American Journal of Botany and Bioengineering
https://biojournals.us/index.php/AJBB
ISSN: 2997-9331

Nanodosimetry and Its Role in Bridging Medical, Biological, and Applied Physics in Cancer Therapy

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Received: 2025 19, Jul
Accepted: 2025 28, Aug
Published: 2025 29, Sep

Annotation: Nanodosimetry emerges as an interdisciplinary link connecting medical, biological, and applied physics with cancer therapy. The presence of nanotechnology in all these fields, alongside clinical progress witnessed in several cancer centers, underlines its integrative capacity.

The adoption of innovative radiation fields and ion beams, exemplified in advanced centers and associated applications, provides impetus for new forms of radiation protection and modulating technologies for cancer radiosensitivity. The fundamental role of nanodosimetry lies in elucidating molecular mechanisms underpinning radiation interactions at the cellular level. As a result, foundational knowledge and experimental data serve as a basis for developmental tools, enveloped by modeling and simulation of radiation interactions at the organ scale.

1. Introduction to Nanodosimetry

Nanodosimetry is the field of dosimetry that introduces the nanometric scale in the measurement or characterization of ionizing radiation with particular emphasis on the assessment of radiation damage of biological targets.

The motivation of nanodosimetry is that because the critical targets for the effects of radiation of biological interest are at the sub-cellular level, knowledge of the radiation track structure, i.e. the pattern of energy deposits by individual ionizing particles of radiation, is required to predict the resulting biological effects. This requires the introduction of the nanometric scale, as the critical dimensions of the cellular targets range down to a few nanometres. Knowing the radiation track structure is important also to the assessment of the radiation damage to micro-electronics.

The physics principles underpinning nanodosimetry are identical to those encountered in the clinical radiotherapy context where the physics of kiloelectron volt-effects on DNA strands in cells is paramount. The medical relevance of nanodosimetry lies in the importance of accurate knowledge of the radiation track structure in general, and of the radiation track structure at sub-cellular scale in particular, in assessing absorbed dose to radiosensitive targets at the cellular and sub-cellular level. [1][2][3]

2. Fundamental Principles of Dosimetry

Dosimetry is the methodology used for assessing the energy delivered by radiation to matter. Cancer treatment heavily depends on knowledge of dose distributions in order to achieve an effective clinical outcome while protecting healthy tissue. Due to the common occurrence of clusters of damage within nanometres of DNA, the assessment of dose at the nanoscale plays an important role in understanding the biological effects related to radiation exposure. Nanoscopically distributed damage to the DNA can be linked to biological effects, providing a direct connection between the physical and biological components that constitute the medical physics discipline [4]. Nanodosimetry has the potential to become the common point of the interdisciplinary space bridged between medical, biological and applied physics, linking physical quantities with biological effects through measurement and modelling. Owing to its long development, nanotechnology shows tremendous potential for medicine, biotechnology and biology and its applications. The possibility of developing indirectly selective agents in order to analyse the biological response to radiation represents the first step towards the application of nanodosimetry in cancer therapy [5]. Modern cancer therapies have an increased need for a better evaluation of dose at the nanometre level. Nanodosimetry can therefore be regarded as a fundamental tool for such purposes, bridging the gap between radiation and biology and helping to understand how cancer develops. Combining medical physics and nanodosimetry principles can provide novel insights into understanding cancer progression and improve differential analyses of clinical radiobiological outcomes [6].

3. Nanotechnology in Medicine

In the field of medicine, nanotechnology has progressed rapidly and is widely utilized; its application continues to expand with ongoing technological advances. This submicroscopic field plays a critical role across multiple disciplines, particularly in the health sciences. Controlling physicochemical and biological interactions at the nanolevel offers insight and capabilities with significant implications for drug delivery, diagnostics, and therapy [7]. A particularly dynamic area involves the interactions between nanomaterials, the surrounding microenvironment, and single cells. The nanoscale structures and physicochemical properties of nanomaterials significantly influence their uptake and distribution within cells. These unique properties are exploited to streamline the delivery of drugs and immunomodulators to both extracellular and intracellular sites, thereby enabling combination therapies that modulate the cellular environment to improve therapeutic outcomes [8]. Previously unseen insights now emerge as nanomaterials advance, offering powerful tools to understand and intervene at the cellular level [5].

