy vs. Cluster Radius

Cluster target scaling: \[\text{ion energy} \sim \frac{1}{\text{(cluster radius)}}\]

Kishimoto, Tajima (2009)
Compact beam therapy
Toward Compact Laser-Driven Ion Therapy

PET or γ-ray image of autoradioactivation

Laser particle therapy (image-guided diagnosis → irradiation → dose verification) targeting at smaller pre-metastasis tumors with more accuracy
Artist’s view of the Heavy Ion Therapy Center (HIT) in Heidelberg
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: 50%, Yellow: 75%, Orange: 90%, Red: 110%.

Miyajima (JAEA) 2005
Comparison of radiotherapy with the Bragg peak: Intensity Modulated Radio Therapy

X-ray IMRT

Proton IMRT

prostate cancer

rectum
Compact generation of radioisotopes
Compact laser-driven isotope generation

Some isotopes: so short life times that next door generation necessary

Compact sources for energy-specific electrons, ions, radio-isotopic ions, neutrons, monoenergetic energy-specific X-ray (and gamma) photons

Technologies: *CPA lasers, CAN fiber lasers, TFC (Thin film Compression), CAIL acceleration of ions, wakefield acceleration
F-18-FET

Brain tumor

Neuroinflammation
$[^{18}\text{F}]\text{CHOLINE}$

$[^{18}\text{F}]\text{Fluoromethylcholine}$

$[^{18}\text{F}]\text{Fluoroethylcholine}$
Prostate cancer
\[^{11}C\text{]Tracers}\]

**\[^{11}C\text{]Choline}\]**
- Synthesis of cell membrane phospholipids

**\[^{11}C\text{]Methionine}\]**
- Protein synthesis

**\[^{11}C\text{]Acetate}\]**
- Fatty-acid metabolism
Astrocytoma (no response)
(courtesy by PET Centre St. Orsola Hospital, Bologna)

Before therapy

After therapy

[¹¹C]Methionine
Emerging radioisotopes and (alternative) production routes

All medical radioisotopes now produced in reactors can be produced alternatively or can be replaced by isotopes which can be produced other than in a nuclear reactor.

Particle Accelerators
Linear
• Ge-68/Ga-68, and Sr-82/Rb-82, Zn-65, Mg-28, Fe-52, Rb-83 (200 MeV proton beam, 150 uA)
Cyclotrons (10-100 MeV, up to 2 mA)
• F-18, Sr-82, Cu-64,O-15, C-11, Br-77, I-124, Y-86, Ga-66/68, Cu-60/61, Zr-89, Tc-99m

New routes
Compact systems (Bench-scale electronic devices for achieving various high-energy nuclear reactions):
  proton accelerator: production of F-18, In-111, I-123, C-11, N-13, O-15
  alpha linac: Sn-117m, Ac-225, As-73, Fe-55, At-211, Cd-109, Y-88, Se-75, Po-210
neutron sources
Electron-beam accelerator
• Bremsstrahlung 10-25 MeV electrons proposed for isotope production through:
  □ Photo-fission of heavy elements
  □ (γ ,n) reactions
  □ Photo-neutron activation and (n,2n) reactions
# Emerging radioisotopes and (alternative) production routes

**Emerging medical radioisotopes: β-emitters and theragnostic agents – in preclinical and clinical research:** Lu-177, Ho-166, Re-186/188, Cu-67, Pm-149, Au-199, Y-90

<table>
<thead>
<tr>
<th>Radio nuclide</th>
<th>Emission</th>
<th>Half-life (hrs)</th>
<th>Production Mechanism</th>
<th>Particle/gamma Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Cu</td>
<td>β (0.14 MeV) γ (0.18 MeV)</td>
<td>62</td>
<td>$^{68}$Zn(p, 2p) $^{70}$Zn(p,α) $^{67}$Zn(n,p) $^{68}$Zn(γ,p)</td>
<td>Ep (&gt;&gt; 30) Ep (&gt;&gt; 30) Reactor Ey (&gt;19) $\sigma = 0.03$ barn</td>
</tr>
<tr>
<td>$^{47}$Sc</td>
<td>β (0.16 MeV) γ (0.16 MeV)</td>
<td>3.35 d</td>
<td>$^{48}$Ti(γ,p)</td>
<td>Ey (&gt;27) $\sigma = 0.01$ barn</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>β (0.35 MeV) γ (0.14 MeV)</td>
<td>3.7 d</td>
<td>$^{187}$Re(γ,n)</td>
<td>Ey (&gt;15) $\sigma = 0.6$ barn</td>
</tr>
<tr>
<td>$^{149}$Pm</td>
<td>β (1.072 MeV)</td>
<td>53.08</td>
<td>$^{150}$Nd(γ,n)$^{149}$Nd</td>
<td>Ey (&gt;12.5) $\sigma =0.22$ barn</td>
</tr>
<tr>
<td>$^{152/155/161}$Tb</td>
<td>β⁺ (1.08 MeV) EC (0.86, 0.10 MeV) β⁻ (0.154 MeV), Auger</td>
<td>17.5/127,2/165.3</td>
<td>$^{152}$Tb/$^{155}$Tb proton-induced spallation $^{160}$Gd(γ,$^{161}$Gd)</td>
<td>Neutron source Reactor</td>
</tr>
</tbody>
</table>

