JOINT INSTITUTE FOR NUCLEAR RESEARCH

Laboratory of Radiation Biology

FINAL REPORT ON THE START PROGRAMME

"Application of the Boron Neutron Capture method for the treatment of Rheumatoid Arthritis"

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Participation period:
July 08 – August 30,
Summer Session 2025

Dubna, 2025

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Abstract

This report presents a first approach to a feasibility study on the application of accelerator-based Boron Neutron Capture Synovectomy (BNCS) as a therapeutic approach for rheumatoid arthritis (RA). BNCS integrates nuclear physics and biomedical engineering to achieve targeted ablation of inflamed synovial tissue using high-linear energy transfer particles generated through neutron capture by boron-10. The study focuses on the simulation and optimization of a Beam Shaping Assembly device (BSA) along with the modification of a voxel phantom geometry of the knee for in vivo studies. Simulations were conducted using the Monte Carlo N-Particle Transport Code (MCNP6) to evaluate neutron flux and energy spectra and the deposited energy in the affected synovial fluid and in the bone and healthy tissue. The optimized configuration of the BSA was found using BeF_2 as the moderator, MgF_2 as the reflector and LiF as thermal neutron shielding, yielding an epithermal spectrum suitable for BNCS.

1. Introduction

1.1 Overview of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease primarily characterized by persistent inflammation of the joints, which can lead to progressive joint destruction, functional disability, and decreased quality of life. The disease arises when the immune system mistakenly attacks synovial tissues, causing inflammation, pain, and swelling. Over time, this inflammatory response may extend beyond the joints to affect other organ systems.

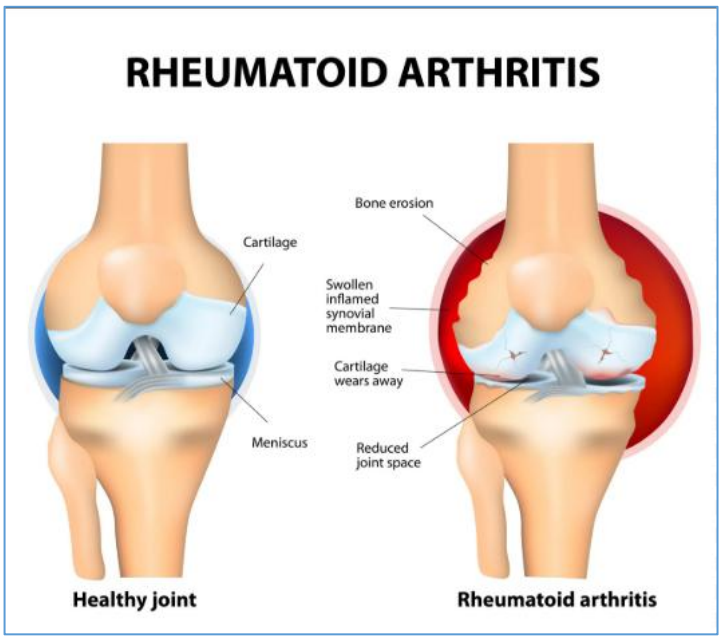

Figure 1. *Example of a comparison between a healthy joint and a joint with Rheumatoid arthritis*

Globally, RA affects approximately 18 million people, with a higher prevalence observed among women and older adults [1]. The onset typically occurs between the ages of 30 and 60, and the disease exhibits a female-to-male ratio of approximately 3:1. If left untreated, RA can lead to severe complications, including cardiovascular disease, interstitial lung disease, and peripheral neuropathy. These systemic manifestations underscore the importance of timely and effective intervention strategies.

Given the complex and systemic nature of RA, the development of advanced diagnostic tools and therapeutic monitoring techniques is of critical importance. In recent years, the integration of nuclear physics into biomedical research has enabled the application of high-resolution, non-invasive imaging modalities—such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT)—to visualize and quantify inflammatory processes at the molecular level. These techniques, coupled with novel radio-tracers targeting specific biomarkers of inflammation, offer promising avenues for early detection, patient stratification, and treatment assessment in RA.