4. Mechanisms of Radiation Interaction at the Nanoscale

The mechanisms through which ionizing radiation deposits energy at the intracellular level is of paramount importance to radiotherapists. The topic is of active interest within a multidisciplinary debate involving medical physicists, medical doctors, physicists, chemists, and biologists. It is in this context that nanodosimetry provides a profound link connecting applied, medical, and biological physics.

A vast share of current radiotherapy techniques relies on the exploitation of interaction mechanisms of radiation with matter. Advancements in delivery devices (e.g., the introduction therein of multileaf collimators), novel techniques (e.g., ablative stereotactic body radiotherapy), new energy sources (e.g., protons and hadrons) have opened new frontiers for treatment.

Upon deposit in synapses, the energy given by the radiation interacts directly or indirectly with key biomolecules, thus producing legitimate cellular effects. These events are, by nature, in the domain of the nanometric scale. On this basis, accurate determination of the dose at the cellular or DNA level plays a fundamental role in understanding the biological effects of radiation and assessing the treatments' effectiveness.

More specifically, these processes start at the subcellular and molecular level, closely connected to the social development in nanotechnology, which has dramatically advanced in the past decades. Nanotech in clinical medicine largely concerns the development of early diagnosis and therapeutic tools [5]. Nanometric dose determination, blending medicine, physics, and biology, sets the basis for the physics of the interaction mechanisms of radiation with matter, the core physics that enables and complements medical and biological interpretations.

5. Biological Effects of Radiation at the Nanolevel

The consequences of irradiation depend on complex pathways involving physical, chemical and biological processes, the investigation of which requires expertise from various disciplines including physics, chemistry, biology and medicine. At the same time, the applications of radiation in medicine provide a strong motivation to characterize these processes and forecast their outcomes. Radiation therapy provides a typical example. The medical treatment of cancer by ionising radiation benefits from an interdisciplinary approach that employs physics, chemistry and biology to link the characteristics of the particle beam to macroscopic observations of cell survival [5]. Tumour irradiation involves the interaction of radiation with a chemical matrix followed by a cascade of chemical reactions culminating in damage in cell DNA [4]. The physics of radiation tracks is routinely used to bridge the gap between the characteristics of the particle beam and tumour response, but the link between the cell level and the biological response remains difficult to quantify. Multi-scale models of radiation damage are therefore instrumental in the context of cancer cells, with a strong focus on nanodosimetry since the size of the sensitive targets is comparable to nanometric patterns of ionisation [9]. As models of cell response to radiation clearly show, nanodosimetry plays a key role in representing the initial event that triggers the subsequent biological response and hence in linking applied, medical and biological physics.

6. Applications of Nanodosimetry in Cancer Therapy

Nanodosimetric methods have been widely applied to cancer therapy in medicine, biology, and applied physics. Implantable nano dosimeters for in-vivo real time measurements are particularly needed for modern radiotherapy, which often delivers higher doses over fewer sessions to maximize tumor dose while minimizing damage to surrounding tissues. Nanomaterials play an important role as drug carriers, imaging contrast agents, photothermal agents, photoacoustic agents, and radiation dose enhancers in biomedical imaging and cancer therapeutic methods. Nanodosimetric models accurately reproduce cell survival curves under diverse radiation qualities and particle types, approaching a universal description independent of particle type and cell line [5] [10] [4].

7. Measurement Techniques in Nanodosimetry

Microdosimetry techniques provide a consolidated tool for correlating internal energy deposition with the biological effects of ionizing radiation [5]. However, in the sub-100 nm domain, experimental measurements of nanodosimetric distributions become necessary to obtain accurate assessments of the number of radicals and reactive species produced during oxidative stress. Current measurement models operate as systems of differential equations with the interaction mechanisms described by individual micro- and nanodosimetric distributions [4]. Elastic cross sections incorporate rotational-vibrational excitation and electronic collisions, while inelastic cross sections are adjusted as functions of both the isolated molecule and the cross sections of the gas targets employed in measurements.