D. Niculae, seminar at UCIrvine October 2016 37
### Emerging medical radioisotopes: α-emitters and Auger-electrons emitters

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<tbody>
<tr>
<td>$^{211}$At</td>
<td>$\alpha$</td>
<td>7.2</td>
<td>$^{210}$Bi($\alpha$,2n)</td>
<td>$E\alpha$ (30)</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>$\alpha$ (5.8 MeV), $\beta$ (0.1 MeV)</td>
<td>240</td>
<td>$^{229}$Thorium generator ion exchange from $^{225}$Ra $^{226}$Ra($p$,2n) $^{226}$Ra($\gamma$,p)</td>
<td></td>
</tr>
<tr>
<td>$^{224}$Ra/$^{212}$Pb/$^{212}$Bi</td>
<td>$\alpha$ (5.7 MeV)/ $\beta^-$ (0.1 MeV)/ $\alpha$ (6.0 MeV), $\beta$ (0.77 MeV)</td>
<td>3.7/ 10.64 h/60.6 m</td>
<td>$^{226}$Ra($\gamma$,2n)</td>
<td>$E\gamma$ (&gt;16) $\sigma = 0.1$ barn</td>
</tr>
<tr>
<td>$^{165}$Er</td>
<td>$A$ (0.038 MeV), $\gamma$ (0.05 MeV)</td>
<td>10.3</td>
<td>$^{166}$Er($\gamma$,n)</td>
<td>$E\gamma$ (&gt;13) $\sigma = 0.3$ barn</td>
</tr>
<tr>
<td>$^{149}$Tb</td>
<td>$\alpha$ (3.967 MeV), $\beta$ (0.7 MeV)</td>
<td>4.12</td>
<td>$^{152}$Gd($p$,4n)$^{149}$Tb, $^{152}$Gd($p$,2n)$^{149}$Tb</td>
<td></td>
</tr>
</tbody>
</table>
MOLECULAR IMAGING / SYSTEMIC RADIOThERAPY 
RADIOPHARMACEUTICALS

Antibody
+ Diversity
+ Affinity
+ Specificity
+ Clinically approved
- Immunogenicity
- Long blood life
- Slow penetration

Peptides
+ Diversity
+ Non-toxic
+ High affinity
+ Penetration
+ Clearance
- Unknown binding site
- Low immunogenicity
- Formulation is complex

Aptamers
+ Diversity
+ Small size
+ Short blood life
+ Penetration
- Formulation is complex
- Cost

Affibody
+ High affinity
+ Small size
+ Short blood life
+ Penetration
- Formulation is complex
- Toxicity

Nanoparticle
+ Strong signal
+ Signal:background ratio
- Formulation is complex
- Toxicity

Activatable probe
+ Specific signal

D. Niculăe, seminar at UCIrvine October 2016

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Compact monoenergetic X-rays
Small-angle X-ray scattering (SAXS)

normal tissue contains collagen fibrils in regular, hexagonal-like arrangement

healthy
cancerous

cancer cells degrade regular structure of collagen fibrils, making them thinner and their axial period longer

micro-x-ray beam

vision: direct cancer diagnosis without biopsy
State-of-the-art 3D phase-contrast tomography at highly brilliant synchrotron radiation sources (@ESRF Grenoble/ France)

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

Small tumor detection and therapy
(by such method as Phase Contrast Imaging)

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)
Conclusions

1. **Laser acceleration** introduced: compact, innovative, broad radio-sources (electrons, ions, neutrons, gamma/X-rays)

2. Wakefield: plasma’s unique robust high energy state

3. Convergence of **laser** and **nanotechnology** (and biotechnology): matches well to produce new innovative **radio-sources** (s.a. ions, neutrons, X-rays)

4. Modes of compact **radio-sources**: intra-operative, fiber, portable, ultrafast, endoscopic, short-lived isotopes, theranostics
Thank you!