Neutron - a tool in the cancer treatment - C. Paunoiu

The neutron -a tool in the cancer treatment

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1.1 Radiotherapy

- Radiotherapy means a clinical modality using the deterministic effects of radiation to kill the malignant tumour cells. The efficacy of the radiotherapy is based on the radiosensitivity of the malignant cells and the ability of the healthy tissue to recover from the effects of radiation.
- Treatment is directed to a defined target volume by a treatment planning system (TPS). Thereby a radiation dose is locally directed to the tumour tissue in amount which is assessed to be sufficient to eradicate the tumour but which does not cause intolerable effect on the surrounding healthy tissues. The separation between these two contradictory outcomes can be faint which is the reason for the common adverse effects of radiotherapy The principle of the effects of radiotherapy on the healthy tissue and the tumour as a function of radiation dose is presented in Figure 1.

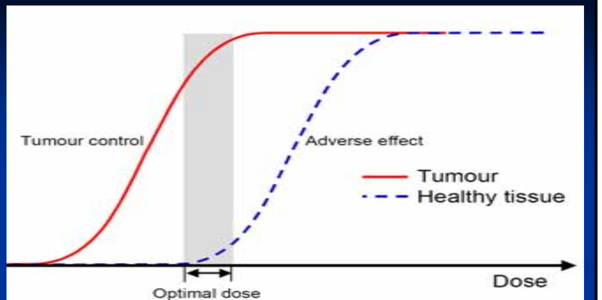

Figure 1. *The optimal dose for the radiotherapy application. The tumour tissue suffers from the radiation dose which is still tolerated by the healthy tissue. The width of the window sets the upper and the lower limit for the dose which is applied to the target volume*

- The separation between two efficacy curves determines the dosimetry window for the radiotherapy application.
- the therapeutic dose should be administered with a high accuracy, enabling the fine balancing between tolerable healthy tissue damage and therapeutic efficacy.
- The accuracy issue is emphasized in the entire area of dosimetric metrology as the traceability chain of the dose calibrations and measurements from the primary standard to the therapy applications should follow almost an unchangeable level of accuracy

1.2 Conventional radiotherapy method

- Conventional external beam radiotherapy utilizes high energy photon or electron beams as the most common form of primary radiation. This kind of radiation is described as low linear energy transfer radiation since the energy depositions to the media in a form of ionizations occur only sparsely . In the typical clinical settings these high energy radiation beams are created by linear accelerators or cyclotrons.

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- Still a 60Co gamma source or betatron for electron acceleration can be seen in some locations as an obsolete technique ,
- In Fast Neutron Therapy (FNT) the high-LET (Linear Energy Transfer) radiation characteristics of neutrons have been utilized for many years. The few successful applications of FNT have focused on the treatments of inoperable salivary gland tumours, locally advanced prostate cancers and soft tissue sarcomas. Proton beams has also been used as a form of high-LET external beam therapy.

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- In modern external beam applications the patient dose distribution for the target volume and the surrounding healthy tissue can be optimised using multidirectional beams with modified shape and intensity. One of the most important advances has been introduced by IMRT (intensity modulated radiotherapy) as a type of three-dimensional conformal radiotherapy which support specifically these complex beam delivery schemes. The beam can be moved while the patient can be fixed in one position. The patient does not have to be in close contact with the beam structure which makes it easier to implement complex beam movements together with simple and comfortable patient positions.

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1.3 BNCT principle

- Boron neutron capture therapy (BNCT) is a binary radiotherapy modality which utilizes epithermal or thermal neutrons together with a boron biodistribution for treatment of cancer. At the beginning the patient is given an intravenous infusion of a non-toxic ^{10}B-carrier compound which is then distributed in various tissues in the body.

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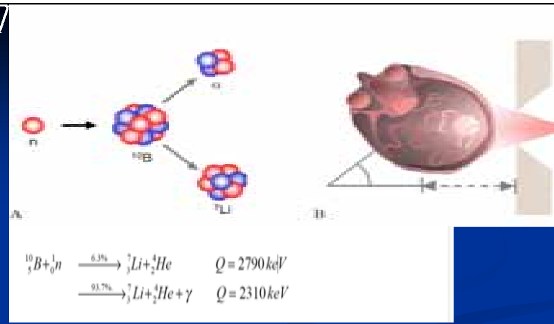
- After a specific time window the tumour with a higher 10B-concentration than the surrounding healthy tissue is irradiated with epithermal neutrons, thermalising and interacting with the boron atoms. Thereby the non-toxic boron atoms in the cancer tumour cells are activated by neutrons producing highly toxic alpha and lithium particles killing the tumour cell. The requirement of BNCT to be successful is to have a large enough amount of ^{10}B in the tumour cell and then have a sufficient amount of thermal neutrons around, reaching the boron atoms and causing the boron neutron capture reaction to occur.



