BNCT is a promising method to treat malignant brain tumors. In fact, BNCT is a method that can be applied in many cases where other treatments cannot be used. In my talk, I will present the contents of a PhD project that IRI has started in collaboration with the Institute of Advanced Materials (IAM) in Petten. The logo in the upper left corner is not the new logo of Delft University of Technology, but it is the logo of the Institute of Advanced Materials, which is the Joint Research Centre (JRC) of the European Union that owns and operates the High Flux Reactor (HFR) in Petten. This reactor is currently being used in the framework of the European collaboration on BNCT to irradiate patients with neutrons. The PhD project I will describe here focuses on the design of a new neutron filter that has better characteristics than the currently installed filter, which is easier to maintain, and which is more flexible. The latter means that, depending on the kind of tumor to be treated, one would like to have the possibility to modify the filter arrangement to shift the neutron spectrum to the preferential energy region. I should emphasize that the design of a new neutron filter is only one aspect among many others that require research.

What is BNCT? Boron Neutron Capture Therapy makes use of the property of Boron-10 to split into two parts upon absorption of a thermal (low-energy) neutron. One particle, a so-called alpha particle, is released with energy of 1.47 MeV, the other particle, the Li-7 nucleus, with energy of 0.84 MeV. Furthermore, in 94% of the time, a gamma ray is released with energy of about 0.48 MeV, which usually escapes from the body without any interaction. The other two particles, however, the alpha particle and the Li-7 nucleus, have a high Linear Energy Transfer (LET), which implies that they deposit their kinetic energy within a very short range. Usually this range is no larger than 10 μm, which corresponds with the diameter of a single cell. So, when we would be capable of injecting the tumor with a boron-containing compound, which in itself does not have to be toxic, and irradiate the tumor with neutrons, the tumor would be destroyed exclusively. Because it is not possible in practice to inject a brain tumor, a tumor-seeking compound is delivered to the patient intravenously, after which the neutron irradiation can start.
BNCT is a bimodal system requiring at the one hand a boron-containing tumor-affinitive drug, and on the other hand a neutron beam to irradiate the boron-containing tissue.

Sheet 3
The cross section for neutron absorption in Boron-10 is very high for so-called thermal neutrons, and decreases with increasing energy of the incoming neutron. In fact, the B-10 cross section has an almost perfect ‘1/v’ shape, which reflects the fact that the chance for neutron absorption is proportional to the time the neutron is near the Boron-10 nucleus. This means that we should deliver preferentially thermal neutrons to the tumor to have as many neutron absorptions as possible.

Sheet 4
To judge whether the B-10 absorption cross section is large or not, we should compare it with that of the other elements in the brain tissue. Compared with Oxygen and Carbon, the absorption cross section of B-10 is larger by a factor of one million (10^6) at least. This means that with a boron concentration of only several parts per million, the dose rate of the boron already dominates. However, compared with the Hydrogen and Nitrogen, the boron cross section is larger by “only” a factor of 1,000 to 10,000. Because of the large atomic density of hydrogen and nitrogen in the tissue, the dose rate due to neutron absorption by these two nuclides can be considerable. Indeed, in practice the (n,gamma) reaction by Hydrogen and the (n,proton) reaction by Nitrogen, which are both ‘1/v’ absorbers, can deliver a high background dose to the normal tissue.

Sheet 5
Demonstration

Sheet 6
BNCT is not a new concept. In fact, as early as 1936, Locher proposed the principle to use neutron absorption reactions to radiation therapy. The first serious trials were performed in the fifties in Brookhaven using the Brookhaven Graphite Research Reactor (BGRR), while from 1959 to 1961, the Brookhaven Medical Research Reactor (a compact High Flux Reactor with a power of 5 MW) was used to this purpose. However, both reactors were used without much success. Neither successful were the irradiations at MIT in the same period using the MIT Research Reactor (MIT-RR). However, due to advancements in the tumor-affinitive boron-containing compounds, the Japanese researchers, who started their experiments in 1968, were more successful. Up till now, more than 200 patients have undergone BNCT treatment in Japan. In this intra-operative radiotherapy, the brain and tumor tissue is directly exposed to thermal neutrons. The success in Japan initiated new research in the US in the late eighties and later on also in Europe.
In the irradiations performed in the US and Europe (Petten), use is made of epithermal neutrons, which are being moderated to thermal energies in the brain tissue itself (in-vivo). As a result the maximum dose to the tumor can be delivered at greater depth up till 6-8 cm. Later on we will define some parameters to characterize the penetration capability of neutron beams.

