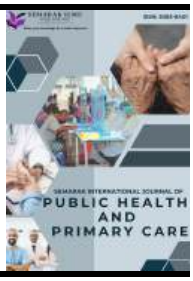
Semarak International Journal of Public Health and Primary Care

Journal homepage:
https://semarakilmu.my/index.php/sijphpc/index
ISSN: 3083-8401



Magnetophoresis in Red Blood Cell Separation: A Narrative Review of the Current Evidence

Myra Ayesha Jafarey[1], Bhuwaneswaran Vijayam[2,3,*]

[1] School of Biomedical, Nutritional, and Sport Sciences, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, NE1 7RU, United Kingdom
[2] Newcastle University Medicine Malaysia (NUMed), 79200 Iskandar Puteri, Johor, Malaysia Fukuoka University, Japan
[4] Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, NE1 7RU, United Kingdom

ARTICLE INFO

Article history:
Received 31 December 2025
Received in revised form 20 February 2026
Accepted 26 March 2026
Available online 20 April 2026

Keywords:
Magnetophoresis; blood magnet separation; RBC separation; haemoglobin magnet; hemoglobin magnet; RBC magnet; erythrocyte magnet; magnetophoretic; magnetofluidics

ABSTRACT

Magnetophoresis is the study and application of magnetic forces to manipulate red blood cells (RBCs). Over the decades, magnetophoresis has evolved beyond its early experimental roots and is now recognised as a versatile platform with potential use in diagnostic, therapeutic, and research settings. Many past studies have delved into the applications of magnetophoresis, including in the context of RBCs but this information remains scattered. Many types of magnetophoresis-based devices have been designed to target varying RBCs for isolation with improvements in separation efficiency and clinical applications. This includes malaria, sickle cell disease, and even non-invasive prenatal diagnosis. Accordingly, RBCs' magnetic susceptibility is dependent on the varying oxidative states. Furthermore, there is a shift of the magnetophoresis concept and application with optimisation of non-microfluidic devices and the rise in the use of microfluidic devices, which are more cost-effective and allow for higher throughput. Despite these advancements, many device concepts remain theoretical, and significant optimisation is still required before widespread clinical adoption can occur. Nevertheless, as physiological and clinical demands evolve, magnetophoresis is poised to become an increasingly relevant tool for RBC isolation and analysis. In this narrative review, we synthesise the physiologic, biophysical, engineering, and clinical foundations of magnetophoresis, spanning early developments to modern applications.

1. Introduction

Magnetophoresis can be understood by breaking it down; 'magnet' refers to the involvement of magnetizable particles while 'phoresis' refers to the motion of these particles being induced by external magnetic fields when placed in a fluid [1]. In essence, it is the manipulation and subsequent migration of particles under the influence of a magnetic field. [2-4] This concept is often applied to devices using either label-based or label-free techniques in the context of the trapping, separation,

* *Corresponding author.*
E-mail address: bhuwaneswaran.vijayam@newcastle.edu.my

mixing, or focusing of microparticles and cells [5]. It is contactless, does not induce heating (and possible degradation of particles), is economical, efficient, and biocompatible, making it an increasingly popular technique in the field of microfluidics [5,6].

Despite the multitude of recent advances in the field, current research and understanding of magnetophoretic red blood cell (RBC) isolation remains relatively limited, with high levels of fragmentation across disciplines namely: physics, engineering, and biomedicine [7]. Accordingly, this paper aims to comprehensively investigate the use of magnetophoresis for red blood cell (RBC) separation by using their inherent magnetic properties. This narrative review synthesizes existing findings to examine the mechanistic basis of magnetophoretic RBC isolation, its clinical and research implications, and the methodological variability and knowledge gaps not addressed in earlier reviews. Such understanding has applications in characterizing RBC behaviour under varying conditions, detecting and treating diseases such as sickle cell disease and malaria, and informing therapeutic and drug development [8,9].

The flow and narrative style of this review is heavily influenced by previous separate works by Hendricks *et al.,* and Vijayam *et al.,* and the review is structured to meet all six Scale for the Assessment of Narrative Review Articles (SANRA) quality domains [10-12]. This includes, i) a clear justification of the topic's relevance, ii) explicit aims, iii) a description of the literature search process, iv) accurate referencing, v) coherent scientific reasoning, and vi) presentation of appropriate outcome data. This ensures transparency and consistency throughout. Most references from this review were obtained from Google Scholar, PubMed, Scopus, IEEE and ResearchGate databases. Searches were set to be from inception till December 2025 with the combination of "search strings" such as "magnetophoresis", "magnet separation", "erythrocyte", "red blood cell" and "RBC".

2. RBC Magnetism and Crucial Terminologies

RBCs, like many other biological substances, have intrinsic magnetic properties, allowing magnetophoresis to be applied in label-free ways [5,13]. However, the magnetism of RBCs varies greatly depending on the form of haemoglobin which would be discussed in-depth at a later part of this manuscript.

A few crucial terminologies that would be used frequently in this manuscript are defined as follows in Table 1.

Table 1
Crucial terminologies in magnetophoresis

Terminology	Definition
Ferrofluid	A ferrofluid is a stable colloidal suspension of nanoscale magnetic particles (typically magnetite or maghemite) dispersed in a carrier liquid and stabilized by surfactants, enabling magnetic manipulation while retaining fluidity [14].
Magnetic Susceptibility	Magnetic susceptibility describes the degree to which a material becomes magnetized in an external magnetic field. RBC susceptibility depends on the haemoglobin state: deoxyhaemoglobin and methaemoglobin are paramagnetic, whereas oxyhaemoglobin is diamagnetic [15].
Magnetophoretic Mobility	Magnetophoretic mobility is the velocity of a particle per unit magnetic force in a viscous medium and is critical for predicting cell separation performance [16].
Paramagnetism	Paramagnetism arises from unpaired electrons causing weak attraction to magnetic fields. Deoxyhaemoglobin (four unpaired electrons) and methaemoglobin (five unpaired electrons) impart paramagnetism to RBCs [8].
Diamagnetism	Diamagnetism occurs when all electrons are paired, causing weak magnetic repulsion. Oxyhaemoglobin exhibits diamagnetism due to its low-spin Fe^{2+} configuration [8].

Dipole (Magnetic Dipole Moment)	A magnetic dipole represents the smallest quantum of magnetic moment. Deoxyhaemoglobin possesses a dipole moment of ~8 μB due to unpaired Fe 3d electrons [14].
Quadrupole (Quadrupole Magnetic Field)	A quadrupole magnetic field has a zero-field centre and steep gradients radially, enabling selective magnetic separation in quadrupole magnetic sorters [17,18].
Positive Magnetophoresis	Occurs when particles with higher magnetization than their surrounding medium migrate toward field maxima (for example, magnetic beads or paramagnetic RBCs) [14].
Negative Magnetophoresis	Occurs when particles with lower magnetization than their medium migrate toward field minima, such as diamagnetic cells in ferrofluid environments [14].
Separation Efficiency / Purity	Efficiency represents the fraction of target cells successfully isolated, while purity reflects the proportion of target cells in the isolated fraction. Modern magnetophoretic devices achieve >95% recovery and purity [8].
Throughput	Throughput refers to the volume or number of cells processed per unit time. State-of-the-art microfluidic magnetophoresis platforms reach >10^8 cells/hour [8].

2.1 RBC Characteristics Affecting Magnetophoretic Mobility

To determine these physiological parameters and their effect on magnetophoretic mobility (MM), Elblbesy applied cell tracking velocimetry (CTV). The movement of individual cells across a glass channel within a magnetic field gradient was tracked and migration velocities were calculated from the sequential images. MM was then determined across a range of field strengths. The results had several findings linked to haemoglobin. Specifically, the oxygenation state of RBCs affects MM. Deoxygenated haemoglobin increases MM values while oxygenated haemoglobin decreases it. This is because oxygen binding to haemoglobin alters haemoglobin's structure thus altering its magnetism [19]. These effects can be understood by dissecting the complex, cooperative binding process of oxygen with haemoglobin molecules. Catalysed by the cell's oxygen concentration, all of haemoglobin's single oxygen binding sites fill up sequentially, followed by a stepwise filling of all four oxygen binding sites per haemoglobin molecule. During this, the intermediate oxygen-haemoglobin binding complexes catalyse subsequent steps. As each oxygen molecule binds, the haemoglobin complex's magnetic moment decreases, producing an inverse relationship between oxygenation and magnetism [13].

Haemoglobin levels per RBC were also strongly correlated with MM. This includes the mean corpuscular haemoglobin (MCH) (total haemoglobin content per RBC) and the MCH concentration (MCHC), both of which showed a direct relationship with MM. Consequently, haemoglobinopathies that modify haemoglobin structure or concentration predictably alter MM [19]. For example, Kwaan *et al*., determined that normal state haemoglobin from thalassemia minor patients has lower diamagnetism compared to haemoglobin from iron-deficient patients [20]. Furthermore, it was also noted that RBC size is significant in that mean corpuscular volume (MCV), RBC distribution width (RDW), and RBC hydrodynamic radius are all directly proportional to the MM [19].

Other plasma factors, such as increases in fibrinogen and immunoglobulins associated with physiologic and pathologic conditions at higher levels, increase whole blood viscosity, lowering MM. Albumin levels were also seen to have a weak direct relationship with MM [19]. Collectively, all these blood components and the effects towards RBC's magnetism are summarised in Table 2.