Furthermore, interdisciplinary approaches involving nuclear instrumentation, radio-pharmaceutical development, and computational modeling have opened new possibilities for precision medicine in autoimmune diseases. The application of these methodologies in clinical and pre-clinical settings not only enhances our understanding of RA pathogenesis but also supports the design of targeted therapeutic strategies aimed at minimizing systemic damage and improving patient outcomes. As such, the convergence of nuclear science and rheumatology represents a pivotal advancement in the pursuit of innovative solutions for complex chronic diseases.

1.2 Treatment Modalities

Traditional treatment of RA includes a combination of pharmacological approaches—such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs)—alongside non-pharmacological interventions like physical therapy and lifestyle modifications. While these methods can alleviate symptoms and slow disease progression, they often fail to achieve long-term remission or prevent irreversible joint damage in all patients.

In recent years, innovative treatment modalities have emerged, aiming to target RA at the molecular and cellular levels. Among these, novel radio-therapeutic techniques have shown potential in addressing both the local and systemic aspects of autoimmune joint diseases. One such promising approach is Boron Neutron Capture Synovectomy (BNCS), which integrates principles of nuclear medicine with targeted tissue ablation.

BNCS is based on the selective accumulation of boron-containing compounds within inflamed synovial tissue, followed by irradiation with low-energy neutrons. The nuclear reaction between boron-10 and thermal neutrons generates high-linear energy transfer (LET) particles—namely alpha particles and lithium nuclei—that induce localized cellular damage. Due to the short path length of these particles, the cytotoxic effect is confined to the boron-loaded cells, minimizing harm to surrounding healthy tissue. This selectivity presents BNCS as a potential alternative to conventional surgical synovectomy or systemic immunosuppression.

The integration of BNCS into clinical research frameworks underscores the growing relevance of nuclear techniques in personalized medicine. Advances in boron compound development, neutron beam optimization, and imaging-guided treatment planning have further refined the feasibility and safety profile of this approach. Moreover, the application of computational simulations and dosimetric modeling supports treatment precision and enhances understanding of radio-biological effects at the micro-scale.

In the context of chronic inflammatory diseases such as RA, BNCS represents a paradigm shift—moving from generalized systemic therapies toward highly localized, targeted interventions at molecular level. Continued interdisciplinary research is essential to evaluate long-term efficacy, optimize delivery protocols, and translate pre-clinical success into standardized clinical practice.

1.3 Boron Neutron Capture Synovectomy (BNCS)

BNCS represents a novel therapeutic strategy designed to selectively destroy inflamed synovial tissue through a two-step process. This method is based on the principles of Boron Neutron Capture Therapy (BNCT), originally developed for cancer treatment. In BNCS, a boron-10 (^10B) enriched compound is first introduced and preferentially accumulates in the synovial membrane. This is followed by irradiation of the volume of interest with a beam of thermal neutrons.

The interaction between the epithermal neutrons and ^10B nuclei results in a nuclear reaction that produces high-energy alpha particles and lithium-7 nuclei. These particles have a very short path length (5–9 micrometers), enabling them to destroy targeted cells while sparing surrounding healthy tissues. This mechanism holds significant promise not only for rheumatoid arthritis but also for other pathologies involving localized tissue proliferation, such as synovial sarcoma or joint-associated metastases.

The present report focuses on designing a Beam Shaping Assembly (BSA) capable of producing epithermal neutrons within the energy range of 10–20 keV. This neutron energy spectrum is considered optimal for BNCS applications since it shifts to the necessary thermal energy on its path up to the volume to be treated. The ultimate aim is to evaluate the technical feasibility of implementing BNCS as a viable treatment for rheumatoid arthritis, thereby contributing to the development of precise, minimally invasive therapeutic options for autoimmune joint diseases.