- ***Figure 2.*** *The concept of boron neutron capture therapy presented in two levels. In A) the boron neutron capture reaction occurs where a neutron activates the ^{10}B atom fission into highly lethal alpha and lithium particles with tissue track lengths of 9 and 5 μm, respectively. In B) the patient head is positioned into the planned location and angle with respect to the collimated epithermal neutron beam. The tumour has a higher boron concentration and is presented lighter than the surrounding healthy tissue which is presented darker. The intracranial vasculature functions as a channel for the intravenously infused boron carrier on its way to the tumour.*

- The main advantages of BNCT are due to the synergistical effects of combining the idea of targeting principles of chemotherapy and the beam localization schemes used in conventional radiotherapy. Those synergistical advantages are listed as follows:

  -existing boron carriers are non-toxic substances without the neutron exposure as used in current concentrations.

  -biokinetics of the boron carrier can be fully utilized by the time interval between the infusion and the irradiation to optimize the boron biodistribution (the concentration difference between the tumour and the healthy tissue) during the treatment.

  -consequently, the primary neutron activated boron damage occurs only in the tumour and the directly adjacent healthy tissue

- During the past decades the developments in chemistry, pharmacology, oncology, nuclear engineering and physics has rendered possibilities that could realize BNCT in a more advanced way. Focus has shifted into development and use of epithermal neutron beams (energy range of 0.5 eV to 10 keV) to solve the previous complications of an insufficient beam penetration. Also the development of new boron compounds and boron delivery schemes has a continuously increasing role in BNCT research.

1.4 Neutron sources

- The epithermal neutron beam for BNCT can be obtained by using a nuclear reactor or linear accelerator as a neutron source.
- The current BNCT facilities use mostly the nuclear reactor approach while the accelerator based sources are still on the way to prove their technological applicability.
- Also the use of 252Cf has been suggested as a highly compact neutron source although the tough obtain ability and the half-life of 2.6 year of the isotope form some obvious shortcomings for its use.
- The nuclear reactors used for research have core reflectors to enhance the power efficiency.
- In BNCT use the core reflector has to be modified in order to direct the maximal neutron flux to the preceding filtering and moderator assembly.

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- The required neutron flux spectral features can be acquired by spectrum shifting (in thermal columns) and filtering (in beam tubes) where the spectrum shifting method is generally more efficient as described in flux-to-power characteristics.
- Filtering can still be used in addition to spectrum shifting to acquire the desired energy structure of the neutron fluency.
- The neutron intensity near the treatment position can be increased by using a fission converter in the beam line between the reactor core and the beam moderator elements. As only epithermal part of the neutron spectrum is desired the gamma radiation and the share of thermal and fast neutrons are tried to get minimal.
- Heavy materials such as Pb and Bi can be used in shielding to block the incident reactor gamma rays but to let the neutrons through. Bismuth has still preferred characteristics in this respect compared to lead.

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- An overall filtration of the beam with respect to the neutrons can be realized with a set of thick layers of ^{60}Ni, ^{32}S, ^{10}B and enriched ^{54}Fe which act as a cross-sectional valley in the energy range of epithermal neutrons.
- Thus a coarse frame can be fixed to pass neutrons between 0.01 to 6-10 keV through the filter assembly. This approach is especially useful in neutron sources which apply filtering as a primary beam methodology.

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- Various approaches and materials are used in moderators which compact the neutron spectra to emphasize the desired epithermal energy range allowing the neutrons to drift deeper into target tissue and thus pass the skull to reach also the deep-seated tumours. The aim is to have the neutrons thermalising maximally in the precise depth and location of a tumour.
- the precise characteristics of an optimal beam in individual treatment cases would be variable and dependent on the individual patient and target geometry.

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2.5 Dose components

- The main therapeutic dose at the target volume in BNCT arises from the neutron capture reaction $^{10}B(n,\alpha)^{7}Li$. The resulting lithium recoil and alpha particles have track lengths of 5 and 9 μm, respectively, keeping the high linear energy transfer of the radiation exclusively in the boron containing cells.
- The neutron capture reactions of hydrogen $^{1}H(n,\gamma)^{2}H$ and nitrogen $^{14}N(n,p)^{14}C^{*}$ contributes also at a significant level to the total dose of the patient. In addition to the capture reactions, elastic scattering between epithermal as well as fast neutrons and hydrogen nuclei are the other essential interactions of neutrons within the tissue producing recoil protons.

