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History of Superparamagnetic Materials and Their Future in Cancer Therapy

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Abstract - Superparamagnetism, is a form of magnetism exhibited by small ferromagnetic nanoparticles and challenges conventional magnetic behaviors observed in larger particles. Whereby as particle size decreases, thermal fluctuations gain prominence, leading to the random reorientation of magnetic moments at a critical threshold, known as the superparamagnetic threshold. This article aims to explore superparamagnetic materials' historical evolution and current state, emphasizing their technological and medical applications. Starting with Louis Néel's foundational work in 1949, introduced the concept of superparamagnetism, to where superparamagnetic materials have found a promising application in cancer treatment. And their ability to be guided by external magnetic fields facilitates targeted drug delivery, offering precise manipulation for localized therapy.

Keywords - Superparamagnets; SPIONs; Nanoparticles; Targeted drug therapy.

1 Introduction

Superparamagnetism is a form of magnetism exhibited by small ferromagnetic nanoparticles. Nanoparticles are single-domain particles, this property allows their magnetization to be approximated as one giant magnetic moment due to the summation of the individual magnetic moments of each constituent atom. This is the "macro-spin approximation."

In conventional magnetism larger particles create magnetic moments in individual atoms or ions within the material which align in a uniform direction, resulting in a collective magnetic behavior. However, in superparamagnetism in nanoparticles, you find that as the particle size decreases the thermal fluctuations increase. At a certain critical threshold, often in the range of a few nanometres, thermal energy becomes influential enough to overcome the magnetic anisotropy. This phenomenon leads to the random reorientation of magnetic moments. When the nanoparticles are small enough, the energy barriers for magnetization reversal, which are proportional to grain volume, are relatively low compared to thermal energy. With enough thermal energy, their magnetization can flip direction randomly over short periods of time and the time between two flips in direction is called the Neel relaxation time. Therefore, superparamagnetic materials exhibit a fluctuating magnetic moment rather than a stable, aligned one. This means that the superparamagnetic material does not possess a permanent magnetic moment at zero applied magnetic field, but it can show magnetic behavior in the presence of an external magnetic field [1]. Once the external magnetic field

is removed, the magnetic moments become randomly oriented due to thermal energy [1]. Superparamagnetic materials include iron oxides, such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) [1].

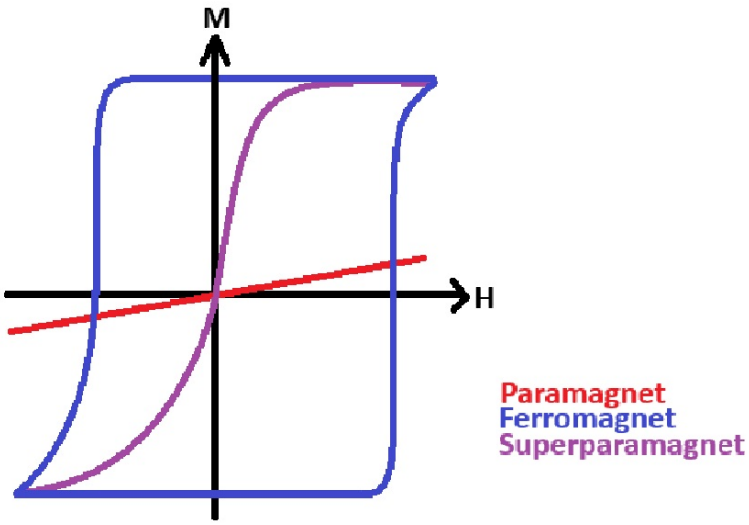

Figure 1: The ferromagnetic response, with increasing particle size leading to quicker saturation and a thinner hysteresis loop. Conversely, decreasing size widens the loop until a critical size, beyond at which its point narrows until reaching the superparamagnetic threshold inspired and adapted from [2].

As we delve into superparamagnetism, it is essential to understand its historical roots and current technological advancements, providing a comprehensive perspective on its evolution over time.