Additionally, advanced computational simulations—such as those based on Monte Carlo transport codes—are employed to model neutron behavior and optimize BSA geometry. These simulations provide valuable insight into the spatial and energy characteristics of the neutron field.

By addressing the engineering and radio-biological challenges associated with BNCS implementation, this study contributes to the broader goal of advancing targeted radio-therapies for autoimmune diseases. The proposed system has the potential to provide a minimally invasive, highly localized alternative to conventional surgical or systemic treatments. As such, BNCS represents a promising direction in the integration of nuclear technologies with precision medicine in rheumatology and beyond.

2. Project Objectives

The objective of this study was to analyze the feasibility of Boron Neutron Capture Synovectomy treatment method (BNCS) by comparing the effective dose delivered to diseased synovial fluid with that delivered to bone and healthy tissue. To this end, a Beam Shaping Assembly (BSA) device was designed and optimized, through simulations using the MCNP 6.1 code the desired device configuration was achieved. The effective dose to the affected synovial fluid and bone was then calculated using the energy deposition data obtained from the simulations.

3. Methodology

This study employed the Monte Carlo N-Particle Transport Code (MCNP6) to model and simulate the production and moderation of neutrons for applications in **Boron Neutron Capture Synovectomy (BNCS)**. The methodology focuses on the simulation of a compact, accelerator-based neutron source coupled with a Beam Shaping Assembly (BSA) designed to moderate fast neutrons into the epithermal energy range (10–20 keV), which is optimal for therapeutic irradiation of inflamed synovial tissues.

3.1 Simulation Framework and Overview

The simulation was performed using MCNP6, which allowed for the detailed modeling of neutron transport, interactions, and energy moderation through heterogeneous materials. The complete geometry included:

- The double-differential spectrum of the neutron beam resulting from the reaction 7Li(p,n)7Be for Ep = 2MeV.
- A specific voxel phantom for in vivo treatment of the Rheumatoid Arthritis in the Knee
- Tallies[2] to characterize the neutron field and the deposited energy so can be used for further comparison

The model aimed to reproduce realistic physics for the proton-lithium interaction and neutron moderation, as well as the spatial and angular distribution of emitted neutrons.

3.2 Accelerator-Based Neutron Source

Neutron production was modeled via the nuclear reaction $^{7}Li(p,n)^{7}Be$ with 2 MeV protons impinging on a layer of lithium-7. The neutron emission spectrum was configured using energy-angle-dependent data consistent with the physical characteristics of the reaction. Importantly, the **angular distribution of the emitted neutrons was constrained to the forward hemisphere**, specifically from **0° to 89°** in the direction of proton beam propagation. This directional bias reflects realistic kinematics of the (p,n) reaction at 2 MeV and was implemented using the SDEF card in MCNP6, with the DIR parameter used to limit the emission to this angular interval.

This directional setup ensured that the majority of the neutrons entered the BSA in a forward-focused cone, increasing moderation efficiency and minimizing neutron loss due to back-scattering or leakage. The source data was generated by the LZYield code program with a Neutron Yield of 96.308 n/pC of accelerator current.

3.3 Construction of the Beam Shaping Assembly (BSA)

The proposed materials for the geometry of the BSA used in this study were Beryllium Fluoride as the moderator, Magnesium Fluoride as the reflector and Lithium Fluoride as the thermal neutron shielding, the geometry is shown in ***Figure.2***