- There is also gamma radiation produced by the reactor core with energy range of 0-15 MeV and the gamma radiation from the neutron capture of hydrogen reaction with energy of 2.2 MeV.
- A vast majority of the ^{7}Li ions from the boron capture reaction are produced in an excited state. The de-excitation occurs instantaneously and a 477 keV gamma rays are emitted. This minor gamma component is called consequently the prompt gamma radiation. Gamma radiation interacts and attenuates in the tissue mainly by Compton scattering and photoelectric effects. Since the boron dose is the main therapeutic dose component and is solely responsible for the targeted tumour effect the remaining dose components should be minimized as not desired portion of the radiation dose.

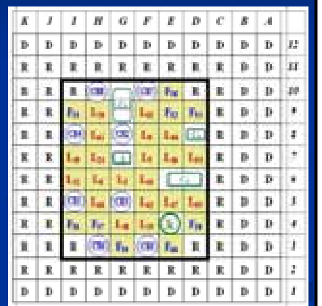
TRIGA RESEARCH REACTORS

- At the INR there are 2 high-intensity neutron sources.
- These sources are in fact the two nuclear TRIGA reactors:
  - 14MW TRIGA research reactor and
  - TRIGA ACPR. (Annular Core Pulsed Reactor).
- Both reactors are open-pool type.

TRIGA RESEARCH REACTOR (cont'd)

TRIGA stationary reactor core

- Rectangular shape with beryllium reflector
- Fuel bundle =29 TRIGA LEU fuel rods
- In-core irradiation channels
- Beryllium irradiation channels



Neutron characteristics

- XC-1 central channel: Thermal neutron (E_{Cd}=0.55eV):Φ_{Scd} =2.46*10^{14}n/cm^2*s

  -Integrated neutron flux (0<E>18MeV): Φ = 3.86*10^{14}n/cm^2*s

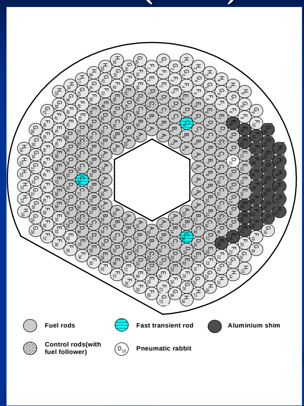
  -Cadmium ratio, R_{Cd}, respectively thermal to epithermal neutron flux ratio, f, are:RCd = 3.02; f = 31
- Beryllium reflector block J-6
- ΦScd = 9.17*10^{13}n/cm^2*s
- Φ = 1.72*10^{14}n/cm^2*s
- RCd = 2.1; f = 18.

Neutron characteristics (cont'd)

- The 14MW TRIGA SSR reactor is also provided with a horizontal radial dry neutron beam tube having a diameter of 280mm. The thermal neutron flux at the beam tube inlet is: Φ_{Scd} = 1.7*10^{13}n/cm^2*s
- The thermal neutron flux at the beam tube outlet is: 1*10^8n/cm^2*s (Neutron flux filtered by a thermal neutron filter silicon single crystal 30mm diameter and 400mm length). This beam can be used for BNCT purposes.

TRIGA Annular Core Pulsed Reactor (ACPR)

- Pulse mode: P=20000MW, FWHM~3.4ms
- Stationary mode: P=500kW
- Two dry irradiation channels



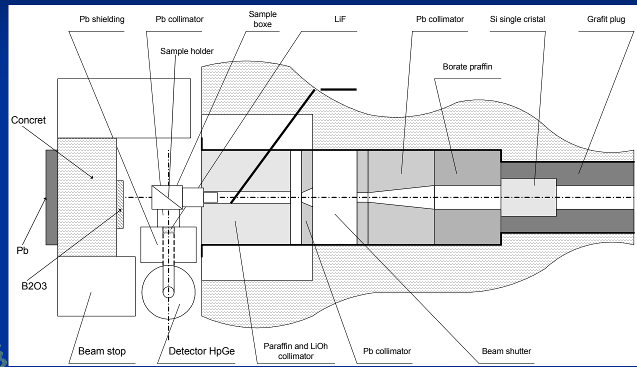
TRIGA ACPR neutron characteristics

- Centrl tube axial distribution
- Cadmium ratio r = 1.22
- Φ_{Scd} = 5.03*10^{11}n/cm^2*s
- Fast neutron flux (E>0.1MeV) :Φ_f = 4.7*10^{13}n/cm^2*s
- Thermal to epithermal neutron flux ratio : f = 4.67 (thermal/epithermal ratio)
- Thermal neutron flux in the pneumatic rabbit from dry channel D10 at P=100kW in stationary mode : Φ_{Scd} = 4.68*10^{12}n/cm^2*s; f= 12.