Table 2
Physiological parameters of RBCs that determine magnetophoretic mobility

Factor	Specific factors	Effect on RBC magnetophoretic mobility (MM)
Haemoglobin	Deoxygenated Hb (paramagnetic)	Increases MM
	Oxygenated Hb (diamagnetic)	Decreases MM
	MCH and MCHC	Strong correlation with MM
	Hb disorders (e.g. thalassemia minor)	Alter diamagnetic response and modifies MM
RBC size	MCV	The larger the volume, the higher the MM
	RDW	The broader the size distribution, the greater the effect on MM
	Hydrodynamic radius	The larger the radius, the lesser the MM
Plasma factors	Fibrinogen	Increases plasma viscosity, decreasing MM
	Immunoglobulins	Increases plasma viscosity, decreasing MM
	Albumin	Minimal effect

Abbreviations: *Hb: haemoglobin, MCH: mean corpuscle haemoglobin, MCHC: mean haemoglobin concentration, MCV: mean corpuscle volume, MM: magnetophoretic mobility, RDW: red blood cell (RBC) distribution width.*

2.2. Magnetism of Different Forms of Haemoglobin

Because human RBC contain a relatively high concentration of haemoglobin (approximately 2.7 x 10^8 haemoglobin), they can undergo magnetically induced migration when exposed to sufficiently strong external fields [21]. Oxygenated RBCs are diamagnetic. This means that these RBCs are weakly repelled by magnets and, essentially, the magnetic flux maxima (away from the magnetic field) [5]. Figure 1 shows the oxygenated and deoxygenated states of haemoglobin and iron atoms. Because electron pairing occurs only once the d shell is half filled, oxyhaemoglobin uniquely contains paired electrons. Consequently, oxy- and deoxyhaemoglobin contain Fe^{2+}, whereas methaemoglobin contains Fe^{3+}.". These in turn affect oxygenated and deoxygenated RBCs' direction of movement under an external magnetic field [22-25] Figure 2 illustrates the inverse relationship between haemoglobin oxygenation and magnetic dipole moment [13]. It is also noteworthy that haemoglobin molecules show cooperative oxygen binding. This means that when a molecule is deoxygenated, it has lower affinity for oxygen and favours oxygen dissociation. Conversely, when it is oxygenated, it favours oxygen binding [13].

Conversely, RBCs may also express paramagnetism. Due to the presence of high-spin unpaired electrons in ferrous haemoglobin, these RBCs are attracted and move towards the magnetic flux maxima as opposed to the diamagnetism properties. As depicted in Figure 1, this applies to deoxygenated haemoglobin due to the presence of four unpaired and methaemoglobin (haemoglobin's non-functional form where iron is unable to bind oxygen) due to the presence of five unpaired electrons. The presence of unpaired electrons causes paramagnetism, as these electrons confer higher magnetic susceptibility in these RBCs due to the magnetic dipole moments generated by the spin of unpaired electrons. Since methaemoglobin contains one extra unpaired electron, it has higher paramagnetism [13,21,25].

On the contrary, it has been further understood that in its carbaminohaemoglobin form (which is produced by CO_2 saturation), there is no direct effect on RBC's magnetism. This is because it binds to haemoglobin's protein chains and not its iron atoms (unlike oxygen), meaning it does not act as a competitor with oxygen. Instead, by binding at high levels, it stabilises haemoglobin's deoxygenated form, lowers its affinity for oxygen, and induces oxygen unloading. This leads to a paramagnetic state being maintained [21].

In Figure 1, the electron configurations shown using *[Ar]*, *4s*, and *3d* notation describe how valence electrons are arranged in the iron centre of haem and how this determines its redox and magnetic properties. The symbol *[Ar]* represents the inert argon core, while the *4s* and *3d* subshells contain the electrons that define the oxidation and spin state of iron. Upon formation of Fe^{2+} or Fe^{3+}, electrons are removed first from the 4s orbital, leaving the 3d electrons to dictate magnetic behaviour. Strong-field ligands such as oxygen promote 3d-electron pairing, producing low-spin, diamagnetic Fe^{2+} in oxyhaemoglobin. In contrast, the weaker ligand field of deoxyhaemoglobin yields high-spin, paramagnetic Fe^{2+}, while oxidation to Fe^{3+} in methaemoglobin increases the number of unpaired 3d electrons and enhances paramagnetism. Carbaminohaemoglobin (CO_2Hb), in which carbon dioxide binds to the N-terminal amino groups of the globin chains rather than the iron centre, does not alter the iron's electronic structure; instead, it stabilises the deoxygenated T-state and therefore exhibits magnetic behaviour essentially identical to high-spin, paramagnetic Fe^{2+} seen in deoxyhaemoglobin. Figure 2 on the other hand, depicts the inverse relationship between haemoglobin oxygenation and dipole moment. This is crucial as healthy RBCs predominantly contain oxyhaemoglobin, with minimal deoxyhaemoglobin, resulting in overall weak magnetic responsiveness.

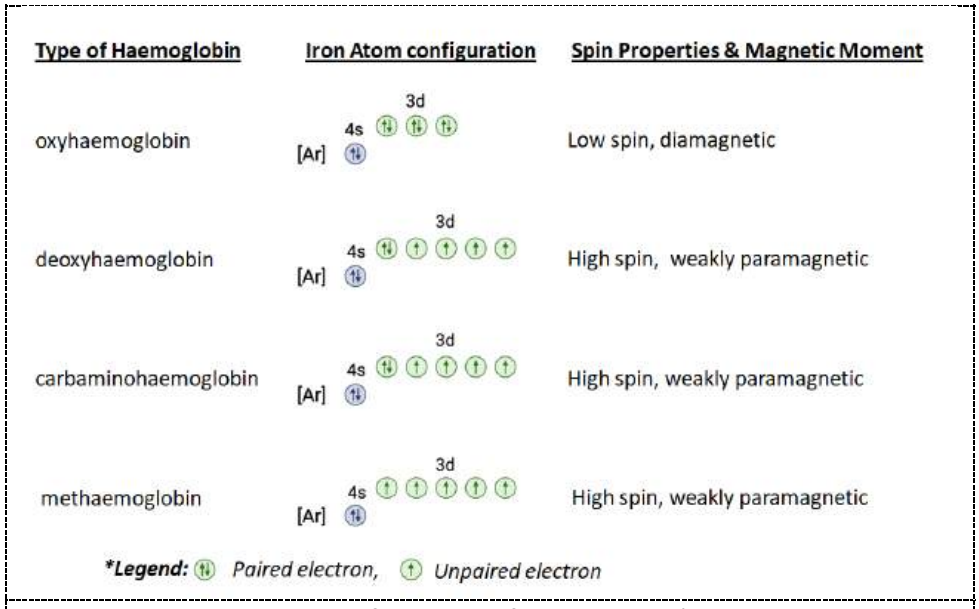


Fig. 1. Varying electron configuration of haemoglobin's iron atom based on oxidation states

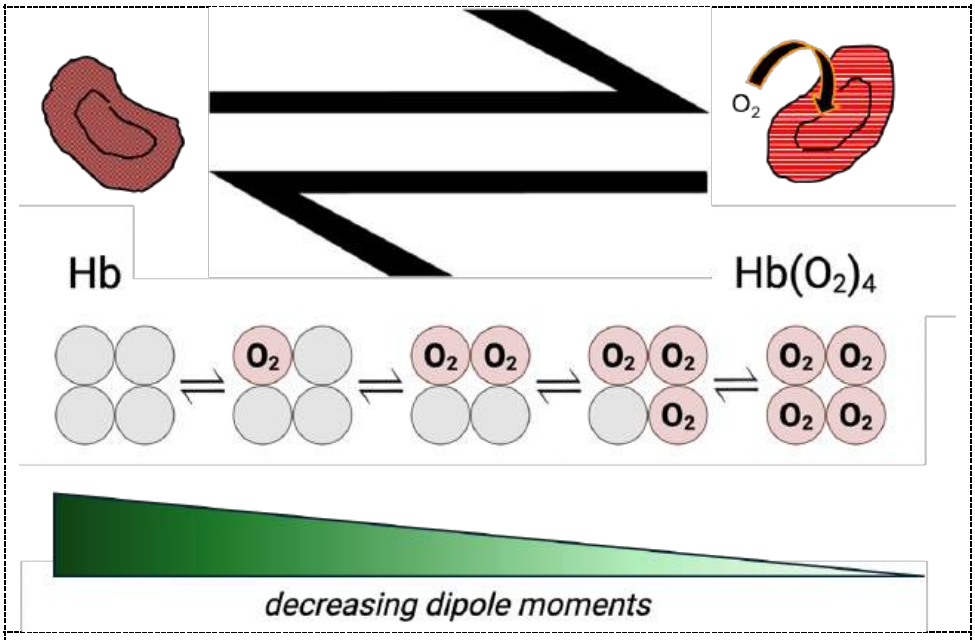


Fig. 2. Cooperative oxygen binding to haemoglobin molecules and associated changes in magnetic dipole moments. (*Figure adapted and modified from Moore et al., [13]*)

2.3 Other RBC Properties that Enable Magnetophoretic Separation

Another important determinant of RBC separation by magnetophoresis is the difference between the magnetic susceptibility of the RBCs and the surrounding medium. For example, the change from diamagnetic oxyhaemoglobin to paramagnetic deoxyhaemoglobin results in the magnetic susceptibility going from lower to higher than that of water, allowing RBCs to be separated magnetophoretically. Magnetophoretic velocity of particles depends on how different their magnetism is to that of water. Since both water and RBCs have similar magnetic properties, this difference is small, meaning RBCs move very slowly under magnetic fields.

Consequently, specialized high sensitivity instruments are required to detect RBC displacement [13]. As discussed earlier, CTV is a commonly used tool due to its much higher sensitivity for RBCs and other cells (as it can measure the magnetism of a single cell at a time) compared to other tools like Superconducting Quantum Interference Device- Magnetic Property Measurement System (SQUID-MPMS) [27].

2.4 Varying Behaviours of Blood Cells during Magnetophoresis

Mammalian blood is composed of RBCs (45%), white blood cells (WBCs) platelets, and plasma. The WBCs comprise neutrophils, lymphocytes, monocytes, eosinophils, and basophils. The magnetic character of certain blood components other than RBCs may also impact magnetophoresis [8].

As illustrated in Figure 3, differing magnetic susceptibilities among blood components cause them to diverge along distinct trajectories when exposed to lateral field gradients within microfluidic channels. Deoxygenated RBCs, being paramagnetic, migrate toward magnetic field maxima. On the other hand, oxygenated RBCs and WBCs have diamagnetic behaviour and therefore move away from the magnet (the opposite direction to that of deoxygenated RBCs) [28]. However, monocytes can deviate from this behaviour due to intracellular iron accumulation, imparting measurable paramagnetism. This renders these monocytes sufficiently paramagnetic to migrate toward magnetic field maxima alongside deoxygenated RBCs [22,29]. Among circulating blood cells, deoxygenated

RBCs exhibit the strongest intrinsic magnetism, making them most susceptible to magnetophoretic isolation. In contrast, most WBC populations and other blood components do not have strong enough intrinsic magnetism and require labelling for effective separation [8].