Current developments focus on the utilization of new neutron sources for BNCT, like a Cf source driving a subcritical assembly, an accelerator-driven source making use of the $^7$Li(p,n) reaction, and neutron sources making use of the D-D and D-T reactions. All this research is driven by the fact that not many research reactors in the neighborhood of hospitals are available or suitable for BNCT. Reactors that are being used for the purpose of BNCT are upgraded by, for example, Fission Converter plates. In these cases, the thermal neutrons of the reactor are guided to an array of fuel assemblies outside the core where they initiate new fissions. The neutrons released are subsequently used for the purpose of BNCT. In other words, the fission converter plates work as a neutron booster.

In Petten, research is restricted by the possibilities and the limitations imposed by the HFR. Within the framework of the European BNCT group, shown on this slide, patients are irradiated with epithermal neutrons coming out of neutron beam HB11.

For people who don’t know the HFR, I can recommend the site in spring, say at the end of April or beginning of May, when it looks like this. This is the Petten HFR in a touristic season.

Usually, research reactors have the nice feature that they are partly shielded by water. This enables one to see the blue-colored Cherenkov radiation, which originates from electrons that are emitted with velocity larger than the velocity of light in the water. Here you see the water basin of the Petten HFR and the characteristic Cherenkov radiation. The reactor core itself is located in an Aluminium reactor vessel which, however, cannot be seen on this picture.

The neutron beam HB11/12 in the Petten HFR has the nice feature that it has a large cross sectional area and that if faces directly one whole side of the reactor vessel. The useful diameter of the beam is 30 cm at the maximum. At present, a neutron filter is
positioned in the beam leg HB11, and the epithermal neutrons are guided through the beam to the irradiation room. Patients can enter this shielded room through a lock, via the reactor emergency exit. Behind this, at the outside, rooms for the preparation of the patient and for further treatment after the irradiation are present. Notice the machinery needed to keep the argon in the liquid state. Argon becomes liquid at a temperature of about minus 185 degrees C, and freezes at a temperature of minus189 degrees C, so you have to keep constant the temperature within a narrow range.

Sheet 13
Currently, the neutron filter consists of a thin layer of Cadmium to capture the thermal neutrons in the beam, 15 cm of Aluminium, 5 cm of Sulphur, 1 cm of Titanium and 150 cm of liquid Argon. All these materials have scatter resonances in the high-energy region to scatter down the fast neutrons to epithermal energies. There is an extra water layer that acts as a shutter. The mean (dose-weighted) neutron energy in the beam is about 10 keV. The epithermal flux is such that a therapeutic dose can be delivered to the patient in four irradiations of 30 minutes each. In total the filter contains 150 liters of Argon.

Sheet 14
Artist’ impression of the neutron filter.

Sheet 15
This sheet shows the cross section of Argon as a function of the energy of the incoming neutrons. It is seen that in the keV range, around 60 keV, there exists a ‘window’ in the cross section. Above this window energy, the elastic scatter cross section of Argon is quite high, while for energies below the window energy, the scatter cross section of Argon is quite low. As a result, fast neutrons have a large probability to scatter with the Argon and to reach the epithermal energy range, while, once they are epithermal, they have only a small probability to scatter down to the thermal energy range. As a result the use of Argon seems to be a clever solution to this problem, with the only disadvantage that it is rather costly to maintain (to keep it liquid). Furthermore, the filter is not flexible.

Sheet 16
This picture shows the cross sections of the Aluminium, Sulphur, Argon and Titanium used in the filter. It is seen that all nuclides have large scatter resonances in the high-energy region to scatter down the fast neutrons, although the Titanium scatter resonance might have an energy too low to be effective. As mentioned before, the mean dose-weighted neutron energy equals about 10 keV, which is much lower than the window energy of the Argon. This degradation of the neutron energy might be due to the large scatter resonance of Titanium. Perhaps a material like Iron or Aluminium with a scatter window at lower energy might perform better.
There exist several parameters to characterize a neutron beam for BNCT.

The first is the Advantage Depth (AD), which is the depth in the tissue at which the dose to the tumor equals the maximum dose to the normal tissue. In this definition, the dose consists of the sum of the total background dose and the B-10 dose in the tumor. The AD indicates the depth of effective beam penetration. In other words, the AD measures the ability to penetrate tissue and to deliver a therapeutic dose at depth.

The second one is the Advantage Ratio (AR). This is defined as the ratio of the dose to the tumor and the dose to the normal tissue integrated from the body surface to a certain depth, for which usually the AD is used. The AR is a measure of the therapeutic gain, which is the ability of the beam to maximize the desired radiation dose to tumors while minimizing background dose to healthy tissue. Both the AD and the AR characterize the beam quality.

The third characterization is the Advantage Depth Dose Rate (ADDR), which is the total therapeutic dose at the AD. In fact the ADDR is a measure of the ability to deliver the desired radiation dose in an acceptable treatment time.

