***Supplementary data***

**Key biological mechanisms involved in high-LET radiation therapies with a focus on DNA damage and repair**

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**Proton-and neutron-boron capture therapy**

To aid the understanding of this topic of proton or boron neutron capture therapy, we present some analysis of the associated phenomena but more is beyond the scope of the present review.

*Proton-boron capture therapy*

We provide an approximate estimation of the kinetic energy that has to be shared among the three α-particles:

0.675\*11/12 + 8.59 = 9.265 MeV (Eq. 1)

From this energy (Eq.1) a fraction of about 2/3 will be transferred to α0 and the rest will be shared by the two other particles, due to the Momentum Conservation Principle. Moreover, the exact amount of depends on the emission angle. We have calculated the range of values for each case using *catkin 2.03* *(*[*http://personal.ph.surrey.ac.uk/~phs1wc/kinematics/*](http://personal.ph.surrey.ac.uk/~phs1wc/kinematics/)*)* kinematics calculator*.* The range of the energy values is calculated by considering several emission angles:

is in the range of 5.476 – 6.837 MeV and the α-particles originating from the subsequent decay of 8Be have an equal amount of T, which is within the range of 1.214-1.89 MeV.

is in the range of 3.58 – 4.7 MeV and the α–particles originating from the subsequent decay of 8Be\* have an equal amount of T, which is within the range of 2.285-2.843 MeV.

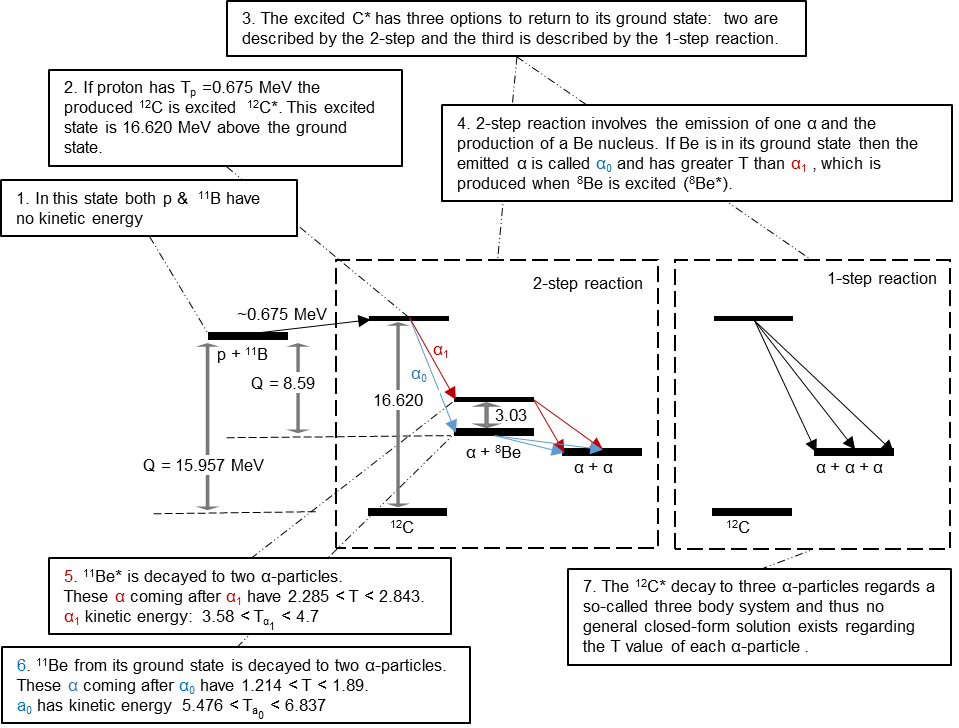
Regarding the one step reaction, since three particles are generated at once, there is a *three body system*, and no general closed-form solution exists.

By utilizing raw data derived from simulations of previous work [1] we have calculated the corresponding LET values for the abovementioned energy values in water (**Table S1**).

**Table S1**: LET values of α-particles in water for characteristic values of Energy in PBCT. The maximum LET value -which corresponds to 0.64 MeV- is also included.