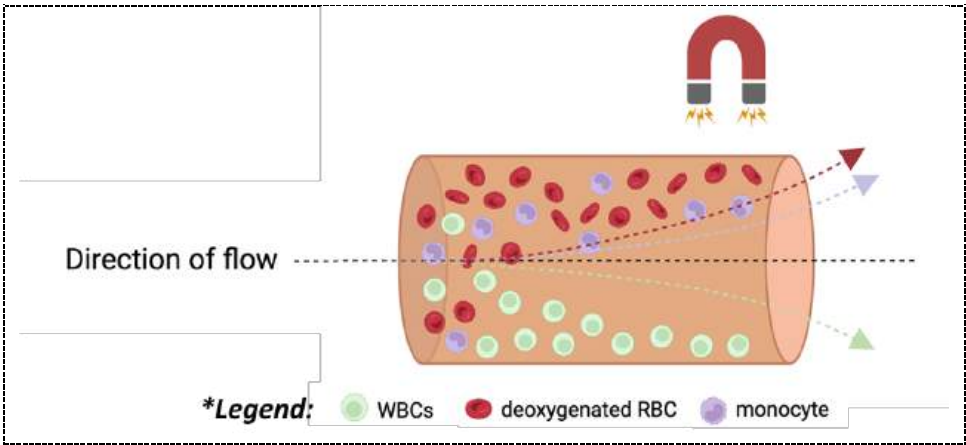


Fig. 3. Varying magnetism of blood components upon magnetophoresis.

Recent studies have further applied magnetophoresis upon WBCs using both direct and indirect trapping. This has been applied for the separation of lymphocytes (T cell subtype) often from peripheral blood mononuclear cells (PBMCs) by applying an external magnetic field using Halbach arrays, immunomagnetic separators, High Gradient Magnetic Separation (HGMS) and permanent magnets [8]. Recent studies have also applied magnetophoretic separation upon monocytes from PBMCs using Magnetic-Activated Cell Sorting (MACS), other column-based devices, and permanent magnets [8]. Different blood components exhibit varying magnetic susceptibilities, determining whether magnetophoresis is label-free or label-based. Among circulating blood cells, deoxygenated RBCs exhibit the strongest intrinsic magnetism, making them most susceptible to magnetophoretic isolation. In contrast, most WBC populations and other blood components do not have strong enough intrinsic magnetism and require labelling for effective separation [8].

3. The Principles and Science of Magnetophoresis

Magnetophoresis often falls under the category of magnetofluidics, which is a broad term referring to any class of devices utilising a magnetic fluid for its function. Due to the favourable force scaling and integration with lab-on-chip technologies, magnetofluids are often applied on the micro-scale, allowing for the emergence of micro-magnetofluidics. When the magnetic particles are smaller than 10 nm and hence disperse well in the fluid, the fluid behaves as a paramagnetic liquid and is labelled a ferrofluid. When larger magnetic particles or cells are manipulated within micro magnetofluidic systems, the process is termed magnetophoresis [30].

Within a magnetophoretic device, many forces act upon particles and determine their motion. This includes the drag force, magnetophoretic force, buoyancy force, gravitational force, and lift force [22]. Understanding how haemoglobin states and magnetic environments influence RBC behaviour requires first examining the underlying physical principles of magnetophoresis.”. Figure 4 shows the relevance of magnetophoresis in relation to magnetofluidics.

3.1 Main Types of Magnetophoresis

A key design consideration is whether to employ positive or negative magnetophoresis. Both modes exploit susceptibility differences to drive particle migration in magnetic field gradients. This force is a product of the magnetic field gradient or the environment's magnetisation gradient, or both. The parameters for both types of magnetophoresis can be explored in Eq. 1 [31]. However, label-based methods are often time-consuming and manually intensive.

In positive magnetophoresis, magnetic or paramagnetic particles suspended in a diamagnetic medium migrate toward regions of highest magnetic field strength [32]. This mode enables separation of particles with differing sizes or susceptibilities by exploiting differential attraction to field maxima [5]. Alternatively, magnetic bead labelling allows this method to be applied to non-magnetic and weakly magnetic particles as well by increasing their magnetic susceptibility [32]. This renders this method time-consuming and manually intensive, as labelling requires hours-long incubation and multiple washing steps [33,34].

In negative magnetophoresis, diamagnetic particles suspended in a paramagnetic medium are repelled from field maxima and migrate toward field minima" [30,32]. This mode is particularly relevant for oxygenated RBCs, which exhibit diamagnetic behaviour. In negative magnetophoresis devices, magnetic field gradients perpendicular to the fluid flow direction are generated by external magnets, making diamagnetic particles produce a deflection velocity. Then, particles with greater magnetic susceptibility flow out through one channel while those with less magnetic susceptibility flow out through another [32].

Alternatively, both positive and negative magnetophoresis may be applied concurrently if the magnetic susceptibility of the surrounding fluid is between the magnetic susceptibilities of both particle types [5]. Because haemoglobin oxidation state determines whether RBCs are diamagnetic or paramagnetic, either positive or negative magnetophoresis can be strategically applied.

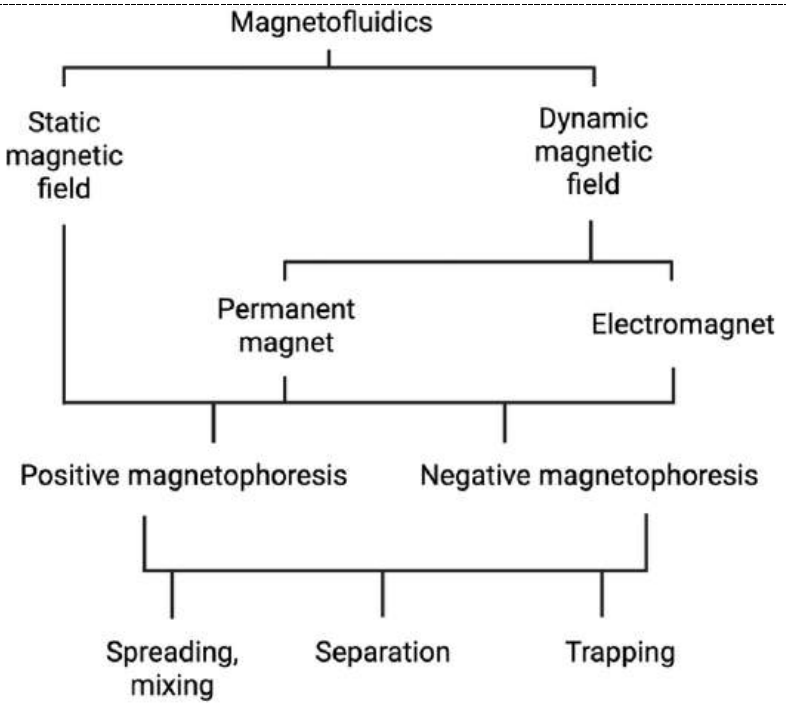


Fig. 4 Types and applications of magnetophoresis *(Figure adapted and modified from Munaz et al., 2018 [5])*

3.2 Effect of Magnetic Susceptibility Upon Cell Separation

These physical properties can be further determined using the following equation detailing the force acting upon a singular particle/RBC in a carrier fluid [30]:

$$F_m = \frac{V(\chi_p - \chi_m)}{\mu_0} (\nabla . B) \quad (1)$$

***Where**; F_m : Magnetic force, V : Volume of the particle (larger particles experience more force, enabling more efficient separation), $(\chi_p - \chi_m)$: Magnetic susceptibility difference between particle (χ_p) and the surrounding buffer/medium (χ_m) (the bigger the difference, the greater the magnetic force able to be applied to a particle), μ_0 : Magnetic permeability, and (∇.B)B : Magnetic force field*

As depicted in Eq.(1), Faraday established that materials acquire magnetisation when exposed to a magnetic field, with the magnitude and direction of particles determined by their magnetic susceptibility (χ_p). The choice between positive and negative magnetophoresis is governed by the relative magnetic susceptibilities of the particle and the suspending medium [30]. This allows for materials to be classified as diamagnetic ($\chi_p < 0$), paramagnetic ($\chi_p > 0$), superparamagnetic, or ferromagnetic, which in turn determines whether the particles are attracted to or repelled by the magnetic flux maxima, as seen in Figure 5 [35–37].

If a diamagnetic object ($\chi_p < 0$) is in diamagnetic medium ($\chi_m < 0$), magnetic susceptibility difference can be either positive or negative, meaning the particle can be attracted to the magnetic field or repelled from it. However, non-magnetic diamagnetic objects may be separated using magnetophoresis if a diamagnetic object ($\chi_p < 0$) is placed in a paramagnetic medium ($\chi_m > 0$). This creates a negative magnetic susceptibility difference ($\chi_p - \chi_m < 0$), meaning the diamagnetic object moves towards the magnetic field minima (as it is repelled from the magnetic field). This can also be applied to paramagnetic objects by placing them in mediums that are even more strongly paramagnetic, causing $\chi_p - \chi_m < 0$, and making the paramagnetic particle get repelled by the magnetic field and move towards the magnetic field minima [37].

Applying this framework to blood, this magnetic susceptibility is largely determined by the oxygenation state of haemoglobin. Oxyhaemoglobin renders RBCs diamagnetic and to have negative magnetic susceptibility of around -9.22 x 10^{-6} [8,30]. This means that negative magnetophoresis may be applied so when oxyhaemoglobin is suspended in a paramagnetic medium, RBCs are repelled from the magnetic flux maxima and move away from the magnetic field [5]. Conversely, deoxyhaemoglobin imparts paramagnetism to RBCs, shifting their susceptibility toward less negative values (approximately -3.9×10^{-6}), which results in their attraction toward magnetic flux maxima [8,30]. Accordingly, under positive magnetophoresis, deoxygenated RBCs migrate toward field maxima due to their higher effective susceptibility [5,38].

Magnetic susceptibility can be largely impacted by physiological factors as these may affect the oxygenation state of RBCs. The Bohr effect states that lower pH (i.e. when more hydrogen ions and carbon dioxide are present), oxygen affinity decreases and when pH is higher, oxygen affinity increases. This is important in the context of magnetophoresis because since magnetism is suppressed within a small electronic energy window, changes in pH alter electron filling in RBCs' haem. This in turn modifies magnetic susceptibility, affecting oxygen binding affinity [39]. The different magnetic properties in relation to the magnetic field applied to various types of magnets are shown in Figure 5. Ferromagnets, unlike paramagnets and diamagnets, retain magnetisation even when the magnetic field is removed [36].