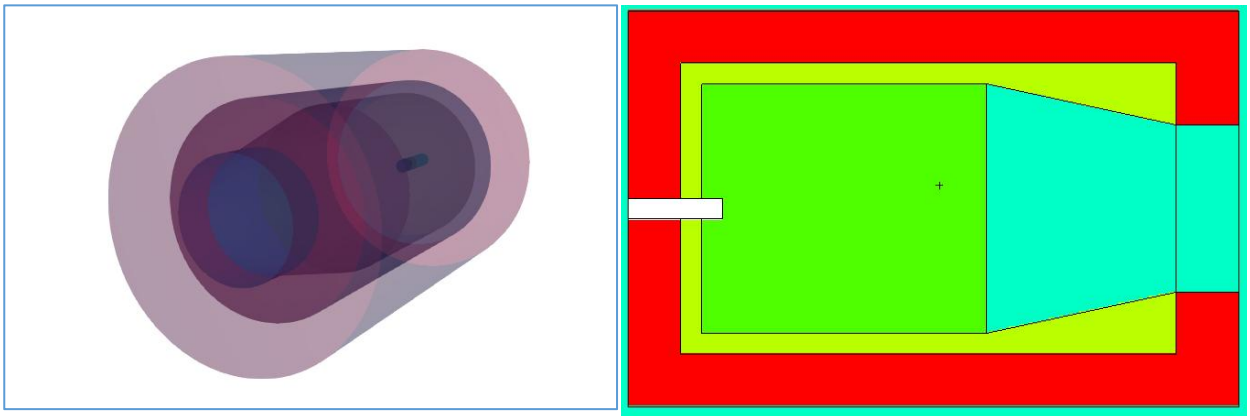

Figure.2 *Beam Shaping Assembly (BSA)*

3.4 Construction of the numerical phantom

The construction of the voxel phantom was based on image processing of a CT scan, in this case, of the Spitz knee phantom. The process is as follows:

- Acquisition of the CT images. The Spitz anthropomorphic phantom [6] representing a human left knee flexed at 208 was scanned at Hospital Puerta de Hierro of Madrid. The original images stack is a matrix of 512 512 pixels, 0.53125 mm of pixel spacing, 5 mm of slice thickness and 4096 grey levels (16 bits).

- Segmentation of the images. The images were segmented on the basis of the different levels of grey by defining threshold levels on the histogram to distinguish between materials (air, bone substitute and soft-tissue substitute). Then, pixel resolution was re-scaled to obtain a phantom consisting of 197 325 voxels (2 x 2 x 5) mm^3 size. The information is stored in an ASCII file (2.76Mb) containing the phantom data in an easily readable format.

- Assignation of proper material characteristics. Compositions and densities according to international recommendations[7] were assigned to each material distinguished in the images. The tissues of the Spitz phantom are polyurethane based substitutes for muscle tissue and trabecular bone tissues.

- Implementation into the MC code. A computer program was developed to read the voxel phantom data and create the corresponding input file[8] using the 'repeated structure' feature of MCNPX[9]. Using this program, a source uniformly distributed in the voxels corresponding to a given organ or tissue can also be specified.

The voxel geometry was provided by the researcher Montserrat Moraleda Chaves of the Centro de Estudios Energéticos, Medio Ambientales y Tecnológicos (CIEMAT).