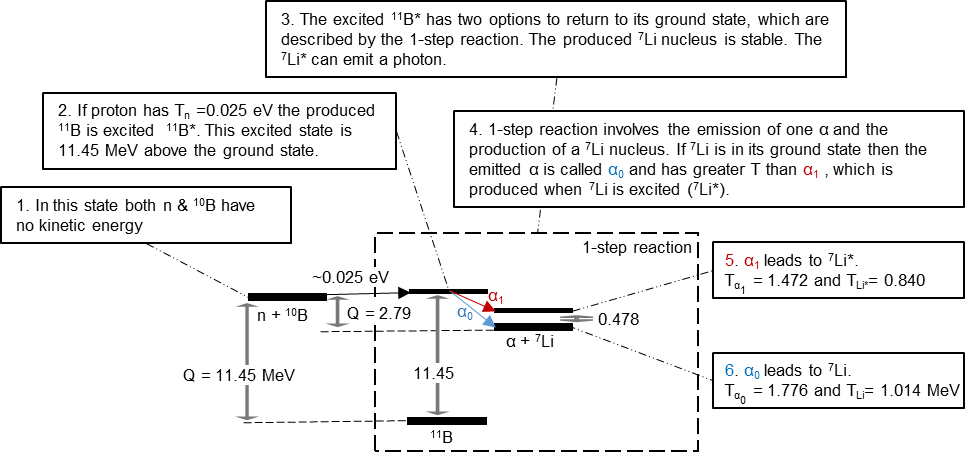
|  |  |
| --- | --- |
| **Energy (MeV)** | **LET in water (keV/μm)** |
| 5.476 – 6.837 | < 91 |
| 4.7 | 93 |
| 3.58 | 96 |
| 2.243 | 132 |
| 2.285 | 149 |
| 1.89 | 166 |
| 1.214 | 207 |
| **0.64** | **231** |
| 0.04 | 68 |

Since, by definition, the emitted α-particles present a continuous angular distribution, and taking into account that the corresponding angular emission probabilities cannot be *a priori* known and have not been thoroughly studied experimentally, e.g. [<https://www-nds.iaea.org/exfor/>], each one of them may have any amount of energy within the abovementioned ranges. Correspondingly, α-particles can be emitted having a plethora of LET values. **Table S1** highlights the PBCT potential, since any emitted particle, during its impeding trajectory will inevitably reach the energy value of 0.64 MeV where the LET reaches its maximum, i.e. 231 keV/μm. It should be noted here that the maximum range of 6.837 MeV a-particles in water is approximately 59.4 μm, following standard SRIM2013 stopping power calculations [2, 3]. It should be noted herein that in contrast to proton-Boron fusion, where the emitted α-particles take energies from a range, in Boron-neutron fusion, the ejectile-α as well as the recoil-Li have –in good approximation- constant values of energy.



**Figure S1.** Energy levels implicated in the proton-11Boron fusion and in the subsequent disassociation to α-particle & 8Be / 8Be\*, involved in proton-boron capture therapy-PBCT. Our illustration begins with the system of proton and 11B being motionless. The amount of kinetic energy that is required for the proton is just 0.675 MeV, then if the fusion happens, a compound nucleus, a 12C\* is created. The excited state of 12C that is produced at the resonance of 0.675 MeV is 16.620 MeV above the ground state. The subsequent 12C\* decay may occur via 1-step or 2-step reactions. In the case of a 2-step reaction the intermediate product is the 8Be or the 8Be\* (excited) nucleus. Both immediately decay to two α-particles. The α-particle that leads the system to the ground state of 8Be is called α0, while α1 is called the one that leads to the excited state 8Be\*. 8Be can be found either in its ground (see n.r. 2 main text) or in its first excited state, at 3.03 MeV (8Be\*). 8Be or 8Be\* in its turn disassociates to two α-particles. Between the mechanisms of the 2-step reaction the predominant is the one that involves 8Be\*. We need to mention here that 8Be is an isotope of beryllium, having a half live of 8 x 10-17 s; the stable isotope is 9Be.

*Boron neutron capture therapy*



**Figure S2.** Energy levels implicated in the 10Boron-neutron fusion and in the subsequent disassociation to α-particle & 7Li /7Li\*, involved in boron-neutron capture therapy-BNCT.

Using simulations from our previous work [1] we have calculated the corresponding LET values for the abovementioned energy values in water (**Table S2**).

**Table S2:** LET values of α-particles in water for characteristic values of Energy in NBCT. The maximum LET value -which corresponds to 0.64 MeV- is also included.

|  |  |
| --- | --- |
| **Energy (MeV)** | **LET in water (keV/μm)** |
| 1.776 | 173 |
| 1.472 | 191 |
| **0.64** | **231** |
| 0.04 | 68 |

**References**

1. Nikitaki, Z., et al. (2021) Construction and evaluation of an α-particle-irradiation exposure apparatus. **97**(10), 1404-16

2. Ziegler, J.F., Ziegler, M.D. and Biersack, J.P. (2010) SRIM–The stopping and range of ions in matter (2010). Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms **268**(11-12), 1818-23

3. Ziegler, J. (2013) SRIM & TRIM. <http://www.srim.org/>