7.1. Microdosimetry

Microdosimetry is a scientific discipline that determines the relevant quantities of radiation action in single cells and small organisms. It may also be defined as the assessment of the spatial and temporal distribution of energy depositions in small volumes (about 1–10 µm and less) to allow a correlation between energy deposit patterns and chemical and biological cellular cues, with the ultimate goal being a comprehensive understanding of radiation damage. While the smallest mechanisms may operate at a sub-micrometre scale, damage to the machinery of life can be observed at the micro- and even macroscale: microdosimetry fits between these extremes, providing a crucial link. All types of ionizing radiation, including charged particles, neutrons and photons, can be characterized in terms of their microdosimetric parameters, investigating how radiation interacts with matter at the microlevel and subsequently tracing biological (cell/organism) effects using a stochastic and probabilistic approach [5] [4] [11].

7.2. Nanodosimetry Tools

Radiation dosimetry describes techniques to measure the effects and doses resulting from ionizing radiation [4]. Nanodosimetry extends this to count ionization events within nanometric targets, thereby bridging between microdosimetry and track structure analysis. Although modern radio-oncology advancements allow extraordinary dose control, the non-uniform spatial pattern of energy depositions at the cellular scale influences biological response [5]. Nanodosimetry addresses these heterogeneities to better characterize the microscopic distribution of damage. Providing data in nanovolumes akin to DNA dimensions, it connects radiobiology of single cells to the macroscopic doses delivered in medical radiation fields. Complex measurement systems now facilitate applications in dose determination from neutron sources, gaseous microstructures, and neutron dose acquisition with tissue-equivalent, space-like or gaseous nanometric targets. Refining incident-radiation identification at the nanometer scale, nanodosimetric tools enhance modelling capacities.

Microdosimetry extends absorbed-dose measurements to individual events within volumes ranging from millimetres down to 10 nanometres. However, volumes at DNA scale—few nanometres—permit only zero or one event, rendering absorbed dose ill defined. Nanodosimetry emerges as a complementary experimental methodology in nanometric volumes small enough to attribute biological effects solely to ionization concentrations. As the science underpinning the evaluation of radiation impact on cellular media, nanodosimetry quantifies the distribution of ionization events within a defined target volume.

Three experimental approaches yield nanodosimetric distributions of ionization cluster-size probabilities: the extraction of µm-sized gas cavities susceptible to scaling organizations, the use of wall-less counters measuring free-electron transport through gas at low pressure with variable target geometries, and the detection of ions formed in a simulated sensitive nanometric volume. Innovative gaseous methods transform measured ion distributions into absorbed-dose distributions; combined with Monte Carlo simulation, these data produce comprehensive models of beam interactions with biological material.

Experimental systems developed to determine ionization cluster-size distributions for various charged-particle qualities and energies include a prolonged time-of-flight (TOF) line extracting ions generated in an evacuated, nanometric-scaled cavity. Ions drift to a counting tube, enabling cluster-size measurements from individual events to thousands of ions. Such methods have elucidated cluster-size distributions, highlighting the superiority of nanodosimetry over absorbed dose in nano-scale damage evaluation. Further developments include hybrid systems capable of assessing track segments with various diagnostic parameters simultaneously. [12][13][14]

8. Modeling and Simulation in Nanodosimetry

Modeling and simulation in nanodosimetry play an essential role in describing and predicting radiation interactions at the nanometre scale in biologically relevant scenarios. Such computational approaches complement measurements performed using the relatively few existing setups for microdosimetry and nanodosimetry [4]. They also offer a route to bridging the gap between measured quantities and those optimally suited to derive quantities of interest such as biological outcome or radiation damage [5]. Due to their small size, experimental nanodosimeters rely on simulated transport of primary particle species and their secondaries (where applicable) to assess the relationship between measured quantities and those of direct relevance to the scenario under study. Event-based Monte Carlo transport codes are generally used, since deterministic codes—and mixed or condensed-history Monte Carlo codes—cannot provide the level of detail required to study the intricate particle track structure necessary to account for the radiation field inside a nanometre-sized target.

Computable nanodosimetry emerged over a decade ago with the availability of first track-structure models. At that time, the focus was, naturally, on investigating the effects of nanometre targets on a particle tracks and related quantities; macroscopic Monte Carlo of the assessment of nanodosimetric quantities or application to models relating radiation effects to nanodosimetric quantities were not yet extremely widespread [15]. Injection of results from simplified, nanometre-scale track-structure simulations or models of secondary production in condensed-phase materials promoted by Geant4-DNA into larger-scale, generic particle-transport Monte Carlo is allowing the assessment of quantities of interest in user-defined scenarios. General-purpose Monte Carlo codes can provide the detail needed to support the development of nanodosimetry models and methods with a considerable reduction in systematics, compared to full track-structure simulations subject to uncertainties due to non-optimised or incomplete physics modeling. Injection of a versatile nanodosimetry model into a general-purpose Monte Carlo allows direct application of modeling and simulation tools also in domains relevant to medical physics, biology, and radiation protection, with large potential for interdisciplinary studies and fair interoperability of results.