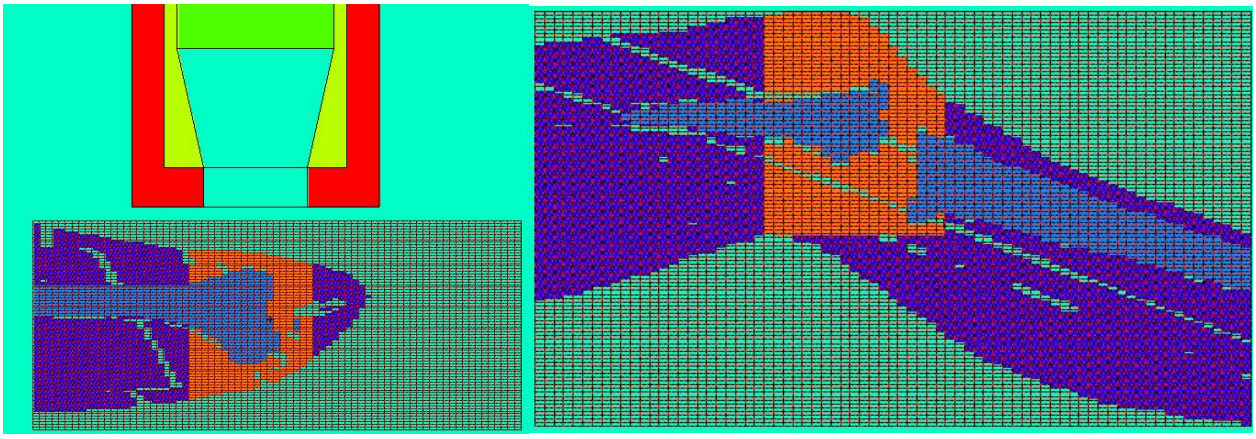

Figure 3. *Measurement geometry of the knee*

4. Results

4.1 Analysis of the source spectrum

The graph presented in ***Figure 4*** show the spectral distribution of neutrons emitted by the source used, considering one specific directions: 15º. The graph is plotted on a logarithmic scale (base 10) for both the energy (MeV) and probability axes. The curve shows a distribution where the probability of neutron emission increases with energy, reaching a clear maximum around 0.03 MeV (30 keV), and then decreases. This behavior indicates a significant concentration of neutrons within the epithermal range, which is favorable for applications such as Boron Neutron Capture Synovectomy (BNCS), where neutrons in that energy interval are required.

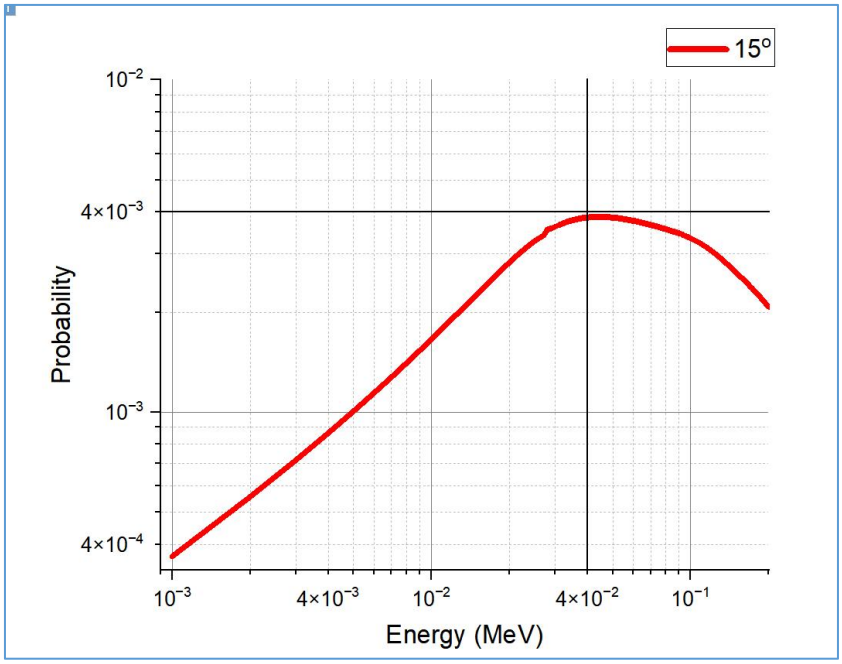

Figure 4. *Spectral distribution of neutrons emitted by the source at 15º*

In contrast, the curve corresponding to the 90° direction shows a different distribution. In this case, the probability also increases with energy, but there is no well-defined peak within the analyzed range. Instead of being concentrated at a specific energy, the curve

suggests a broader distribution, with a greater proportion of neutrons at relatively higher energies. Unlike the frontal direction, where a clear energy selection is observed, the lateral direction exhibits a more extended spectrum.

When comparing all curves, it is evident that the 0° direction provides a higher probability of neutron emission within the epithermal range, while at 89° the emission is more dispersed toward higher energies. This behavior is consistent with the kinematics of the (p,n) reaction, in which neutrons are preferentially emitted along the beam direction, resulting in a spectrum more aligned with the energy requirements of the proposed clinical application.

