

A COMPUTATIONAL METHODOLOGY FOR THE EFFICIENT AC-225 PRODUCTION VIA PROTON IRRADIATION OF RA-226

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Abstract

²²⁵Ac is a crucial isotope for targeted alpha therapy, yet its clinical application is severely constrained by supply shortages. The use of high-intensity proton beams to irradiate ²²⁶Ra targets offers a viable approach to significantly enhance ²²⁵Ac production, as it enables higher yields and greater scalability. However, the process is also accompanied by the generation of other isotopes of actinium, especially the long-lived ²²⁷Ac, which challenges the purification process. This work establishes a parameterized model that combines beam energy, target thickness, and cooling time for optimizing ²²⁵Ac production while minimizing ²²⁷Ac impurity levels and target material consumption. We determine the optimal parameters, which effectively maximize ²²⁵Ac yield while controlling impurity levels and target material consumption. This method provides a valuable reference for the efficient production of ²²⁵Ac.

INTRODUCTION

Actinium-225 (²²⁵Ac) is a highly promising radionuclide that has attracted considerable interest in Targeted Alpha Therapy (TAT) [1]. However, its relatively short half-life of $T_{1/2} = 9.92$ days poses a severe challenge to the stability of its supply chain. Currently, the accelerator-based production methods including proton irradiation of thorium or radium targets and photonuclear reactions induced by gamma irradiation, have been developed to increase the yield of ²²⁵Ac. However, these methods are accompanied by the production of other impurity isotopes of actinium, especially the long-lived actinium-227 (²²⁷Ac, $T_{1/2} \approx 21.8$ years). The radiation toxicity of ²²⁷Ac, lasting for decades, may offset therapeutic benefits and pose serious safety hazards. Therefore, the stringent control of ²²⁷Ac and other actinide impurities is of paramount importance.

The method of proton irradiation of ²²⁶Ra achieves a balance between product yield and impurity ratios. Given the high cost of ²²⁶Ra target material, optimizing target thickness to maximize yield while minimizing target consumption is crucial. Although previous studies generally consider an energy around 16 MeV as the optimal incident energy for producing ²²⁵Ac via proton irradiation of radium targets [2, 3], this conclusion is largely based on yield alone as the criterion. To address this issue, this work proposes

an optimization methodology. By systematically regulating the target thickness d , incident proton energy E , and cooling time t_c after irradiation, the optimization process aims to achieve the dual objectives of maximizing ²²⁵Ac yield while minimizing the impurity ratio and target consumption. The optimal combination of process parameters determined in this work provides theoretical basis and reference for the actual production and quality control of ²²⁵Ac.

METHOD

The Monte Carlo (MC) method is widely used for simulating proton irradiation. However, its high computational cost and long processing times make it less suitable for a systematic optimization algorithm. Therefore, we employed ISOTOPIA [4] to calculate nuclide generation from proton bombardment of radium targets. The ISOTOPIA code is designed for predicting isotope production using an analytical method, by calculating the energy loss and isotope production rate, which is much faster than MC methods.

To validate the reliability of the analytical calculation, we compared the ²²⁵Ac production cross section obtained from MC simulations with ISOTOPIA and experimental data [5]. We adopt PHITS [6] and Geant4 [7] tools for MC simulation. PHITS version 3.28, coupled with the INCL 4.6 intranuclear cascade model and the GEM evaporation model [8], is employed to simulate proton irradiation of radium targets. The GEANT4 toolkit with the QBBC physics list [9] is used for comparison. The simulation geometries are shown in Fig. 1. Using the simulated results, the corresponding cross sections can be calculated as follows [8]:

$$\sigma = \frac{-\ln\left(1 - \frac{N_{\text{prod}}}{N_{\text{in}}}\right)}{nd} \quad (1)$$

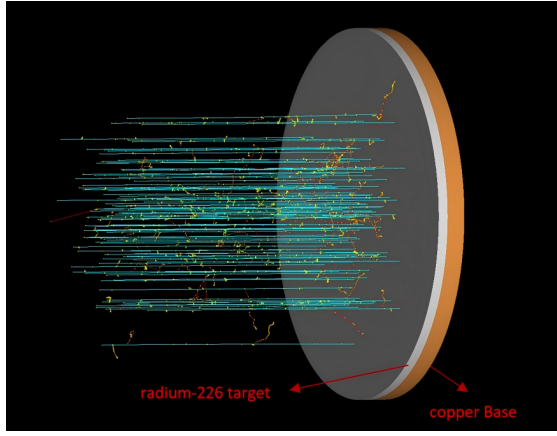
where N_{prod} is the number of product nuclei, N_{in} is the number of incident particles, n is the number density of target nuclei, and d is the target thickness.