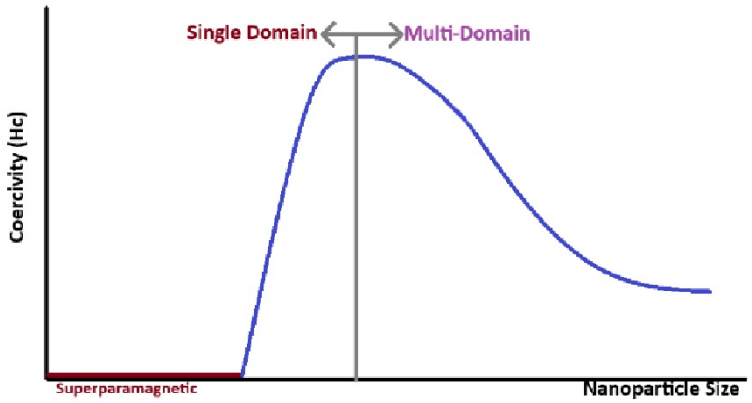

Figure 2: Illustrates this trend in coercivity, the intensity of the applied magnetic field to yield a zero magnetization, plot against nanoparticle size, showcasing the transition to superparamagnetic behavior inspired and adapted from[2].

This starts with French physicist Louis Néel and his study of magnetic properties in 1949. He observed that when finely divided, these nanoparticles lose hysteresis, displaying a unique lag or delay in magnetization response, when above a certain size as illustrated in Figure 1. To which he then theoretically proposed an equation inspired by the Arrhenius equation formulated by chemist Svante Arrhenius in 1889 [3]. This equation estimates the characteristic time for the relaxation of magnetic moments within a material to its lowest energy state, particularly evident in single-domain ferromagnetic minerals exhibiting thermoremanent magnetization. He used this equation to develop a model of thermoremanent magnetization in single-domain ferromagnetic minerals (superparamagnetic materials). To which he referred to "superparamagnetism" as the case of ferromagnetic nanoparticles [4,6,7,8,9] and "superantiferromagnetism" as the case of antiferromagnetic nanoparticles [4,10,11,12,13,14,15].

$$\tau_N = \tau_0 \cdot e^{\frac{KV}{K_b T}} \tag{1}$$

- K = Magnetic anisotropy energy density
- V = Volume
- K_b = Boltzmann Constant
- T = Temperature and their product is thermal energy
- τ_0 = Length of time
- τ_N = Neel relaxation time

Another factor used in observing superparamagnetic waves is the measurement time τ_m which is an experimental parameter chosen so that we can examine the behavior of a system change over time. Where magnetic moments can spontaneously flip, the measurement time influences the ability to capture such rapid changes. So, when the measurement time is much less than the Neel relaxation time ($\tau_m \ll \tau_N$), a blocked state occurs in which the measured magnetization is just the instantaneous magnetization at the beginning of the measurement because there was no direction flip. The blocking temperature (T_B) serves as a pivotal parameter, defining the temperature boundary between blocked and superparamagnetic states, calculated using equation (2) [2].

$$T_B = \frac{KV}{K_b ln\left(\frac{\tau_m}{\tau_0}\right)} \tag{2}$$

The use of T_B in physics cannot be further illustrated when, in a single domain structure (superparamagnetic materials), thermal fluctuations play a significant role. At high temperatures, these materials undergo random fluctuations, while at low temperatures, thermal energy decreases, leading to a blocked state referred to as the blocking temperature. This transition can be shown through zero-field-cooled (ZFC) and field-cooled (FC) magnetization curves, as depicted in Figure 3. A Zero-Field Cooled (ZFC) process is when a sample is cooled without an applied magnetic field, transitioning into a ferromagnetic state as the temperature decreases. Subsequently, a magnetic field is applied, and the magnetization is measured during temperature increase, providing insights into its properties. Whereas the Field Cooled (FC) process involves the same cooling of the sample, this time, in the presence of a magnetic field but removing the presence when the magnetization is measured during the temperature increase, we can see these effects in Figure 3.