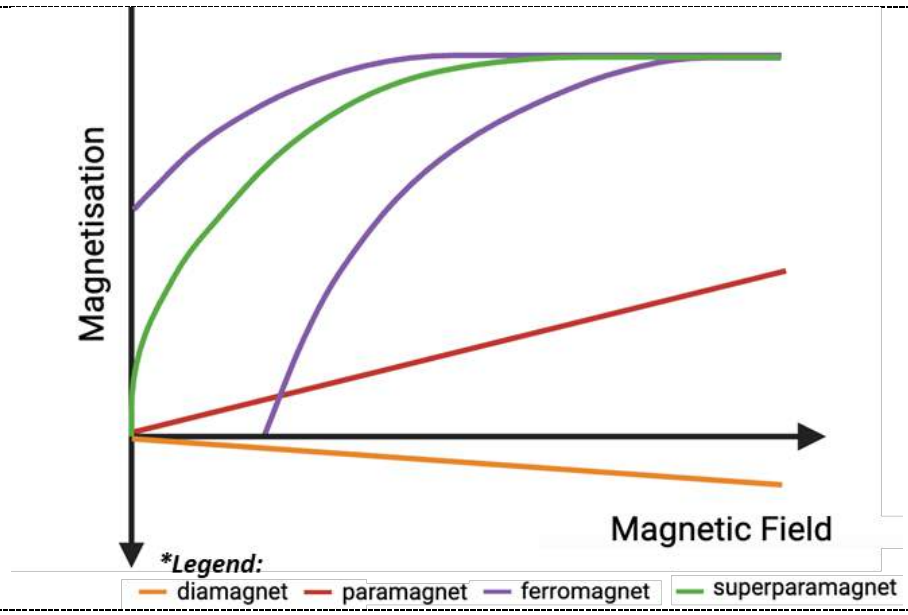


Fig. 5 The relationship of magnetisation and magnetic field in different magnetic properties. *(Figure modified from Rathi et al., [36])*

3.3 Effect of Field Gradients Upon Cell Separation

Field gradients represent the rate at which the magnetic field strength changes. Stronger gradients generate greater net magnetic force on RBCs, enhancing their deflection and separation efficiency. Thus, separation performance improves with increasing magnetic field gradient. This was demonstrated by Xia *et al*., [40] who increased the local field gradient upon RBCs and *Escherichia coli* using microcomb and microneedle structures; this allowed for high throughput and highly efficient isolation of the magnetically tagged particles.

Following studies demonstrated that the magnetic field gradient can also be strengthened by using micro ferromagnetic nickel structures between, along, or even beneath the permanent magnets and microchannels being used [41-43]. The findings of Jung *et al*., further demonstrate the utility/efficacy of applying ferromagnetic structures in the context of magnetophoresis. They showed that when using a paramagnetic mode magnetophoretic separation system with ferromagnetic structures, in which RBCs experienced magnetic attraction to the ferromagnetic structures due to the magnetic force generated by the magnetic field gradient. This allowed RBCs to be progressively deflected into the central microchannel in repeated separation stages while other non-target cells like WBCs did not experience attraction to the ferromagnetic structures and were displaced along outer channels [44]. This shows how ferromagnetic structures can greatly strengthen the magnetic field gradient.

It is also important to note that field gradients play a big role in the performance of both labelled and unlabelled magnetic isolation and are mainly sourced from either permanent magnets or electromagnets [5,45]. Permanent magnets generate stable magnetic fields, are relatively economical, and simple. Electromagnets, on the other hand, generate much greater fields and have high energy consumption, but may damage biological samples [5,8].

The local magnetic field gradient, especially of permanent magnets, can be increased by soft metals like nickel. Nickel microarrays have significantly enhanced local magnetic field gradients in microchannels of magnetophoretic devices, allowing for higher recovery rates and separation efficiency of target cells [46]. Similarly, permalloy microbars magnetized by external permanent magnets generate strong localized gradients suitable for high efficiency separation [8].

This is highly significant as this knowledge can be applied to maximise separation while conserving energy and resources.

3.4 Efficacy of Magnetophoresis

As an active separation modality, magnetophoresis offers advantages over passive techniques such as centrifugation and filtration, particularly in selectivity, processing time, and sample preservation. This is because the active nature of this method generally allows for many benefits in terms of efficiency, simplicity, cost, purity, and scalability.

Firstly, magnetophoresis is highly efficient. In some studies, RBC recovery rates range from 55-95% (variability exists due to differing flow conditions and RBC oxygenation state) and can be further optimised using Halbach devices and quadruple magnetic sorters. This was demonstrated by Moore *et al*., which also showed that applying quadrupole magnetic sorters are also able to achieve such rates while using relatively minimal energy and at low costs. Purity levels exceeding 96% have been demonstrated, and high purity fractions can be obtained rapidly compared with alternative methods. Scalability is also an added advantage of the method, as separation rates as high as 10^{11} cells/30 min have been seen in certain examples [47].

On the other hand, efficiency, purity, and scalability are all generally of lower levels in other separation techniques. Fluorescence-activated cell sorting (FACS) is a commonly used separation method, but compared to magnetophoretic separation, it's complex, expensive, and ineffective as it takes several hours or even days to achieve high-purity samples [48]. Dielectrophoresis and acoustophoresis can achieve high purity and moderate throughput, but magnetophoresis generally offers higher scalability and reduced operational cost [8,49,50]. Moreover, filtration and centrifugation, while very commonly applied and simple, are non-specific, time-consuming, and require large blood sample volumes. Hence, they yield samples with lower purity as compared to magnetophoresis [46].

4. Magnetophoretic Architectures

The quantitative parameters differ according to the specific magnetophoresis-based device or platform being used. Many have been developed in recent years and can either be classified as microfluidic or non-microfluidic devices.

4.1 Microfluidics Magnetophoresis-Based Devices

Microfluidic devices are miniaturised lab-on-a-chip (LOC) devices. LOCs are biotechnological microdevices which are becoming more widely used for more efficient and portable biological and chemical analyses. Microfluidic magnetophoresis devices rely on the usage of microparticles' magnetic susceptibility/labelling paired with microfluidic flow channels (microchannels) through which the microparticles are transported, allowing them to achieve more precise control over separation in micro-environments and overcome a limitation of non-microfluidic devices: the relatively small magnetic flux gradient [51,52]. Microfluidics-based devices also have a lower cost, better portability, and higher throughput. These devices also have several applications within diagnostic and therapeutic settings due to their faster detection rates, including in the context of RBC separation [51,52]. These characteristics make microfluidic systems well suited for point of care diagnostics, prenatal testing, and forensic analysis"[53,54].

Although Phurimsak *et al*., [55] magnetofluidic platform was developed for immunoassays, it demonstrates important concepts of controlled fluid management in microchannels and magnetic bead capture. For this immunoassay platform, a plug is formed in the microchannel, followed by the addition of reagents or the target analyte to bind particles. Buffer is then used to rinse the microchannel, allowing for separation of target analytes (i.e. RBCs) from a sample [55].

Interestingly, one of the first implementations of microfluidics-based magnetophoresis was upon RBCs using their intrinsic magnetism. Han *et al.,* introduced the concept of using nickel ferromagnetic wires under external magnetic fields, allowing them to achieve a 92% efficiency in RBC separation from blood. They also extended these findings by altering the external magnetic field's direction, allowing for insights into both diamagnetic and paramagnetic RBC separation, showing an 89.7% efficiency using diamagnetic modes and 93.5% efficiency using paramagnetic modes. This showed that paramagnetic separation may be more effective for RBC isolation [56,57]. This knowledge has since been applied often. Studies went on to use microfluidic chips with nickel wires running through them; nickel wire generates a magnetic gradient within the channel, and this feature, in conjunction with the external magnetic field, generates a magnetic gradient, allowing for studies showing highly efficient RBC separation of 93.7% and flow rates of 0.23 μL/min [58].

Another widely applied approach involves high gradient magnetic separation (HGMS) microstructures. These can be applied in microfluidic ways and capture weakly paramagnetic cells like deoxygenated RBCs with high capture efficiency by using a strong permanent magnet with ferromagnetic structures to create high magnetic field gradients. This enables effective pulling of paramagnetic cells towards ferromagnetic areas. Throughput is said to be 380x higher than other microfluidic devices, with a flow rate of over 77 μL/min (much higher values than many other microfluidics-based devices) [38].

A paramagnetic capture model based on HGMS presented by Takayasu *et al*., showed a magnetic separator containing a long flow channel with a cross-section tube and ferromagnetic wire. The flow channel contains multiple outlets, through which particles flow through following separation induced by a vertically applied magnetic field. The ferromagnetic wires attract paramagnetic particles while diamagnetic particles are repelled [59].

Another commonly applied HGMS system is MACS. MACS systems employ ferromagnetic microbeads to label target cells, enabling selective retention within column based high gradient fields. This allows for even higher throughput, quality, specificity, and lower cell loss to be achieved by using higher feed concentrations (however, this will compromise capture efficiency, is costly, and has many steps) [60,61]. On the contrary, HGMS devices can also have label-free methods. For example, Jin *et al*., developed an HGMS platform for isolating maturing RBC populations, achieving high capture rates despite their weak intrinsic magnetism. This device was able to achieve a high level of separation; the magnetically enriched fraction captured 80% of mature RBCs. This showed that despite the weak intrinsic magnetism of RBCs, the paramagnetic haemoglobin in mature RBCs makes label-free methods feasible for separation [62].

Halbach arrays of magnets are another microfluidics-based method. These create a strong magnetic field on one side and a strong reduction on the other side by rotating magnetisation patterns. It is a method used to prove that RBCs (paramagnetic when deoxygenated) can be separated from WBCs (diamagnetic) and other non-magnetic plasma components label-free due to both their intrinsic magnetic properties. In microfluidics configurations, Halbach arrays are integrated with microchips that use cladding flows to concentrate particles efficiently, offering good separation efficiency (i.e., purity and recovery). However, these systems suffer from extremely low throughput, with reported flow rates around 0.13 μL min^{-1}, making them impractical for processing clinically relevant sample volumes [31].

Further, Descamps *et al.,* [63] also assembled micromagnets in a polymer-based microfluidic device for WBC depletion, which used ferromagnetic materials to amplify gradients. The embedded ferromagnetic structures enhanced local magnetic gradients and allowed fine control over separation efficiency. Nonetheless, achieving efficiencies above 85% required the use of strong external magnetic fields, especially at high flow rates (≈1000 µL min^{-1}). Thus, although the device demonstrated good efficiency under optimized conditions, the high field requirements and performance drop at elevated flow rates limit its overall throughput, making it a relatively weak candidate for large-volume or high-speed applications.

4.2 Non-Microfluidics Magnetophoresis-Based Devices

Non microfluidic magnetophoresis systems have also been developed, many sharing similar physical principles with their microfluidic counterparts but operating at larger volumetric scales.