System description

- A prompt gamma neutron activation analysis (PGNAA) system was designed and constructed at the TRIGA reactor. The system is linked at the radial neutron beam tube at ACPR TRIGA reactor. During the PGNAA – system is in use the ACPR reactor will be operated in steady – state mode at 500 kW maximum power.
- PGNAA was designed also for BNCT purposes, especially for boron concentration measurement and for sample boron doped irradiation
- The main parts of the PGNAA – system are:
  - Gamma and neutron filter and collimator
  - Sample holder and low background shielding
  - Induced prompt gamma rays detection system

Fig.1 Schematic layout of PGNAA at TRIGA-ACPR reactor



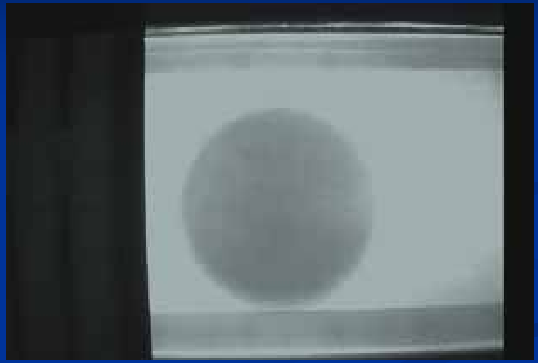
Gamma and neutron filter

- The filter is composed by a sintered nuclear graphite plug (L= 1413mm and Φ=200mm) in which a two-diameter hole was bored. Over a length of 450mm hole diameter is 101.2mm and over the rest the length it is 100mm. In the largest diameter portion a silicon single crystal having a length of 450mm and diameter of 101mm was inserted. Silicon single crystal acts as a filter by rejecting most of the fast neutrons and gamma rays and in the same time transmitting most of thermal neutrons. Thermal neutron transmitting factor for silicon single crystal at room temperature is about 40%

- Neutron beam collimation by use four collimators
- 1. First collimator: filled with borated paraffin (30%) and L=575mm
- 2. Second collimator: lead annuli
- 3. Beam-shutter.
- 4. The third collimator: lead annuli
- 5. The fourth collimator: paraffin and LiOH filled cylinder

- **Gamma ray detection system**
- HpGe(20% efficiency and 1.8KeV FWHM) detector for gamma ray and AQUSPEC multi-channel analyzer
- Gamma ray detector shielding: lead +LiF
- **Neutron beam**
- The beam shape determination by indium foil irradiation.(Figure 2)
- -Circular spot, good contrast and slightly diffuse edge.

Figure 2



- Thermal neutron current measurement (P=100kW)
- $\phi_{scd}=1*10^6 n/cm^2*s$ (E<0.55eV)
- $R_{cd}=80$

3.2. Measurements results

Measurements for method sensitivity and LLD determination were done for B. To accomplish this, a number of aqueous dilutions, which contained the specified element in various concentrations, were prepared .In the Figure 3 is presented the gamma ray spectrum for a solution containing boron. In figures 4 the curves which show the count rate versus elemental concentration, is plotted. Sensitivities and concentrations are presented in Table 1.

Figure 3.Gamma ray boron spectrum

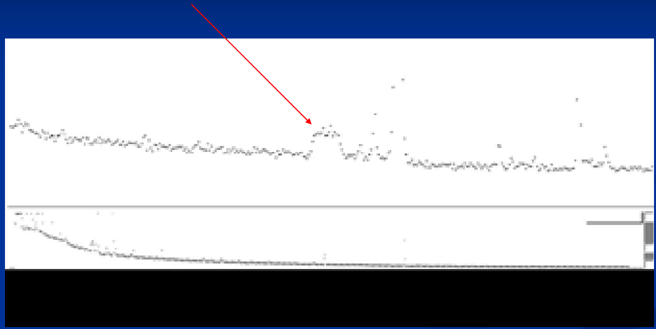


Figure 4. Boron calibration curve

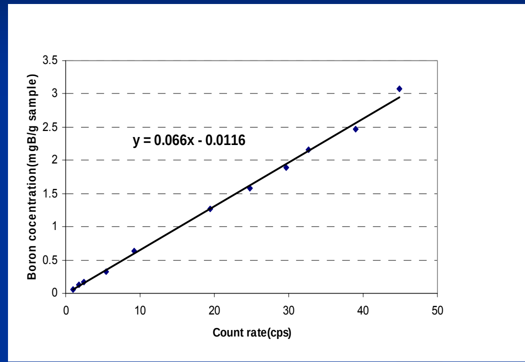


Table 1.

Element	Concentration (ppm)	
B	<10	

THANK YOU FOR YOUR ATTENTION!