A comparison of the ²²⁵Ac production cross sections is shown in Fig. 2. The ISOTOPIA calculations, Monte Carlo simulation results, and experimental data demonstrate good agreement, with all curves peaking located in the 15–18 MeV energy range. This consistency confirms the reliability of the activity data calculated by ISOTOPIA.

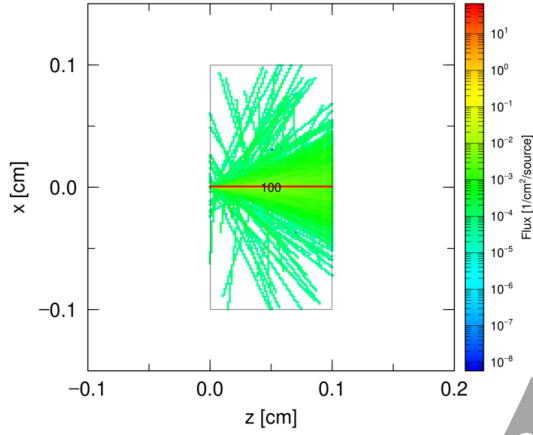
Using ISOTOPIA, the yields for four nuclides ²²⁴Ac, ²²⁵Ac, ²²⁶Ac, and ²²⁷Ac were calculated on a two-dimensional grid covering a proton energy E range of

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(a) GEANT4 simulation of proton irradiation.



(b) PHITS simulation of proton irradiation.

Figure 1: The MC simulations for the target bombardment process.

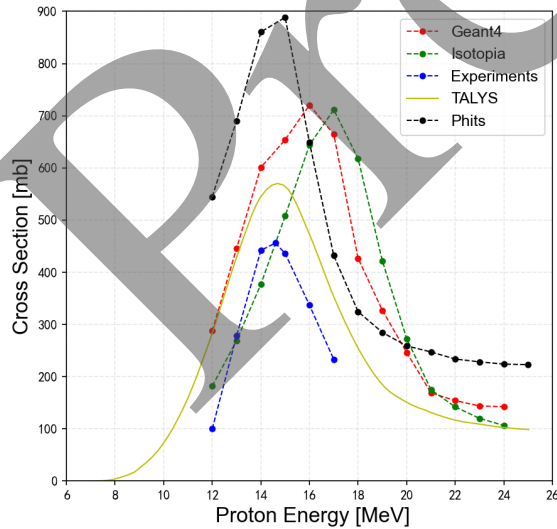


Figure 2: Comparison of the $^{226}\text{Ra}(p, 2n)^{225}\text{Ac}$ reaction cross section from different methods. The results from PHITS, GEANT4, TALYS 1.96 [5, 10], experimental data [5], and ISOTOPIA are shown.

14–24 MeV and a target thickness d range of 0–3 mm. The irradiation time was set to 1 hour. The yield of ^{225}Ac is shown in Fig. 3 for illustration. We construct two-dimensional inter-

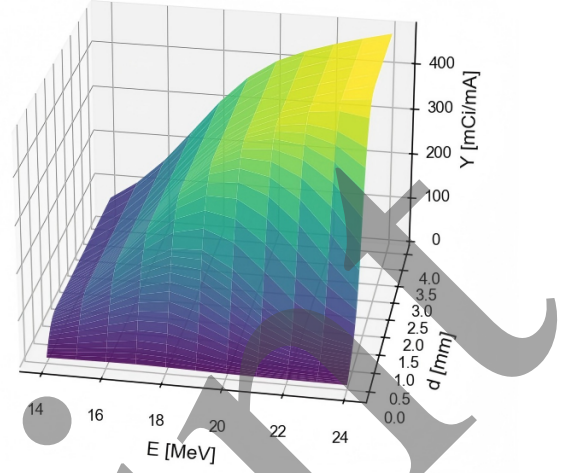


Figure 3: ^{225}Ac yield distribution as a function of E and d calculated by ISOTOPIA.

polation functions based on the yield data for numerical calculations. We also take into account the cooling time t_c after irradiation, which is important for the removal of short-lived impurities. The t_c dependence follows the law of exponential decay, which can be expressed as $Y(t_c) = Y_0 (1/2)^{t_c/T_{1/2}}$, where Y_0 is the EOB (end of bombardment) yield calculated by ISOTOPIA and $T_{1/2}$ is the half-life of the corresponding nuclide.