For example, Halbach arrays can also be applied to RBC isolation in non-microfluidics contexts. These arrays consist of sequentially oriented permanent magnets, each rotated by 90°, producing a unidirectional field on one side and a near null field on the opposite side. This geometry allows their magnetic fields to cover larger distances, primarily on the upper side of the array. When placed adjacent to test tubes, these arrays can rapidly concentrate magnetic or paramagnetic components within the sample volume. In Eppendorf tubes, Halbach array magnets enabled a 99.9% concentration after just one minute, unlike alternating magnet arrays. Hence, this shows that this method is useful for the separation of biological samples, including RBCs [64].

Quadrupole magnetic sorters also allow for paramagnetic RBCs to migrate towards the magnetic field maxima. They do this by utilising an annular flow channel within the quadrupole, allowing for high throughput of around 1.5 x 10^6, but this was at lower flow rates, meaning RBC recovery remained under 100%. Because of this, throughput is not high enough for clinical applications [47].

4.2.1 Enhancing RBC magnetism in non-microfluidics devices

Certain non-microfluidics devices have also been applied in ways to optimise RBC magnetism, allowing them to be more comparable to microfluidics techniques in terms of efficiency. This includes the use of functionalized magnetic beads and carefully positioned permanent magnets to augment cell–magnet interactions [8].

Automated benchtop High Efficiency Rapid Magnetic Erythrocyte Separator (H.E.R.M.E.S.) exemplifies this approach Vemulapati *et al*., developed this to offer a portable, efficient, and simpler way of capturing RBCs from plasma using magnetic beads. H.E.R.M.E.S. uses solenoids and permanent magnets to generate a magnetic field for thorough mixing, allowing for plasma extraction through a capillary. This device showed over 99.9% purity in samples, demonstrating its virtue, particularly in lower-resource environments and in the context of point-of-care settings [65]. This was extended by the same group by scaling the H.E.R.M.E.S. device into a self-sufficient sleeve. This design employs gentle manual inversion followed by placement in a magnetic stand to generate a radial magnetic field for rapid bead RBC aggregation. This results in a radial magnetic field being generated and subsequent separation of RBCs with 99.9% plasma purity. This device is also particularly useful in low-resource environments as no specialised skills are needed [66]. Evidently, both methods optimise RBC magnetism using effective mixing, which maximises bead-RBC contact interactions. This in turn allows higher capture efficiency, essentially optimising RBC magnetism.

These methods also optimise RBC magnetism by switching from mixing states to static magnetic capture states (e.g. turning off solenoid or stopping inversion). This, paired with the magnets'

positioning, helps to produce a radial field, allows for attraction of labelled RBCs to the test tube's walls, allowing for more efficient separation [65,66]. An even older study done by Takeuchi *et al.,* gave an insight on how to optimise a magnet's position in such a context. They stated that since the intrinsic magnetism of RBCs caused them to orient parallel to an applied magnetic field. This indicates that for optimal RBC magnetism and separation in non-microfluidic devices, it is best to orient the field along a test tube's long axis [67].

Previous studies have also studied blood-magnetic particle dynamics in cylindrical tubes. Findings indicate that strong magnetic fields reduce axial blood velocity and promote rapid RBC aggregation near vessel walls. This can be exploited by applying high magnetic fields to allow for faster cell immobilisation and aggregation of bead-RBCs near the tube's wall, essentially speeding up RBC isolation. However, excessively strong fields may alter blood rheology, necessitating careful optimization of field strength [68].

Other factors such as temperature and the buffers used are also important controls to conserve RBC activity and integrity, both physically and in response to magnetic fields [69]. Here, it is apparent that while these devices and approaches have the same end-goal, their magnetic principles and performance benefits, especially when comparing microfluidic devices to non-microfluidic ones. While microfluidics techniques focus on using miniature LOC devices and handle smaller volumes, non-microfluidics use macroscale equipment like test tubes, Eppendorf tubes, syringes, etc. Hence, separation techniques also greatly vary as microfluidics mostly use flow-based migration relying on intrinsic RBC magnetism while non-microfluidics rely more on manual factors focused on the state and positioning of the RBCs themselves, such as inversions and magnetic bead-cell interactions. As a result, microfluidic devices typically achieve higher throughput per unit volume, whereas non microfluidic systems accommodate larger sample masses at the cost of reduced precision. All of these discussions are summarised in Table 3.

Table 3
Comparison of microfluidic and non-microfluidic magnetophoresis-based devices for RBC isolation

Device / Approach	Microfluidic / non-microfluidic	Magnetic principle	Labelling	Key Performance Characteristics	Reference(s)
Nickel wire microfluidic chips	Microfluidic	Ferromagnetic nickel wires generate local magnetic field gradients under external field	Label-free (intrinsic RBC magnetism used)	High separation efficiency (89.7-93.7%); flow rates of ~0.23 µL/min; low throughput and limited scalability.	[56–58]
High Gradient Magnetic Separation (HGMS)	Microfluidic	Ferromagnetic microstructures amplify magnetic gradients	Label-free or labelled	High flow rates of over 77 µL/min; ~380x. higher throughput than many other microfluidic devices; high capture efficiency but device is complex and requires strong magnets.	[38,62]
Magnetic-Activated Cell Sorting (MACS)	Microfluidic or column-based	Magnetic microbeads work with external magnetic fields	Labelled	Well-established method with very high purity, specificity, and throughput but costly and low efficiency at high feed	[60,61]

Halbach array	Microfluidic	Asymmetric magnetic field is generated by rotated magnetisation	Label-free	High RBC capture (~80%); simple; moderate efficiency	[62]
Micromagnet polymer microdevices	Microfluidic	Ferromagnetic micromagnets amplify gradients	Usually labelled	High efficiency (>85%) with very high flow rates (1000 µL/min) but requires strong external fields.	[63]
Tube-based Halbach array	Non-microfluidic	Macroscale Halbach magnet geometry	Label-free	Rapid with high concentrations (99.9% concentration in a minute); limited selectivity.	[64]
Quadrupole magnetic sorter	Non-microfluidic	Migration toward magnetic field maxima in annular flow	Label-free	High throughput (~1.5 × 10^6 cells); continuous flow; incomplete RBC recovery	[47]
H.E.R.M.E.S. benchtop device	Non-microfluidic	Solenoids and permanent magnets with the help of magnets with bead mixing	Labelled	Very high plasma purity (99.9%); portable and point-of-care applications but bead dependence	[65]
Sleeve-based H.E.R.M.E.S. system	Non-microfluidic	Radial magnetic field via inversion and magnetic stands	labelled	Very high plasma purity and useful in low-resource settings as no specialised skills needed	[66]

5. Clinical and Biomedical Applications of RBC Isolation using Magnetophoresis

Given its operational advantages over conventional separation methods, magnetophoresis has been increasingly applied in clinical and biomedical contexts that leverage altered haemoglobin states or magnetic properties of RBCs. Although healthy deoxygenated RBCs display weak paramagnetism, diseased RBCs often exhibit substantially stronger magnetic responses. Out of these three disease states, end-stage malarial RBCs are the most paramagnetic due to hemozoin build-up. Various anaemias also alter magnetic susceptibility through changes in haemoglobin concentration or structure. This includes disorders such as sickle cell disease, which produces structurally altered RBCs, and thalassaemia, which yields microcytic or hypochromic cells [22].

5.1 Magnetophoresis in Malaria

Magnetophoresis-based RBC separation has been utilised in malaria detection. In malaria infected RBCs (iRBCs), the parasite metabolizes host haemoglobin, altering its oxidation state and promoting the formation of paramagnetic by products. The parasite converts haem into crystalline hemozoin to avoid the cytotoxicity associated with free haem. Haemoglobin is converted to hemozoin crystals, which accumulate, causing the RBCs to have a magnetic dipole moment; the presence of hemozoin and iron in the form of Fe^{3+} results in high spin paramagnetic iRBCs with respect to surrounding plasma, allowing magnetophoresis to be applied [36,38]. Martin *et al.,* therefore applied magnetophoresis using HGMS devices to isolate the paramagnetic iRBCs from whole blood in label-free ways. This allows for i) reduction of parasitaemia, ii) speed up treatment is sped up, iii) removal rate of ~77 µl/min [38].

An earlier example of such a device is the microfluidics magnetic aphaeresis system developed by Kim *et al.,* [70] in 2012. This was also an experimental HGMS device (mPharesis™) and uses micro-channels exposed to periodic magnetic field gradients to achieve a capture efficiency of 99% for iRBCs, essentially treating malaria. Also, in theory, MACS can also be used for the separation of malarial RBCs for diagnostic purposes [60].

Other LOC devices have also been developed for malaria. Giacometti *et al.,* [71] developed a device which places silicon chips and glass slides containing blood smears in the presence of a static external field, causing iRBCs to move towards nickel posts in the silicon chips while healthy RBCs sediment due to gravity, effectively separating the two. Using this, the extent of parasitaemia in a patient may be determined (percentage of iRBCs compared to the total number of RBCs).

5.2. Other Clinical Applications of Magnetophoretic Separation of RBCs

Magnetophoresis has also been applied it for anaemia diagnosis. Anaemic RBCs can exist in different forms, including vitamin deficiency anaemia, thalassemia, and sickle cell anaemia. [22] In anaemic patients, concentrations of haemoglobin are often lower than the normal levels (hypochromia), often caused by vitamin D deficiencies in children, premenopausal women, and pregnant women. This is significant as RBCs exhibiting hypochromic anaemia have been seen to have different magnetophoretic velocities compared to normochromic anaemias [72]. Thalassemia, an anaemia with a genetic basis, causes the formation of hypochromic and microcytic (small) RBCs. Hence, a clinical diagnostic application of magnetophoresis is the quantification of iron and haemoglobin content in RBCs and the red cell distribution width to detect anaemia [22]. These factors that vary between healthy and anaemic RBCs but also between different anaemia types [72]. Using CTV, which uses a permanent magnet-based microsystem, the concentration of haemoglobin in blood samples can be determined. The CTV system does this by combining a microscope camera and microfluidic channel within a magnetic field. The camera tracks cell movement in response to magnetic and gravitation fields, and fractions of cells below 27 pgHb/cell are considered anaemic [22,73]. This method is advantageous over current clinical methods such as flow cytometry as it's relatively inexpensive and portable [22].