8.1. Computational Models

Measurement and simulation techniques play an increasingly important role in modelling and predicting the interactions between ionising radiation and matter. These models address the physical, chemical, biological, and clinical consequences of particle tracks at both the cellular and sub-cellular length scale. Ionising radiation can induce oxidative stress, which at the cellular level results in cell cycle arrest, epigenetic alterations, apoptosis, necrosis, and senescence; such information is essential in therapeutic contexts [4]. The subsequent death of tumour cells following radiation delivery is a key aim of cytotoxic cancer treatment. Nanodosimetry offers a means to bridge medical, biological, and applied physics, helping to integrate the cause-and-effect dynamics of ionising radiation impacting living matter across multiple disciplines [16].

8.2. Simulation Techniques

Simulation tools provide guidance in the design and optimization of the relevant experimental setup. Low-energy electron extraction has been integrated into the detector design, allowing measurements with a good energy threshold by means of a dedicated interface for electrons of a few tens of eV kinetic energy [5]. Monte Carlo simulations have been performed to characterize this setup and tailor it to specific applications [4].

9. Integrating Medical Physics with Nanodosimetry

Medical, biological, and applied physics have been established as paramount research fields with significant potential to facilitate and advance cancer therapy. Encouragingly, these critical areas are poised to be further enhanced through the emergent discipline of nanodosimetry, which aims to deepen understanding of radiation interactions at the nanometric level and bridge existing knowledge gaps in radiobiology and radiotherapy physics. Outstanding questions continue to motivate nanodosimetry research, supporting the conjecture that medical physics remains deeply intertwined with the study of radiation interactions in nanometric targets. This ongoing relationship is expected to intensify, thereby linking the diverse contributions of medical, biological, and applied physics in cancer therapy more closely than at any previous time [5] [4].

10. Interdisciplinary Approaches in Cancer Treatment

Cancer treatment for patients diagnosed with the disease has improved significantly because of the in-depth understanding of cancer gained through the collaboration of medicine, biology, and medical physics. To deepen the relationship between medicine, biology, and physics in cancer treatment, Professor Marco Durante of the GSI Helmholtz Centre for Heavy Ion Research and the Institute of Nuclear and Particle Physics at the Technical University of Darmstadt (Germany) and colleagues reviewed the use of nanodosimetry—an emerging field that measures stochastic variation in energy deposition by ionizing particles at the cellular and subcellular levels—to generate fundamental physical quantities of radiation interaction on the biological level [4]. As well as reviewing its applications in radiation therapy, they highlight the potential of nanodosimetry to unify medical, biological, and applied physics by applying physical principles to biology-based applications such as cancer therapy.

Macroscopic characterization of energy deposition fails to account for the stochastic nature of radiation interactions, which affects the biological response especially at the DNA and cellular level—the diagnosis and treatment of which is a major focus in cancer research. Because nanometric energy-deposition events are too small to be measured directly, nanodosimeters instead sample a simulated site containing materials with the efficiencies of cells, viruses, or strands of DNA. Current techniques for characterizing events at these energy levels include Monte Carlo simulation codes, such as Geant4 and PTra, to model particle interactions with matter as well as experimental setups that count the number of ionizations produced in a simulated nanometric volume. The integration of nanodosimetric models and data with cellular models directly links physical processes and biological consequences when investigating the effects of ionizing particles [5].