4.2 Analysis of the neutron energy spectrum at the BSA outlet

The graphic shown in ***Figure 5.*** display the neutron energy spectra obtained for different configurations of the thickness of the moderator used in the design of the BSA system. These plots help analyze how each value affects the energy distribution of the neutrons.

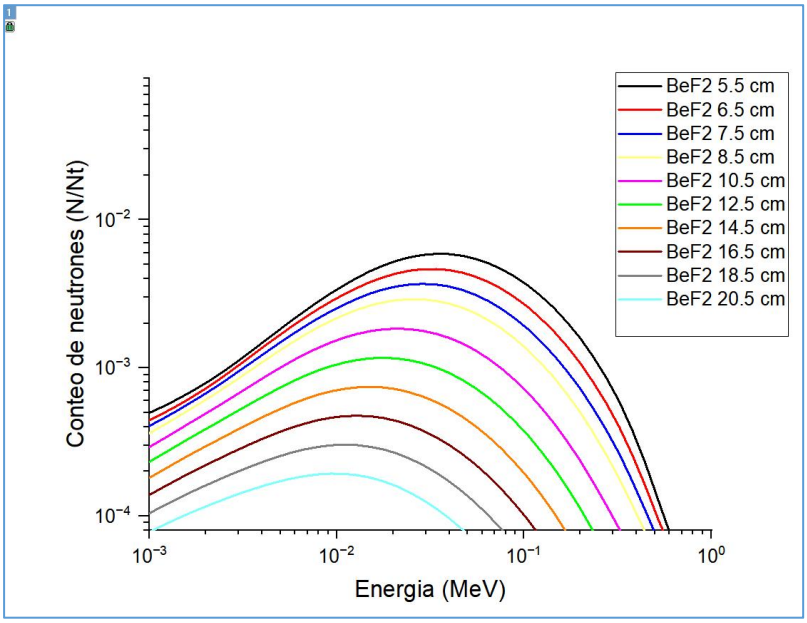

Figure 5. *Neutron energy spectra obtained for different thickness levels of the BeF_2 as moderator*

When comparing all curves its evident that the maximum value it's found for a thickness of 5.5 cm at the energy of 0,03 MeV (30 KeV), but it is not the most optimal configuration for the BSA moderator as will be seen later in the report.

4.3 Analysis of the energy deposition ratio in the synovial fluid with ^{10}B and in the soft tissue and bone combined:

In the present case study, a human knee affected by rheumatoid arthritis has been selected, in which the immune system unleashes an aggression on its own cells,

producing inflammation of the synovial membrane and the effusion of fluid loaded with high concentrations of antibodies that damage ligaments and erode bones. This therapeutic alternative, based on the Boron neutron capture method, is aimed at reducing the concentration of interleukins and preventing them from entering the bloodstream and damaging the vital organs of the body. The synovial fluid loaded with different concentrations of Boron-10 has been reflected in **Figure 3** to model and evaluate the feasibility of the therapeutic proposal.

The ***Figure 6*** show the BSA optimization taking as *figure of merit (FOM)* the ratio between the energy deposited in the affected synovial fluid with Boron and the energy deposited in both, the surrounded healthy soft tissue and the knee bone, for different thickness of the moderator:

$$\boldsymbol{FOM = \frac{Dose\ (Synovium + Boron)}{Dose\ (Soft\ tossue) + Dose\ (Bone)}}$$