Magnetophoresis has also been theoretically applied to sickle cell disease (SCD), a disease that can cause sickle cell anaemia (SCA), a chronic anaemia [22]. SCD causes the sickling of RBCs to take place, forming crescent-shaped RBCs with increasing numbers of protrusions as severity of SCD increases [74,75]. Sickle cell RBCs have paramagnetic haemoglobin in deoxygenated or methaemoglobinated state, meaning they have higher magnetic moment than healthy RBCs, shown in Figure 6. This is because SCD patients have HbS, an altered form of haemoglobin with lower affinity to oxygen. As can be seen in Figure 6, this causes a rightward shift in haemoglobin-oxygen dissociation curve and less oxygen saturation compared with healthy RBCs [74]. While there are currently no magnetophoresis-based devices applied for SCD diagnosis and determination, CTV analysis shows future potential of such an application by due to the RBCs' paramagnetism [74,76].

Magnetophoresis has also been experimentally applied to blood transfusions by separation of healthy and unhealthy cells according to iron content. The better quality of transfusions would help to avoid giving multiple transfusions, avoiding associated harm and side effects [22].

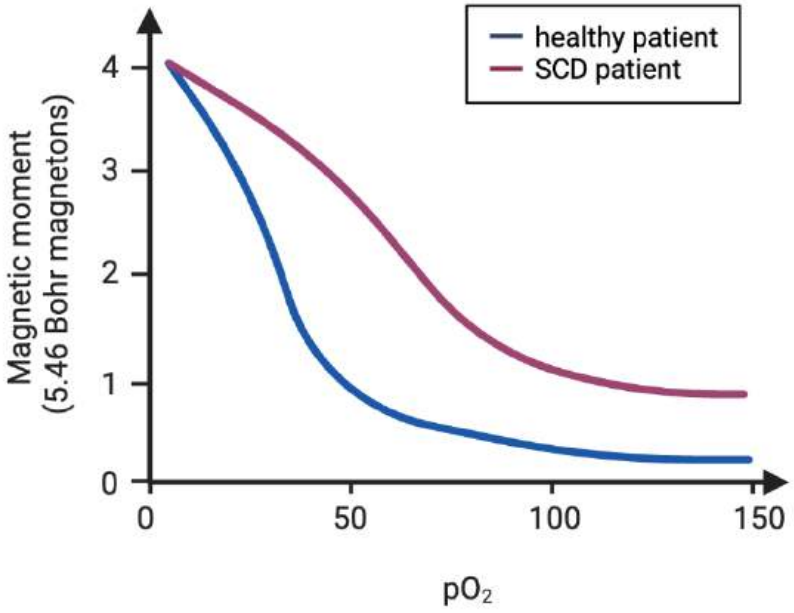


Fig. 6 The relationship of magnetisation and magnetic field in different magnetic properties. *(Figure modified from Rathi et al., [36])*

Another virtuous application of magnetophoresis has been non-invasive prenatal diagnosis. In 2015, Byeon *et al.,* [77] isolated neonatal RBCs (NRBCs) from maternal blood using a two-step method. The workflow began with positive enrichment to remove WBCs through RBC hyper aggregation, followed by negative enrichment via a lateral magnetophoretic microseparator to selectively isolate NRBCs. The lateral magnetophoretic microseparator also uses ferromagnetic wire arrays, so when an external magnetic field is applied, the magnetically labelled WBCs move along the wire and are collected in an outlet while the unbound NRBCs flow with the fluid and are collected at a different outlet. This method depletes 93.98% of WBCs and gives a very high average NRBC purity of 86.8%. This has important implications as it allows for non-invasive prenatal diagnosis from high purity NRBCs from very small volumes of maternal blood (just 1 mL). Similar to malaria applications, MACS approaches can also be adapted for foetal diagnostic workflows [61].

5.3 Biomedical Applications of Magnetophoresis-Based RBC Isolation

As portrayed in Table 4, magnetophoresis-based RBC isolation devices have many clinical uses. These applications arise from the ability of magnetophoresis to detect disease induced alterations in RBC mechanical, biochemical, and magnetic properties. This enables deeper investigation into conditions that modify haemoglobin behaviour, RBC morphology, or magnetism. Although alternative analytical methods exist, magnetophoresis offers high specificity, minimal sample requirements, and the advantage of label free operation in many contexts. Hence, there is smaller room for error while furthering research.

In clinical genetics, magnetophoresis may facilitate the diagnosis of haemoglobinopathies such as β thalassemia and SCD. For example, Karakukcu *et al.,* [78] showed that nucleated RBCs were detectable in all patients with an inherited genetic disorder, β-thalassemia major, and 87% of those with thalassemia intermedia while those with favourable genotypes showed none. Therefore, magnetophoretic enrichment of NRBCs may support early, minimally invasive assessment of

thalassemia risk in paediatric and prenatal populations. This is relevant as it can be challenging to retrieve large volumes of blood samples from younger patients. Non-invasive pre-natal diagnostics are also relevant for foetal genetic profiling for those seeking pre-natal diagnostics. Magnetophoresis-based devices would help to more reliably and efficiently separation foetal nucleated RBCs using, for example, high gradient MACS for subsequent PCR-based genetic analysis achieves high depletion rates (780-fold) and high enrichment rates (500-fold). The method's relative simplicity and speed make it well suited for clinical translational uses [79]. In this context, it can be applied for the detection of chromosomal aneuploidies and other single-gene disorders [80].

The ability to magnetically isolate nucleated RBCs in pregnant women can also be applied to determining health outcomes and abnormalities in these women themselves. For examples, MACS has been applied to isolate nucleated RBCs to determine their frequency in women with intrauterine growth restriction (IUGR) compared to normal pregnancies. This was able to determine that foetal nucleated RBCs are in much higher levels in pregnant women with IUGR. This helps to further our knowledge on women's health and opens avenues for research to determine the implications of such a finding, as well as potential diagnostic and preventative measures [81].

Beyond clinical diagnostics, magnetophoretic RBC isolation offers utility across diverse biomedical research domains. Its ability to discriminate disease altered RBCs supports research and monitoring of infectious conditions such as malaria. It may also aid the study of immune mediated RBC disorders, including haemolytic anaemias. Magnetophoretic isolation may further contribute to vaccine related research by enabling controlled *in vitro* studies of RBC interactions. However, many of these potential applications remain underexplored. Given recent advances in device engineering and analytical performance, research is increasingly expanding toward broader biomedical applications.

Table 4 summarises the different clinical and biomedical applications of RBC isolation using magnetophoresis. While over time there has been an attempt to diversify the clinical applications, there are also continuous attempts at optimising existing devices. These developments are promising but further modifications are needed for implementation beyond research and within actual clinical contexts.

Table 4
Summary of clinical and biomedical applications of magnetophoresis-based RBC isolation

Application	Target cell population	Underlying magnetic basis	Magnetophoretic approach	Performance metrics and virtues	Reference(s)
Malaria diagnosis and treatment	Malaria-infected RBCs (iRBCs)	Paramagnetic nature of iRBCs allows for label-free isolation.	HGMS devices	Label-free removal rates of around 77 µl/min: reduction of parasitaemia, lesser requirements of donor blood, faster treatment	[38]
			HGMS e.g. mPharesis™	99% capture efficiency: malaria treatment	[70]

			HGMS e.g. MACS	Malaria diagnosis	[60]
			LOC devices	Determination of malaria burden	[71]
Anaemia diagnosis	Haemoglobin levels	Inherent magnetism of haemoglobin	CTV system to track cell movement	Relatively inexpensive and portable	[73]
Blood transfusions	Separation of cells according to their iron content	Inherent magnetism of iron		Avoidance of multiple transfusions and associated side effects	[22]
Non-invasive prenatal diagnosis	Neonatal RBCs (NRBCs)	Magnetic labelling	Microseparation using ferromagnetic wires	86.8% NRBC purity from very small volumes of material blood	[77]
	Foetal RBCs for diagnosis and genetic profiling (e.g. detection of chromosomal aneuploidies and other single-gene disorders)		MACS	High depletion and enrichment rates, relatively simple, and efficient	[61,79]
Haemoglobinopathy (β-thalassemia major, SCD) diagnosis and treatment	Disease RBCs	Differing inherent magnetism of disease RBCs	e.g. CTV system has shown potential of diagnostic applications for SCD	Allows for non-invasive determination of disease presence and severity	[76,78]
Determining health outcomes of pregnant women e.g. in the context of intrauterine growth restriction (IUGR)	Nucleated RBCs in pregnant women	Magnetism of RBCs	MACS	Allows further understanding of women's health	[81]

6. Challenges and Limitations in Isolating RBCs using Magnetophoresis

While magnetophoresis-based isolation in the context of RBCs has many virtues, many of which make it a better technique compared to many others, it also has its challenges and limitations such as throughput, cost, and sample variability.

Many devices and methods have been developed to increase magnetophoretic throughput (e.g. HGMS devices) but it is hard to achieve as blood has very high cell concentration with high diversity. Most existing systems remain at the prototype stage and have yet to achieve the throughput required for routine clinical implementation A persistent trade off exists between efficiency and throughput; increasing flow rates typically reduces magnetic residence time and compromises recovery. Thus,

further optimization is required to overcome these fundamental constraints. [8,38,71]. On a related note, the trade-off between purity and recovery when altering flow rate is another challenge. High flow rates allow for faster processing and higher purity, but lower recovery. On the other hand, lower flow rates have slower processing and lower purity. Emerging device designs aim to mitigate this trade off, such as continuous flow microfluidic systems engineered with exponential field gradients to maintain both purity and recovery [8].

While often considered cost effective relative to alternative separation approaches, magnetophoresis still presents notable cost related challenges. For instance, microfluidic devices that are developed for magnetophoresis often have higher manufacturing costs. Also, labelling is often required to make magnetophoresis more efficient (as RBCs' intrinsic magnetism is weak), which adds cost. As a result, improving throughput often increases operational cost, while cost saving measures can restrict throughput [8]. This limitation is particularly relevant for deoxygenated RBCs, whose weak paramagnetism restricts separability unless field gradients or residence times are substantially increased. These constraints can be mitigated through magnetic labelling or by employing devices capable of generating stronger field gradients and extended exposure times [8].

Sample variability is also a concern; the normal RBC population is heterogenous, meaning there is a mix of oxygenated RBCs and deoxygenated RBCs at different oxygen gradient. This causes sample variability and allows for the more efficient capture of some, but not the others, due to varying intrinsic magnetism [21]. These differences, although challenging, may provide diagnostic value in clinical applications. Inter individual variation in haematocrit further alters blood viscosity, which can influence magnetophoretic mobility. Although not extensively studied in this context, theoretical considerations suggest that viscosity driven changes in cell motion may affect separation outcomes. [82].