To achieve an optimal balance between yield and purity in the production of ^{225}Ac as well as the cost of target material, we propose an objective function F as follows:

$$F(E, d, t_c) = \frac{Y_{225}}{1 + \sum_i w_i R_i + w_{\text{Ra}} d}, \quad (2)$$

where Y_{225} is the yield of ^{225}Ac , $R_i \equiv Y_i/Y_{225}$ are the impurity ratios of actinium isotopes relative to ^{225}Ac for $i = 224, 226, 227$ with corresponding weights w_i , and d is the thickness of the ^{226}Ra target material with a weight denoted by w_{Ra} . This function is designed to find the global optimum by minimizing its negative value (i.e., $-F$). F is proportional to Y_{225} since the main goal of the optimization is to maximize ^{225}Ac yield. The denominator introduces a weighted penalty term, which constrains the yield of isotope impurities and the usage of the target material. The constant 1 is introduced to avoid division by zero.

The weight coefficients w_i are used to impose predefined constraints on impurities and target material mass. When a term in the denominator is much less than 1, its contribution to the objective function can be neglected, which means the optimization process constrains the terms with $w_i R_i \geq 1$ (or $w_{\text{Ra}} d \geq 1$). Thus, the condition of $w_i R_i = 1$ can be used to determine the weights w_i by specifying R_i and d limits from medical or economic requirements.

For the nonlinear objective function F constructed above, we employ the L-BFGS-B algorithm (Limited-memory

Broyden-Fletcher-Goldfarb-Shanno with Bounds) for numerical optimization. Given that the E , d , t are all subject to strict non-negativity and equipment threshold constraints in physical experiments, the L-BFGS-B algorithm is an ideal choice due to its efficiency in handling bound-constrained problems.

RESULTS

The targeted alpha therapy field has yet to establish a universally accepted limit for ^{227}Ac . However, such a limit is crucial for standardizing the production and quality control of ^{225}Ac . We specify that the ^{227}Ac limit per patient dose (approximately 10 MBq of ^{225}Ac) be equal to the exemption level for ^{227}Ac disposal [11]. Referring to the recommended exemption quantities by the International Atomic Energy Agency (IAEA) [12], the exemption level for ^{227}Ac is 1 kBq. This corresponds to a limit of R_{227} on the order of 0.01%. Similarly, the impurity constraints for R_{224} and R_{226} are established at 10% and 1% respectively. Accordingly, using the condition $w_i R_i = 1$, the weighting coefficients w_{224} , w_{226} , and w_{227} are assigned values of 10, 100, and 10,000, respectively. The consumption of target material is constrained by w_{Ra} . As an example, we impose constraint on $d > 0.5$ mm, which determines $w_{\text{Ra}} = 2 \text{ mm}^{-1}$ by setting $w_{\text{Ra}} d = 1$.

Under the defined weighting scheme, the optimization algorithm successfully converged to a solution that balances production efficiency with stringent radiopurity constraints. The optimized parameters, along with the corresponding impurity ratios and the yield of the target nuclide ^{225}Ac , are summarized in Tab. 1.

Table 1: Optimal values of E , d , t_c , the optimized values for impurity ratios, and the yield of ^{225}Ac .

E [MeV]	d [mm]	t_c [h]	R_{224}	R_{226}	R_{227}	Y_{225} [mCi/mA]
19.56	0.85	226.90	2.57×10^{-23}	4.46×10^{-3}	2.32×10^{-6}	1.73×10^2

The results demonstrate that all impurity ratios fall well within acceptable ranges. Although the yield of ^{225}Ac always increases as energy and thickness increase simultaneously, a preferred energy $E = 19.56$ MeV, which is slightly greater than 16 MeV, is obtained due to the constraint on $d > 0.5$ mm set by the weight factor w_{Ra} , which results in an optimal thickness of $d = 0.85$ mm. The optimal cooling time $t_c = 226.90$ h is mainly determined for decreasing R_{226} . The final value of the objective function F and the ^{225}Ac yield are determined to be 54.6 mCi/mA and 1.73×10^2 mCi/mA, respectively, which implies the penalty term in the denominator of F is 3.17. Since there are five terms in the penalty term including the constant 1, the resulting value $3.17 < 5$ suggests that the optimization approach is appropriate for the $^{226}\text{Ra}(p, 2n)^{225}\text{Ac}$ production routine.