10.1. Collaboration between Disciplines

Recent advances in radiotherapy facilitate increased dose per treatment with decreased session numbers, elevating the criticality of precise accuracy of each delivered session. Hence, real-time verification of session implementation would be desirable. Dosimeters for this purpose must be small, implantable for in vivo measurements, low-cost, remotely reading, non-toxic, dose non-perturbing, and ideally resorbable; size must balance statistical event collection with tissue retention. Within these constraints, nanodosimeters have potential to monitor delivered dose in tumours and organs at risk, especially critical sites. Nanomaterials permeate surgery, therapy, diagnostics, imaging, and cancer treatments. Modern radiation therapy delivers higher dose per fraction to maximize tumour dose and minimize healthy tissue exposure, requiring strict verification to avoid deviations with potentially catastrophic consequences. Cancer treatment is essentially multi-disciplinary. Treatment is based on understanding cells, tissue, and radiation effects at the nanometre scale; delivery depends on accelerators and equipment design supported by dosimetry; delivery and outcome relate to diagnosis and treatment planning; and external factors include environmental impact and prevention. Interactions span diverse scales and expertise, ranging from quantum electronics and confinement, micro-beam design, dosimetry at the micrometre and nanometre scale, computational methods for dose prediction, mechanisms of radiation damage in tissues, to target element analysis. The transition between scales gives rise to challenging scientific questions and requires integration of a vast variety of methodologies, material, and procedures. Establishing effective bridges between these disciplines is often difficult but is required if system understanding and improvements are sought, or if validation of treatments and planning are to be undertaken. [1][17][18]

10.2. Case Studies in Interdisciplinary Research

The strong medical, biological, and applied physics interdisciplinarity found at cancer-treatment centres lends itself naturally to the last point. The fields are generally very broad and very specialized and the big picture tends to be lost in the details. Interdisciplinary research is a very useful way to gain insight of the big picture; the interaction between disciplines is a natural source of nontrivial viewpoints [5]. The nanodosimetric study of nano-target interactions under low-energy electron and multiply charged ion irradiation is a very good example where the interplay between medicine, biology, and applied physics becomes explicit.

The approach consists in examining the DNA damage pathways initiated by different types of projectiles to gain insight into the physical and chemical effects at play [4]. Disentangling the influence of each property therefore necessitates a comparative approach involving ions and electrons, since energy, charge state, and mass are intimately connected for ions. Measurements of fragment production of nucleobases and nucleosides under different projectiles provide a suitable platform for a comparison of the influence of these four parameters [19]. The highly interdisciplinary framework formed by nano-chemistry, nanotechnology, medical physics, and biology allows a growth strategy that could entail the incorporation of additional disciplines; the understanding of ionization mechanisms in macroscopic water radiolysis would be naturally enhanced, for instance, through the inclusion of chemistry and physics of water in the approach.

11. Challenges in Nanodosimetry Research

Several challenges confront contemporary research in nanodosimetry. One important limitation arises from the accuracy needed to determine parameter ranges required to reproduce experimental cell survival curves, which remains a topic of ongoing inquiry [4]. Another significant difficulty is the development of a general scaling law relating further parameters to the site size, a challenge not yet resolved. Additionally, current modeling approaches based on nanodosimetry provide valuable insights into relative biological effectiveness (RBE), but other forms of biological response remain inadequately represented, underscoring the need for further theoretical advancements. Many proposed solutions do not yet satisfy these requirements comprehensively [5].

12. Future Directions in Nanodosimetry

Performing projects of greater scope and magnitude requires considering the acute and chronic effects of ionizing radiation in multidimensional contexts where medical, biological, and physical sciences converge. Nanodosimetry facilitates a synergistic collaboration between these disciplines, enabling mutually advantageous feedback. The field nonetheless confronts a spectrum of profound scientific, technological, and practical challenges. Several promising research trajectories are envisaged, which could alleviate current obstacles and broaden the array of potential applications [5] [4].

12.1. Emerging Technologies

Current progress in nanotechnology applied to radiation therapy is beginning to enable new in vivo real-time measurements capable of improving patient safety and increasing treatment success probability. Techniques based on intensity-modulated radiation therapy and volumetric modulated arc therapy allow the delivery of very high doses over a limited number of fractions. It becomes, therefore, essential to verify continuously the doses actually delivered during each fraction to ensure the success of the treatment [5].

The future dosimeters for this application need to be very small in order to be implantable inside the tumour volume. Wireless data transmission from the body to the external receiver avoids percutaneous fibres and makes the measurement less invasive. They need to be relatively low-cost in order to become disposables and therefore reduce contamination problems. The materials for the detector should be tissue-equivalent to prevent dose perturbation and compatible with the human body for implantation purposes. They should ideally be resorbable, avoiding the necessity for retrieval. They should be energy and angular independent and able to maintain their position inside the tissue.