To visualize the parameters used for the characterization of the beam, I have an example from the beam used at the MITR-II reactor (the so-called M-67 beam). EXPLANATION.

A plot of the AD as a function of the AR for a range of ideal mono-energetic mono-directional neutron beams shows like half a donut. Thermal neutrons have very high AR values because of the relatively low dose to normal tissue. High-energy neutrons have small AR values and small AD values because the radiation dose from the fast neutrons at the surface of the body becomes comparable to the therapeutic dose from B-10. In fact, in this case the contribution of the fast neutron background dose is too large both in the normal tissue and in the tumor. Clearly, in between these two extremes, an optimum exists for epithermal neutrons with both a large AR and a large AD. Unfortunately, in the neutron beam optimization process, the in-phantom FOMs are difficult to use, because of the dosimetric calculations needed.

To overcome this problem, so-called in-air FOMs are defined that characterize a neutron beam without the need of in-phantom studies. The usual parameters are:

- the epithermal neutron flux in the requested energy interval,
- the fast neutron dose rate per unit of the epithermal neutron flux, and
- the gamma dose rate per unit of the epithermal neutron flux.
By means of the flux-to-dose conversion factors provided by, for example, the ICRP-51, the fast neutron dose and the gamma dose can easily be calculated. These should subsequently be converted to equivalent doses by using the so-called RBE values (the Relative Biological Effectiveness) of the different types of irradiation.

Another parameter of interest is the directionality of the beam, which is defined as the epithermal neutron current divided by the epithermal neutron flux density. The neutron beam in the Petten HFR has a very high directionality, because of the large distance between the core vessel and the patient’s irradiation position. In fact such a long beam tube act as a very long collimator.

Sheet 21

When we use these three parameters to characterize the HFR neutron beam, we find that it performs better than the neutron beam used at MITR-II, but that it performs worse compared with the beam used at the BMRR. Both at the BMRR and at the MITR-II reactors, the use of a Fission Converter Plate is considered to boost the performance of the beam. In conclusion, an upgrade of the Petten HFR neutron beam is desirable to keep up with the other beams currently being developed. From this table, we also derive some design goals we should aim at: an epithermal neutron flux of 1E9 n.cm\(^{-2}\).s\(^{-1}\), and of D\(_{\text{fr}}/\Phi_{\text{epi}}=3\times10^{-13}\) Gy.cm\(^2\)/n and D\(_{\gamma}/\Phi_{\text{epi}}=3\times10^{-13}\) Gy.cm\(^2\)/n (Increase of \(\Phi_{\text{epi}}\) with a factor of three without increasing the fast neutron and gamma ray dose rates).

Sheet 22

Besides the fundamental nuclear properties of the materials that should be favorable, the materials used in a neutron filter design should also meet other criteria, like:

- The material should not undergo phase changes,
- The material should not decompose or emit toxic substances in the radiation field, and the potentially elevated temperatures,
- The material should not accumulate high long-term radioactivity,
- The material should not contain impurities or moisture,
- Low cost of material, component fabrication, and maintenance.

A material regularly used is Iron. Just like Argon, Iron has a window in the total neutron interaction cross-section.

Sheet 23

Because of the complex three-dimensional geometry, calculations will be performed mainly by the use of point-wise Monte Carlo codes. However, many calculations are needed with high accuracy, which forces one to use clever variance reduction techniques to reduce computation times. Modern Monte Carlo codes, in which the neutrons and gamma rays are tracked through the geometry from their birth to their escape or
absorption, have many variance reduction methods to reduce the computation time needed. At the IRI, a new method has been developed that can be very suitable to the problem of BNCT. In this method, the so-called Midway Monte Carlo method, particles are tracked from the source to the detector, while so-called adjoint particles are tracked from the detector to the source. Somewhere in between, these particles meet at an artificial surface and the detector response is calculated. Experience has shown that the computation times needed for deep-penetration methods with a relatively small source and a small detector volume may be reduced by a factor of 2-10.

Another method standard available in modern Monte Carlo codes is the so-called differential sampling method. In this method, derivatives of responses are calculated in the Monte Carlo run, which can be used afterwards to calculate the sensitivity of the detector response to certain input parameters. In this way, a first-order guess of the detector response can be made when the neutron filter arrangement is slightly modified, without having to do new Monte Carlo runs. This seems a tool very well suited to this kind of optimization problems.

Sheet 24

This is the end of my presentation. It has an open end, because no results are available yet. The PhD student who will start tomorrow, has to defend his MSc thesis at this very moment in the Kramer’s Laboratory, and I hope that he will stand here at this place four years from now to defend his PhD thesis on this subject. Hopefully, we can present some results at the next IRI symposium about medical applications of radiation.