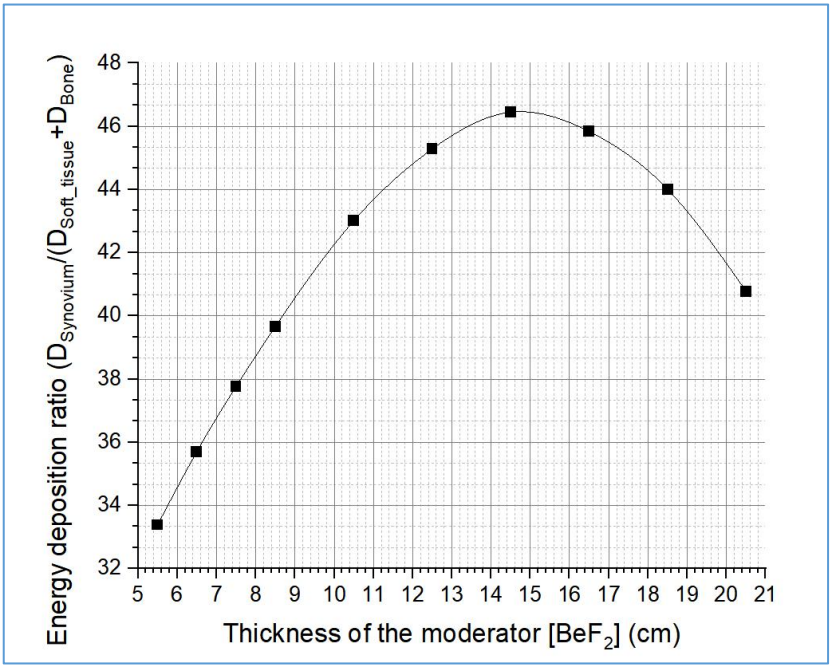

Figure 6. *Relation between the energy deposition ratio and the thickness of the moderator*

When analyzing the graphic, the maximum value of ratio it's found for a thickness of 14.5 cm, which is the optimal thickness of the moderator for the applying of the Boron Neutron Capture Synovectomy therapy.

4.4 Analysis of the effective dose received by the synovial fluid for different concentrations of ^{10}B:

Unlike BNCT, where the concentrations of Boron-10 applied to brain and neck tumors do not exceed 55 ppm due to the existence of the blood-brain barrier, the direct injection of borated compounds using the arthroscopy technique in the damaged limbs, allows to reach concentrations of 2000 ppm in the synovial fluid. These high concentrations make it possible to substantially shorten the irradiation time and, in addition, considerably reduce the requirements in the development of neutron sources for therapeutic uses.

The effective dose in the surrounded soft tissue, knee bone and synovial fluid was calculated using the MCNP6 tally F6 (the energy deposition in [MeV/g] per source-neutron) obtained for different concentrations of ^{10}B using 14.5 cm of moderator, the results are shown in ***Figure 7***. The equivalent dose rate is estimated according to the neutron source Yield= 96.308 n/pCoulomb, the proton energy E= 2.0 MeV and the averaged proton current I=1μAmper.

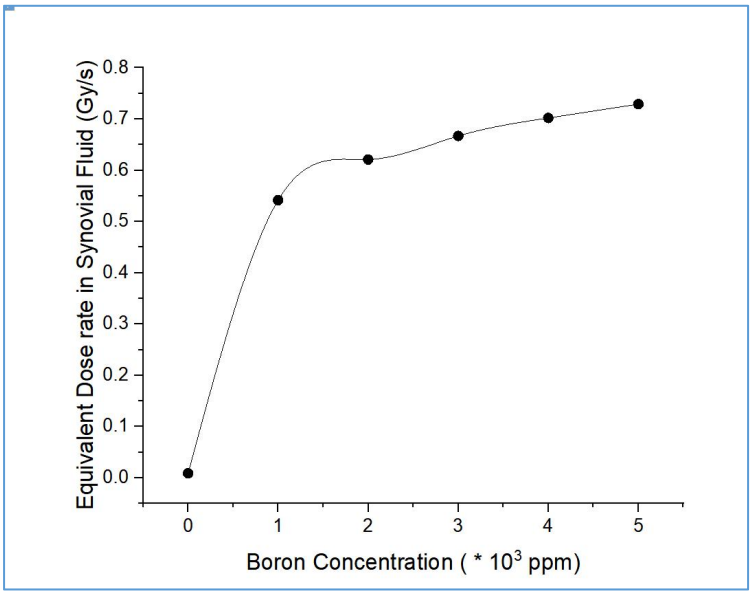

Figure 7. *Relation between effective dose in Synovial fluid and boron concentration*