Otherwise, handling whole blood in microfluidic systems is highly prone to biofouling, as proteins, cells, and micro-clots readily adhere to channel surfaces and disrupt flow [83]. Even with anticoagulation, micro-clot formation and high shear-induced RBC lysis can further obstruct channels and intensify fouling [83].

Additionally, clinically relevant blood volumes are typically larger than the capacities of most microfluidic magnetophoretic devices. As such, microfluidic systems alone are insufficient for large volume processing, prompting the development of alternative high throughput platforms [8].

This is sufficient to understand that while limitations exist for this technique, there are active efforts to counter them, indicating that development of this field is promising and its potential has major implications on the diagnosis and treatment of health and illness in the long run.

7. Future Developments and Implications

While there are currently many emerging clinical and research-based applications of RBC isolation using magnetophoresis, there are also further implications that are yet to be applied.

The point-of-care capabilities, simplicity, and low-power systems of specific magnetophoretic devices enable their application in space biology and microgravity research, especially regarding space-induced RBC diseases. Their non-destructive sample handling further supports potential use in environmental contamination assessment and forensic investigations. Beyond this, it may also be useful in teaching and training spaces to demonstrate RBC separation techniques in novel ways. Broader clinical translation will require further engineering to improve adaptability and integration into theranostic workflows involving RBCs.

8. Conclusions

There has been a marked increase in the use, optimisation, and application of magnetophoresis-based devices in the recent decades, particularly in the context of RBC isolation. While various device applications have been tested, they have been minimally utilised in the clinical practice. By examining the mechanistic, technological, and biomedical foundations of magnetophoretic systems, this review underscores their considerable untapped potential for future research, diagnostic innovation, and therapeutic application."

Acknowledgements
The authors would like to acknowledge and thank Newcastle University Medicine Malaysia (NUMed) for funding this publication. The authors also extend their gratitude to the NUMed Medical Education Society for supporting this project through the MedMentor Connect Research Pairing Programme 2025.

References

[1] Wang, Yuhe, Qi Chen, Chengqi Gan, Bo Yan, Yaquan Han, and Jianhan Lin. "A review on magnetophoretic immunoseparation." *Journal of Nanoscience and Nanotechnology* 16, no. 3 (2016): 2152-2163. https://doi.org/10.1166/jnn.2016.10930.

[2] Bahiuddin, Irfan, Saiful A. Mazlan, Mohd I. Shapiai, Nur A. Nordin, Fitrian Imaduddin, Ubaidillah Ubaidillah, and Dimas Adiputra. "Field dependent-shear stress prediction of magnetorheological fluid using an optimum extreme learning machine model." *J Adv Res Fluid Mech Therm Sci* 70 (2020): 89-96. https://doi.org/10.37934/arfmts.70.2.8996.

[3] Muhamad, P., M. H. Unuh, H. M. Y. Norfazrina, M. A. Ismail, and Z. Tanasta. "Study of Magnetic Flux and Shear Stress of OEM Damper featuring MR Fluid." *Journal of Advanced Research in Applied Mechanics* 41, no. 1 (2018): 9-15.

[4] Jamil, Dzuliana Fatin, Salah Uddin, M. Ghazali Kamardan, and Rozaini Roslan. "The effects of magnetic blood flow in an inclined cylindrical tube using caputo-fabrizio fractional derivatives." *CFD Letters* 12, no. 1 (2020): 111-122.

[5] Munaz, Ahmed, Muhammad JA Shiddiky, and Nam-Trung Nguyen. "Recent advances and current challenges in magnetophoresis based micro magnetofluidics." *Biomicrofluidics* 12, no. 3 (2018).https://doi.org/10.1063/1.5035388.

[6] Alnaimat, Fadi, Sawsan Dagher, Bobby Mathew, Ali Hilal-Alnqbi, and Saud Khashan. "Microfluidics based magnetophoresis: A review." *The Chemical Record* 18, no. 11 (2018): 1596-1612. https://doi.org/10.1002/tcr.201800018.

[7] Choudhari, Rajashekhar, Manjunatha Gudekote, and Naveen Choudhari. "Analytical Solutions on the Flow of blood with the Effects of Hematocrit, Slip and TPMA in a porous tube." *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences* 47, no. 1 (2018): 201-208.

[8] González, Karla Mercedes Paz, Linh Nguyen T. Tran, Poornima Ramesh Iyer, Xian Wu, Hyeon Choe, Bahareh Rezaei, Shahriar Mostufa et al. "Blood cell separation with magnetic techniques: a critical review." *Lab on a Chip* 25, no. 11 (2025): 2521-2565. https://doi.org/10.1039/D5LC00180C.

[9] Iyer, Poornima Ramesh, Xian Wu, Hyeon Choe, Linh Nguyen T. Tran, Karla Mercedes Paz González, Bahareh Rezaei, Shahriar Mostufa et al. "Magnetic-Assisted Manipulation of Rare Blood Cells for Diagnosis: A Systematic Review." *Biotechnology and Bioengineering* 122, no. 10 (2025): 2625-2665. https://doi.org/10.1002/bit.70010.

[10] Baethge, Christopher, Sandra Goldbeck-Wood, and Stephan Mertens. "SANRA—a scale for the quality assessment of narrative review articles." *Research integrity and peer review* 4, no. 1 (2019): 5.https://doi.org/10.1186/s41073-019-0064-8.

[11] Hendricks, Sriwathi Angeline, and Bhuwaneswaran Vijayam. "the interplay between oral, nasal, lungs and gut microbiome ecology in Coronavirus Disease 2019 (COVID-19) infection." *Semarak International Journal of Public Health and Primary Care* 1: 16-36. https://doi.org/10.37934/sijphpc.1.1.1636b.

[12] B. Vijayam, S.A. Hendricks, R. Saha, A.S. Jiwa, A.M. Basheer Ahmad, K.T. Wamumbe, A Narrative Review of Capnography usage in Clinical Medicine, Semarak Current Biomedical Technology Research Journal 1 (2025) 18–39. https://doi.org/10.37934/scbtrj.1.1.1839b.

[13] Moore, Lee R., Nina A. Smith, Samuel J. Pike, Mitchell Weigand, Jenifer Gómez-Pastora, Jacob Strayer, Andre F. Palmer, Jeffrey J. Chalmers, and Maciej Zborowski. "Red blood cell magnetophoresis as a function of oxygen partial pressure." *Journal of Magnetism and Magnetic Materials* 564 (2022): 169982. https://doi.org/10.1016/j.jmmm.2022.169982.

[14] Oehlsen, Oscar, Sussy I. Cervantes-Ramírez, Pabel Cervantes-Avilés, and Illya A. Medina-Velo. "Approaches on ferrofluid synthesis and applications: Current status and future perspectives." *ACS omega* 7, no. 4 (2022): 3134-3150. https://doi.org/10.1021/acsomega.1c05631.

[15] Scherer, Claudio, and Antonio Martins Figueiredo Neto. "Ferrofluids: properties and applications." *Brazilian journal of physics* 35 (2005): 718-727. https://doi.org/10.1590/S0103-97332005000400018.

[16] Zborowski, Maciej, Lee R. Moore, P. Stephen Williams, and Jeffrey J. Chalmers. "Separations based on magnetophoretic mobility." *Separation science and technology* 37, no. 16 (2002): 3611-3633.https://doi.org/10.1081/SS-120014809.

[17] Yang, Wenrong, Yumeng Zhang, Xiaorui Yang, Changxing Sun, and Ying Chen. "Systematic analysis of ferrofluid: a visualization review, advances engineering applications, and challenges." *Journal of Nanoparticle Research* 24, no. 6 (2022): 102. https://doi.org/10.1007/s11051-022-05477-5.

[18] Ciannella, Stefano, Xian Wu, Cristina González-Fernández, Bahareh Rezaei, Jacob Strayer, Hyeon Choe, Kai Wu, Jeffrey Chalmers, and Jenifer Gomez-Pastora. "Kinetic and parametric analysis of the separation of ultra-small, aqueous superparamagnetic iron oxide nanoparticle suspensions under quadrupole magnetic fields." *Micromachines* 14, no. 11 (2023): 2107. https://doi.org/10.3390/mi14112107.

[19] Elblbesy, Mohamed A. "Effect of physiological parameters of blood on magnetophoretic mobility of erythrocytes." *Electromagnetic Biology and Medicine* 30, no. 2 (2011): 86-92. https://doi.org/10.3109/15368378.2011.566777.

[20] Kwaan, Hau C. "Role of plasma proteins in whole blood viscosity: a brief clinical review." *Clinical hemorheology and microcirculation* 44, no. 3 (2010): 167-176. https://doi.org/10.3233/CH-2010-1271.

[21] Zborowski, Maciej, Graciela R. Ostera, Lee R. Moore, Sarah Milliron, Jeffrey J. Chalmers, and Alan N. Schechter. "Red blood cell magnetophoresis." *Biophysical journal* 84, no. 4 (2003): 2638-2645. https://doi.org/10.1016/S0006-3495(03)75069-3.

[22] Barua, Sowrav, Stefano Ciannella, Lukman Tijani, and Jenifer Gomez-Pastora. "Iron in blood cells: Function, relation to disease, and potential for magnetic separation." *Biotechnology and Bioengineering* 120, no. 7 (2023): 1707-1724. https://doi.org/10.1002/bit.28388.

[23] Pauling, Linus, and Charles D. Coryell. "The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin." *Proceedings of the National Academy of Sciences* 22, no. 4 (1936): 210-216. https://doi.org/10.1073/pnas.22.4.210.

[24] Savicki, J. P., G. Lang, and M. Ikeda-Saito. "Magnetic susceptibility of oxy-and carbonmonoxyhemoglobins." *Proceedings of the National Academy of Sciences* 81, no. 17 (1984): 5417-5419. https://doi.org/10.1073/pnas.81.17.5417.

[25] Parizel, P., S. Makkat, E. Van Miert, J. Van Goethem, L. Van den Hauwe, and A. De Schepper. "Intracranial hemorrhage: principles of CT and MRI interpretation." *European radiology* 11, no. 9 (2001): 1770-1783.https://doi.org/10.1007/s003300000800.

[26] Abramczyk, Halina, Jakub Maciej Surmacki, Monika Kopeć, Karolina Jarczewska, and Beata Romanowska-Pietrasiak. "Hemoglobin and cytochrome c. reinterpreting the origins of oxygenation and oxidation in erythrocytes and in vivo cancer lung cells." *Scientific Reports* 13, no. 1 (2023): 14731.https://doi.org/10.1038/s41598-023-41858-z.