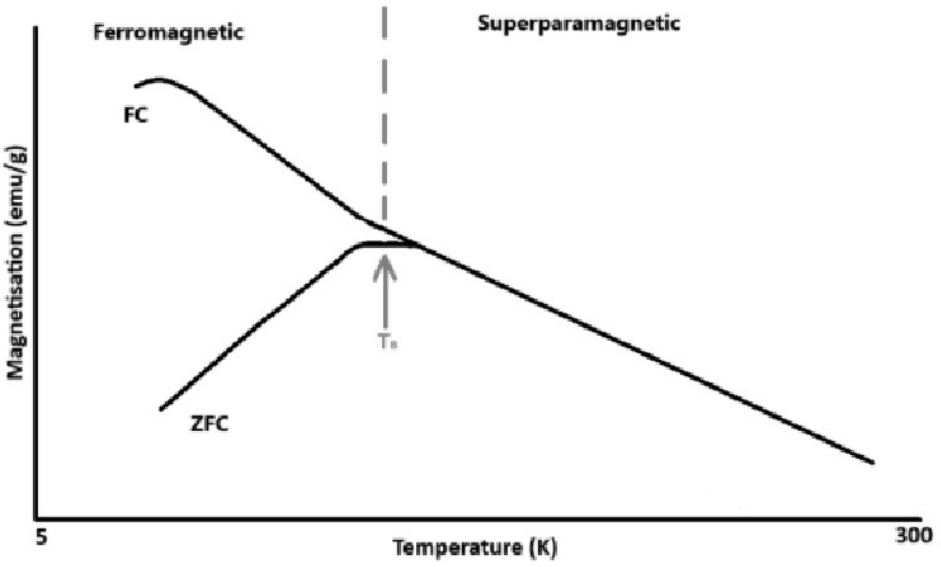

Figure 3: Zero-field-cooled (ZFC) and field-cooled (FC) magnetization curves as a function of temperature taken in an applied field H. Arrow indicates blocking temperature, T_B. This shows the effect of increase of temperature in magnetic materials inspired and adapted from [17].

We then move on to the Landau–Lifshitz–Gilbert equation, where in 1955 Lev Landau, Evgeny Lifshitz, and T. L. Gilbert created a differential equation that provides the theoretical framework to model the effects of a magnetic field on ferromagnetic materials [18]. This equation became crucial in understanding the behavior of superparamagnetic materials.

$$\frac{dM}{dt} = -\gamma\, M \times H_{eff} - \lambda M \times (M \times H_{eff}) \tag{3}$$

where γ is the electron gyromagnetic ratio, λ is a phenomenological damping parameter and H_{eff} is the effective field [18]. This was then further adapted by T. L. Gilbert in 1955 to be:

$$\frac{dM}{dt} = -\gamma \left(M \times H_{eff} - \eta M \times \frac{dM}{dt} \right) \tag{4}$$

This is the Landau–Lifshitz–Gilbert (LLG) equation, where η is the damping parameter, which is characteristic of the material [18]. These equations prove the existence of ferromagnetic properties in materials. However, it wasn't until 1959 that the famous American physicist Richard Feynman unveiled the concept of nanotechnology during a captivating lecture entitled "There's Plenty of Room at the Bottom" at the California Institute of Technology [19,20]. However, it wasn't until 1974 that the term "nanotechnology" was formally coined and defined by Japanese scientist Norio Taniguchi, describing it as the processing of materials at the atomic or molecular level [19,21]. The 1980s witnessed the rise of the interest in nanotechnology, marked by the invention of the Scanning Tunneling Microscope (STM) in 1981 at the IBM Zurich Research Laboratory, courtesy of Gerd Binnig and Heinrich Roher [19,22,23]. This revolutionary instrument paved the way for subsequent advancements like the atomic force microscope (AFM) and scanning probe microscopes (SPM), currently indispensable tools for nanotechnology researchers [19,24,25]. As the field of nanotechnology advanced with these inventions, researchers began to recognize the unique properties and potential applications of materials at the nanoscale. They began synthesizing magnetic nanoparticles with controlled sizes and shapes. Which led to a better understanding of superparamagnetism and its applications. With the start of the 21st century, advances in computational

techniques allowed researchers to model and simulate the behavior of magnetic nanoparticles more accurately and predict their properties. These models helped explain the transition from ferromagnetism to superparamagnetism as particle size decreased [26,27,28,29,30,31]. Fast forward to the present, superparamagnetic materials have emerged as promising assets in cancer treatment. Guided by external magnetic fields, they offer precise manipulation, facilitating in a specific direction [1]. This allows for precise manipulation and can be attached to therapeutic agents which can then be guided to specific tissues or cells, allowing for localized therapy. This targeted drug delivery approach has the potential to enhance the probability of success of treatments while minimizing the side effects on healthy tissues. They have also shown great potential in the field of imaging cancerous tissues, whereby they can be magnetized by magnetic resonance imaging (MRI). They contribute to differences in the MRI signals, which will lead to a change in the signal intensity and provide a contrast in the resulting images. This can help in distinguishing between different types of tissues and help detect abnormalities in them. Additionally, these materials can also generate heat when exposed to an alternating magnetic field, a phenomenon known as magnetic hyperthermia. This localized heat can be used for tumor removal and the destruction of cancer cells due to their low tolerance to moderate increases in temperature [33,34].