Deposited Energy [MeV/g]	**Absorbed Dose per second [MeV/g]**	**H-Equivalent dose [Gy/s]**	
0,00835	8,04E+05	**0,0013**	Dose in Soft tissue
0,00204	1,97E+05	**0,0003**	Dose in Bone
Deposited Energy [MeV/g]	**Dose Synovium [MeV/g]**	**H-Synovium [Gy/s]**	**Boron Concentration**
0.00596	5.74E+06	**0.0009**	Boron-0%
0.35115	3.38E+08	**0.0542**	Boron-1% (1000 ppm)
0.40246	3.88E+08	**0.0621**	Boron-2% (2000 ppm)
0.43249	4.17E+08	**0.0667**	Boron-3% (3000 ppm)
0.45506	4.38E+08	**0.0702**	Boron-4% (4000 ppm)
0.47254	4.55E+08	**0.0729**	Boron-5% (5000 ppm)

Table 1. Relation between the deposited energy and the equivalent dose rate in the synovial fluid for an accelerator current of 1 μA

To preserve the metallic ^{7}Li target it is proposed to limit the proton beam current to 1μA. This is possible due to the high concentration of boron in the synovial fluid of 1000 ppm that was used to evaluate the feasibility of this therapeutic alternative for the treatment of advanced rheumatoid arthritis in the case study of the knee of an adult patient.
As the results in Table 1 show, the absorbed dose due to Boron-10 is 60 times higher in the synovium for 1000 ppm Boron concentration.
Due to the high radiation sensitivity of the bone marrow, the risk of bone metastasis after treatment with radiation therapy is often analyzed. Therefore, in this case of study attention is paid and the ratio between the dose absorbed in the synovium and the dose

absorbed in the femur bone is calculated. As a result of the analysis, the absorbed dose is 172 times higher in the synovium (with 1000 ppm of ^{10}B) than in the bone, increasing up to a factor of 200 for boron concentrations of 2000 ppm.
That is, if we expose the diseased knee for 10 minutes to the epithermal neutron beam at the exit of the BSA, the dose deposited in the synovial fluid will be 32.5 Gy. While the dose absorbed into the bone would be 0.19 Gy.
As a preliminary conclusion, due to the effect of neutron capture by ^{10}B, a high dose is absorbed in the synovium, and that should be sufficient to reduce locally in the knee the excessive concentration of antibodies in the synovial membrane without affecting the global immune response of the organism. Of course, it is up to specialists in rheumatoid diseases to decide whether collateral damage to the surrounding tissue and bones is acceptable. And finally, they could approve and validate this proposal of alternative therapy against rheumatoid arthritis.

5. Conclusions

The study successfully modeled and simulated an accelerator-based neutron source suitable for Boron Neutron Capture Synovectomy using the MCNP6 code. The optimal configuration of the BSA moderator was achieved for a thickness 14.5 cm of BeF_2. The optimal concentration of ^{10}B for a safe amount of equivalent dose in the synovial fluid was 1000 ppm, due to the high values of the deposited energy ratio in the synovial fluid and in the bone and healthy tissue. Simulation results confirmed that the directional emission of neutrons, particularly at 0°, aligns well with the energy needs for BNCS, maximizing therapeutic effectiveness while minimizing collateral tissue damage. These findings support the technical feasibility of implementing BNCS as a non-invasive and highly localized treatment modality for rheumatoid arthritis and potentially other localized immune joint disorders. Further research is needed to refine neutron beam shaping, optimize boron delivery agents, and validate clinical protocols for safe and effective implementation.

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