CONCLUSION

We propose and elaborate on a novel methodology for the multi-parameter optimization of ^{225}Ac production via

proton bombardment of radium targets. By constructing a parameterized model, this approach achieves a systematic characterization of key process parameters, including yield, beam energy, and target thickness. The results provide a valuable reference for the practical production of ^{225}Ac .

REFERENCES

- [1] C. Kratochwil *et al.*, “ ^{225}Ac -psma-617 for psma-targeted α -radiation therapy of metastatic castration-resistant prostate cancer”, *Journal of Nuclear Medicine*, vol. 57, no. 12, pp. 1941–1944, 2016.
- [2] C. Apostolidis, R. Molinet, J. McGinley, K. Abbas, J. Möllenbeck, and A. Morgenstern, “Cyclotron production of ac-225 for targeted alpha therapy”, *Applied Radiation and Isotopes*, vol. 62, no. 3, pp. 383–387, 2005.
- [3] K. Nagatsu *et al.*, “Cyclotron production of ^{225}Ac from an electroplated ^{226}Ra target”, *European journal of nuclear medicine and molecular imaging*, vol. 49, no. 1, pp. 279–289, 2021.
- [4] *Isotopia-2.2: simulation of medical isotope production with accelerators*, Nuclear Data Section, IAEA, Vienna, Austria, 2025. nds.iaea.org/talys
- [5] O. Lebeda, K. O. Fialová, L. Ondrák, J. Červenák, J. Ráliš, and J. Štursa, “Cross sections of the ^{226}Ra (p, xn) reactions relevant for ^{225}Ac production”, *Nuclear Medicine and Biology*, vol. 142, p. 108995, 2025.
- [6] Y. Iwamoto *et al.*, “Benchmark study of particle and heavy-ion transport code system using shielding integral benchmark archive and database for accelerator-shielding experiments”, *J. Nucl. Sci. Technol.*, vol. 59, pp. 665–675, 2022. [doi:10.1080/00223131.2021.1986686](https://doi.org/10.1080/00223131.2021.1986686)
- [7] J. Allison *et al.*, “Recent developments in geant4”, *Nucl. Instrum. Meth. A*, vol. 835, pp. 186–225, 2016. [doi:10.1016/j.nima.2016.06.125](https://doi.org/10.1016/j.nima.2016.06.125)
- [8] N. Burahmah, J. R. Griswold, L. H. Heilbronn, and S. Mirzadeh, “Transport model predictions of ^{225}Ac production cross sections via energetic p, d and α irradiation of ^{232}Th targets”, *Applied Radiation and Isotopes*, vol. 172, p. 109676, 2021.
- [9] A. V. Ivantchenko, V. N. Ivanchenko, J. M. Q. Molina, and S. L. Incerti, “Geant4 hadronic physics for space radiation environment”, *International Journal of Radiation Biology*, vol. 88, no. 1-2, pp. 171–175, Sep. 2011. [doi:10.3109/09553002.2011.610865](https://doi.org/10.3109/09553002.2011.610865)
- [10] A. Koning, S. Hilaire, and S. Goriely, “Talys: modeling of nuclear reactions”, *The European Physical Journal A*, vol. 59, p. 131, 2023. [doi:10.1140/epja/s10050-023-01034-3](https://doi.org/10.1140/epja/s10050-023-01034-3)
- [11] A. K. Robertson *et al.*, “ ^{232}Th -spallation-produced ^{225}Ac with reduced ^{227}Ac content”, *Inorganic Chemistry*, vol. 59, no. 17, pp. 12156–12165, 2020.
- [12] IAEA, “Exemption from regulatory control of goods containing small amounts of radioactive material; iaea-tecdoc-1679”, Vienna, 2012