Magnetic hyperthermia can also be used in conjunction with the release of a loaded drug using thermal cues to improve the efficacy of treatment [33]. However, the incorporation of superparamagnetic materials in cancer treatments presents challenges, chiefly concerns regarding potential toxicity and immune system responses. Ensuring the bio-compatibility and safety of these materials is paramount for their successful clinical application. Additionally, there is the inherent cost associated with working on and developing new technologies. This article endeavors to offer a user-friendly overview of superparamagnetic materials in targeted drug delivery for cancer treatment their current technological landscapes, and potential future direction. The objective is to provide readers with a nuanced understanding of the promise and challenges associated with this cutting-edge approach.

2 Application: Targeted drug delivery

An application which utilizes superparamagnetic materials, the above-mentioned, is in targeted drug delivery. This is the transport of therapeutic agents to a designated area using external magnetic fields. One of the earlier problems in this discovery was finding a suitable material to carry the agent. With known nanoparticles being toxic to the body like manganese- and gadolinium [35]. This stalled the development of this form of treatment. Until a front runner emerged in the form of Superparamagnetic iron oxide nanoparticles, or SPIONs [35]. A type of nanomaterial characterized by iron oxide cores. They are relatively nontoxic; they exhibit excellent magnetic resonance imaging (MRI) and possess good bio-compatibility. All these features make them attractive candidates for their use as a drug delivery system, as seen in Figure 4, and as a contrast agent in MRI [35,36,37].

However, the application of SPIONs is limited as they tend to form into a mass and are not stable in aqueous solutions. This could be solved by coating the SPION surface with various materials to modify their surface properties [35,38]. On the other hand, size and surface characteristics of the SPIONs are factors that are closely related to their biodistribution and bio-compatibility, cell adhesion, clearance and potential toxic effects. The ideal size for nanoparticles in drug delivery systems based on SPIONs should be from 10 nm to 200 nm so that they can escape an attack from the immune system [35,39,40]. Various materials can modify the surface of SPIONs, including non-viral materials such as polymers, liposomes, and inorganic nanoparticles. Viral vectors, which are tools used to deliver genetic material into cells, including non-enveloped viruses, are also often conjugated with SPIONs. However, the application of viral vectors has been limited by their drawbacks, such as toxicity and immunogenicity. Therefore, the materials coated on the surface of SPIONs should not only maintain sufficient capability to interact with water but also be non-toxic

and bio-compatible. This ensures that they can be dispersed in water without forming solid particles [35,42,43,44,45,46] Recently, tremendous progress has been made in the field of magnetic nanoparticle-based non-viral drug delivery systems by the surface modification of SPIONs [35, 47,48]. Such systems can now accumulate in the tumor site through the superparamagnetic SPION properties under an external magnetic field [35,49]. However, that is not the only challenge we are facing. We are facing problems in the clearance of nanoparticles in vivo, in a living organism, which is a complicated process controlled by numerous characteristics such as particle size, surface properties and possibly other compositional characteristics that are not fully understood at this time [50]. Where we see smaller nanoparticles are cleared by the kidney and larger particles are cleared by the immune system and can be predominantly located in the liver and spleen [50,51].