Despite these very demanding constraints, there is a clear drive towards the integration of nanomaterials inside all medical applications, ranging from surgery to therapy, via diagnostics and cancer therapy. The progress in radiation therapy techniques, on the other hand, now allows higher dose values per fraction to maximise the dose delivered to the tumour while preserving healthy organs and tissues at the surrounding. Continuous progress in nanotechnology combined with that of current radiation-therapy techniques therefore brings new possibilities to nanodosimetry and motivates the need for new considerations regarding these emerging technologies. [20][21][22]

12.2. Potential Research Areas

Current research should focus on developing precise experimental and computational tools that underpin nanodosimetry and supports its application to oncological physics. Accelerators and detectors have the capacity to investigate the full spectrum of biological effects of radiation at the nanometric level from first physical interactions to cell response. A nanodosimeter could be exploited to derive experimental models of double-strand breaks and other biological mechanisms with direct application in radiobiology.

Advances in nanotechnology provide unprecedented methods for real-time control of treatment and are expected to enhance the outcome of primary ion beam therapy. In this context dosimetry performed in the nanometric scale is considered as an essential instrument for radiation protection and research in medicine and biology. Nanodosimetry is a particularly promising strategy to improve follow-up clinical protocols by deepening the understanding of radiation effects on human cells. It also complements experimental radiobiology by investigating the structures damaged by radiation and bridges radiobiology with molecular and cellular physiology [5].

13. Ethical Considerations in Nanotechnology Applications

Due to its numerous implications and applications, nanotechnology may affect many facets of society. Nanotechnology, especially nanomedicine, has raised numerous ethical issues. Nanomedicine raises concerns about patient safety and the release of new nanomaterials into the environment [23]. Ethical issues related to nanomedicine may be classified into risk, access, and justice. Nanotoxicity has raised significant concerns about safety and the permanence of nanomaterials in the human body and the environment. It is argued that there is insufficient data on the safety of nanomedicine, particularly in the long term. In addition, the involvement of barriers to universal and cost-effective access to nanomedical technologies may further exacerbate the healthcare disparity between the rich and poor, developed and underdeveloped nations, thus raising a myriad of ethical concerns about equity and social justice. Nanotechnology will reportedly be able to provide solutions to a variety of medical problems, such as drug delivery, chronic disease control, and organ repair. The ongoing debate about the approach and extent of the use of human subjects in medical research and human trials may become even more complex and nuanced with the emergence of nanomedical technologies, particularly if the latter provide the ability to monitor patients in real time.

14. Regulatory Framework for Nanomedicine

Regulatory aspects play a crucial role in the further development and marketing of nanotechnology-based health products for both industry and healthcare providers. Current characterisation techniques are often inadequate for evaluating diverse nanomedicines or lack sufficient standardisation for regulatory use. Certain critical domains suffer from methodological gaps, prompting concerted efforts on method development and standardisation through collaborative initiatives. Adaptation of transferable methods and standards from other sectors is also under consideration. With the advent of generic nanomedicines or “nanosimilars,” patent expirations have intensified scrutiny, yet physicochemical complexity frequently precludes complete comparability, necessitating novel frameworks for equivalence demonstration. Regulatory pathways may become convoluted when the primary mode of action is ambiguous or when multi-component products fall under multiple governance structures. Enhanced integration of translational and regulatory science into academic curricula is advocated to prepare innovative health products for adaptive approval processes. The ubiquitous challenge posed by nanomedicines underscores the need for harmonised oversight to expedite patient access. The Nanomedicines Working Group within the International Pharmaceutical Regulators Programme supports information exchange, capacity building, and methodological discourse to facilitate global alignment [24].

15. Conclusion

Nanodosimetry enhances understanding of the clustered damage at the scale of biological targets, constituting a promising candidate for developing a measurement-based concept of radiation quality directly correlated with biological outcomes [4]. Properly treated, nanodosimetry represents a valuable tool to connect the science of radiation physics with radiation biology, fostering cancer therapy planning at a new level of precision. Nanotechnology already contributes capabilities suited to cancer diagnosis and treatment, offering additional possibilities for research initiatives focusing on applications where nanoscale energy deposition plays a significant role [5].

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