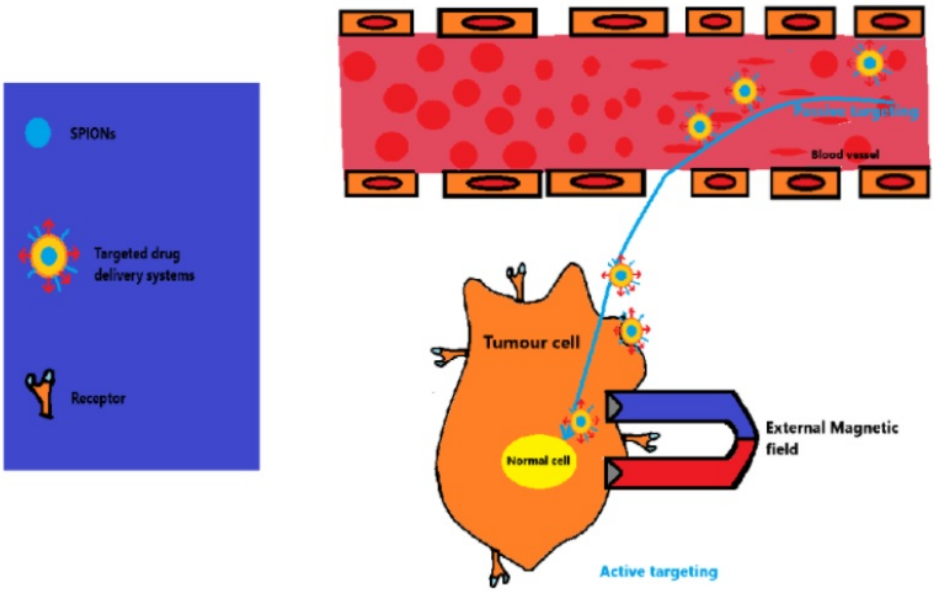

Figure 4: Basic illustration of how SPIONs would function in targeted drug delivery inspired and adapted from [35].

Another challenge we are facing is in the release mechanics and achieving a controlled release of therapeutic agents from superparamagnetic nanoparticles due to their size and composition. A solution for these problems are proposed as that nanomedicines could be composed of a nanoparticle population of mixed sizes to intentionally introduce different rates of drug release for sustained delivery over time [50]. However, introducing mixed sizes of nanoparticles could lead to the problem of it exceeding 200nm. So, researchers keep looking for the answer to how to solve these, at times contradictory, problems and solutions. Not all hope should be lost in this method, as there seems to be a bright future which lies in SPIONs, where all we need to find is the correct variation of the structure of the core, the material of coating and the attaching agents. And should we be able to find those out, we will find more solutions to other problems such as Alzheimer's, breast cancer and bacterial diseases [52].

3 Beneficiaries

With the evolution of the use of superparamagnetic materials in cancer treatment, we can stand to see the immediate beneficiaries of this treatment. The first, and foremost is the patients. With more than 14 million new cases and 8.8 million deaths per year worldwide, cancer remains one of the most dangerous threats to human health [35,53]. This enhanced precision of targeted drug therapy can only contribute to more effective treatments, potentially leading to improved outcomes whilst also minimizing the damage to healthy tissues and organs, and decreasing the likelihood of experiencing adverse effects during and after

the treatment. With the advancements, another benefit can emerge with the convergence of superparamagnetic nanocarriers with personalized medicine, which could allow for a more tailored treatment based on individual profiles. Another beneficiary in this matter is physicians, they also stand to benefit from being able to make more accurate and informed decisions when treating or adjusting medical issues. With the ability to monitor specific tissues in real-time using the MRI machine and nanoparticles. A third beneficiary would be healthcare systems whereby, this would help effectively reduce the burden by minimizing the need for extensive and resource-intensive interventions. Which conversely would reduce the costs of traditional cancer treatment, and allow for the reallocation of funds to other areas of need.

4 Conclusion

In conclusion, the exploration of superparamagnetic materials, particularly in the context of cancer treatment, reveals a fascinating journey from fundamental physics to the cutting-edge of medical applications. This transition from ferromagnetism to superparamagnetism in nanoparticles, by Louis Néel's innovative work, paved the way for understanding the dynamic behavior of magnetic moments at the nanoscale. The historical timeline, from the formulation of the Neel relaxation time equation to the development of the Landau–Lifshitz–Gilbert equation, highlights the theoretical frameworks that underpin the study of superparamagnetic materials. The intersection of physics and nanotechnology, catalyzed by visionaries like Richard Feynman, which has led to the synthesis and manipulation of magnetic nanoparticles with controlled properties. The current landscape sees superparamagnetic materials in the forefront of cancer treatment, particularly in targeted drug delivery. The potential applications are promising, with the ability to precisely manipulate therapeutic agents and visualize tissues in real-time through magnetic resonance imaging. However, challenges such as bio-compatibility, clearance mechanisms, and controlled drug release underscore the complexity of implementing these materials in clinical settings. Despite these challenges, superparamagnetic materials offer significant benefits to patients, physicians, and healthcare systems. Enhanced precision in treatment, reduced side effects, and the potential for personalized medicine contribute to improved patient outcomes and physicians gain valuable tools for accurate decision-making, while healthcare systems stand to benefit from resource-efficient interventions, thereby alleviating the economic burden associated with traditional cancer treatments. As we navigate the future of superparamagnetic materials in cancer therapy, the ongoing research and technological advancements will likely address current challenges. The integration of multi-modal imaging, coupled with innovative approaches, holds promise for overcoming current limitations and open new avenues for effective cancer treatment. In this evolving landscape, superparamagnetic nanoparticle will continue to shape the present and the distant future with a great potential benefits for broader societal well-being.

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