[27] Xue, Wei, Lee R. Moore, Naruhiko Nakano, Jeffrey J. Chalmers, and Maciej Zborowski. "Single cell magnetometry by magnetophoresis vs. bulk cell suspension magnetometry by SQUID-MPMS–A comparison." *Journal of magnetism and magnetic materials* 474 (2019): 152-160. https://doi.org/10.1016/j.jmmm.2018.10.108.

[28] Gossett, Daniel R., Westbrook M. Weaver, Albert J. Mach, Soojung Claire Hur, Henry Tat Kwong Tse, Wonhee Lee, Hamed Amini, and Dino Di Carlo. "Label-free cell separation and sorting in microfluidic systems." *Analytical and bioanalytical chemistry* 397, no. 8 (2010): 3249-3267.https://doi.org/10.1007/s00216-010-3721-9.

[29] Gómez-Pastora, Jenifer, James Kim, Victor Multanen, Mitchell Weigand, Nicole A. Walters, Eduardo Reátegui, Andre F. Palmer, Mark H. Yazer, Maciej Zborowski, and Jeffrey J. Chalmers. "Intrinsically magnetic susceptibility in human blood and its potential impact on cell separation: Non-classical and intermediate monocytes have the strongest magnetic behavior in fresh human blood." *Experimental hematology* 99 (2021): 21-31. https://doi.org/10.1016/j.exphem.2021.05.003.

[30] Nam-Trung, Nguyen. "Micro-magnetofluidics: interactions between magnetism and fluid flow on the microscale." *Microfluidics and Nanofluidics* 12, no. 1-4 (2012): 1-16. https://doi.org/10.1007/s10404-011-0903-5.

[31] Shiriny, Afshin, and Morteza Bayareh. "On magnetophoretic separation of blood cells using Halbach array of magnets." *Meccanica* 55, no. 10 (2020): 1903-1916.https://doi.org/10.1007/s11012-020-01225-y.
[32] Su, Peng, Chunhui Ren, Yusheng Fu, Jinhong Guo, Jiuchuan Guo, and Qi Yuan. "Magnetophoresis in microfluidic lab: Recent advance." *Sensors and Actuators A: Physical* 332 (2021): 113180.https://doi.org/10.1016/j.sna.2021.113180.
[33] Pamme, Nicole, and Claire Wilhelm. "Continuous sorting of magnetic cells via on-chip free-flow magnetophoresis." *Lab on a Chip* 6, no. 8 (2006): 974-980https://doi.org/10.1039/b604542a.
[34] Zhu, Taotao, Rui Cheng, Yufei Liu, Jian He, and Leidong Mao. "Combining positive and negative magnetophoreses to separate particles of different magnetic properties." *Microfluidics and nanofluidics* 17, no. 6 (2014): 973-982. https://doi.org/10.1007/s10404-014-1396-9.
[35] Frenea-Robin, Marie, and Julien Marchalot. "Basic principles and recent advances in magnetic cell separation." *Magnetochemistry* 8, no. 1 (2022): 11. https://doi.org/10.3390/magnetochemistry8010011.
[36] Rathi, Ashutosh, Z. Chowdhry, Anand Patel, Siming Zuo, Thulya Chakkumpulakkal Puthan Veettil, John A. Adegoke, Hadi Heidari, Bayden R. Wood, Vidya Praveen Bhallamudi, and Weng Kung Peng. "Hemozoin in malaria eradication—from material science, technology to field test." *NPG Asia Materials* 15, no. 1 (2023): 70. https://doi.org/10.1038/s41427-023-00516-6
[37] Pamme, Nicole. "Magnetism and microfluidics." *Lab on a Chip* 6, no. 1 (2006): 24-38.https://doi.org/10.1039/B513005K .
[38] Blue Martin, A., Wei-Tao Wu, Marina V. Kameneva, and James F. Antaki. "Development of a high-throughput magnetic separation device for malaria-infected erythrocytes." *Annals of biomedical engineering* 45, no. 12 (2017): 2888-2898.https://doi.org/10.1007/s10439-017-1925-2.
[39] Mayda, Selma, Zafer Kandemir, Nejat Bulut, and Sadamichi Maekawa. "Magnetic mechanism for the biological functioning of hemoglobin." *Scientific reports* 10, no. 1 (2020): 8569.https://doi.org/10.1038/s41598-020-64364-y.
[40] Xia, Nan, Tom P. Hunt, Brian T. Mayers, Eben Alsberg, George M. Whitesides, Robert M. Westervelt, and Donald E. Ingber. "Combined microfluidic-micromagnetic separation of living cells in continuous flow." *Biomedical microdevices* 8, no. 4 (2006): 299-308. https://doi.org/10.1007/s10544-006-0033-0.
[41] Shen, Fengshan, Hyundoo Hwang, Young Ki Hahn, and Je-Kyun Park. "Label-free cell separation using a tunable magnetophoretic repulsion force." *Analytical chemistry* 84, no. 7 (2012): 3075-3081.https://doi.org/10.1021/ac201505j.
[42] Nam, Jeonghun, Hui Huang, Hyunjung Lim, Chaeseung Lim, and Sehyun Shin. "Magnetic separation of malaria-infected red blood cells in various developmental stages." *Analytical chemistry* 85, no. 15 (2013): 7316-7323.https://doi.org/10.1021/ac4012057.
[43] Kim, Seonyoung, Song-I. Han, Min-Jae Park, Chang-Wan Jeon, Young-Don Joo, In-Hak Choi, and Ki-Ho Han. "Circulating tumor cell microseparator based on lateral magnetophoresis and immunomagnetic nanobeads." *Analytical chemistry* 85, no. 5 (2013): 2779-2786. https://doi.org/10.1021/ac303284u.
[44] Jung, Youngdo, Yoonsu Choi, Ki-Ho Han, and A. Bruno Frazier. "Six-stage cascade paramagnetic mode magnetophoretic separation system for human blood samples." *Biomedical microdevices* 12, no. 4 (2010): 637-645. https://doi.org/10.1007/s10544-010-9416-3.
[45] Huang, Shuang, H. E. Yong-Qing, and Jiao Feng. "Advances of particles/cells magnetic manipulation in microfluidic chips." *Chinese Journal of Analytical Chemistry* 45, no. 8 (2017): 1238-1246.https://doi.org/10.1016/S1872-2040(17)61033-8.
[46] Lin, Shujing, Xiao Zhi, D. I. Chen, Fangfang Xia, Yihuan Shen, Jiaqi Niu, Shiyi Huang et al. "A flyover style microfluidic chip for highly purified magnetic cell separation." *Biosensors and Bioelectronics* 129 (2019): 175-181. https://doi.org/10.1016/j.bios.2018.12.058.
[47] Moore, Lee R., Daichi Mizutani, Tomoya Tanaka, Amy Buck, Mark Yazer, Maciej Zborowski, and Jeffrey J. Chalmers. "Continuous, intrinsic magnetic depletion of erythrocytes from whole blood with a quadrupole magnet and annular flow channel; pilot scale study." *Biotechnology and bioengineering* 115, no. 6 (2018): 1521-1530.https://doi.org/10.1002/bit.26581.
[48] Plouffe, Brian D., Shashi K. Murthy, and Laura H. Lewis. "Fundamentals and application of magnetic particles in cell isolation and enrichment: a review." *Reports on Progress in Physics* 78, no. 1 (2015): 016601. https://doi.org/10.1088/0034-4885/78/1/016601.
[49] Urbansky, Anke, Andreas Lenshof, Josefina Dykes, Thomas Laurell, and Stefan Scheding. "Affinity-bead-mediated enrichment of CD8+ lymphocytes from peripheral blood progenitor cell products using acoustophoresis." *Micromachines* 7, no. 6 (2016): 101. https://doi.org/10.3390/mi7060101.

[50] Zare, Mahdi, Mahdi Khatibi, and Seyed Nezameddin Ashrafizadeh. "Synergistic effects of dielectrophoretic and magnetophoretic forces on continuous cell separation via pinched flow fractionation." *Physics of Fluids* 37, no. 2 (2025). https://doi.org/10.1063/5.0250792.
[51] Khashan, Saud, Abdulkarem A. Odhah, Marwan Taha, Anas Alazzam, and Mohamed Al-Fandi. "Enhanced microfluidic multi-target separation by positive and negative magnetophoresis." *Scientific Reports* 14, no. 1 (2024): 13293. https://doi.org/10.1038/s41598-024-64330-y.
[52] Civelekoglu, Ozgun, A. Bruno Frazier, and A. Fatih Sarioglu. "The origins and the current applications of microfluidics-based magnetic cell separation technologies." *Magnetochemistry* 8, no. 1 (2022): 10.https://doi.org/10.3390/magnetochemistry8010010.
[53] Pandey, Chandra M., Shine Augustine, Saurabh Kumar, Suveen Kumar, Sharda Nara, Saurabh Srivastava, and Bansi D. Malhotra. "Microfluidics based point-of-care diagnostics." *Biotechnology journal* 13, no. 1 (2018): 1700047.https://doi.org/10.1002/biot.201700047.
[54] Verpoorte, Elisabeth. "Microfluidic chips for clinical and forensic analysis." *Electrophoresis* 23, no. 5 (2002): 677-712. https://doi.org/10.1002/1522-2683(200203)23:5<677::AID-ELPS677>3.0.CO;2-8.
[55] Phurimsak, Chayakom, Mark D. Tarn, and Nicole Pamme. "Magnetic particle plug-based assays for biomarker analysis." *Micromachines* 7, no. 5 (2016): 77.https://doi.org/10.3390/mi7050077.
[56] Han, Ki-Ho, and A. Bruno Frazier. "Diamagnetic capture mode magnetophoretic microseparator for blood cells." *Journal of Microelectromechanical Systems* 14, no. 6 (2005): 1422-1431. https://doi.org/10.1109/JMEMS.2005.859097.
[57] Han, Ki-Ho, and A. Bruno Frazier. "Paramagnetic capture mode magnetophoretic microseparator for high efficiency blood cell separations." *Lab on a Chip* 6, no. 2 (2006): 265-273.https://doi.org/10.1039/B514539B.
[58] Qu, Bai-Yan, Zhi-Yong Wu, Fang Fang, Zhi-Ming Bai, Dong-Zhi Yang, and Shu-Kun Xu. "A glass microfluidic chip for continuous blood cell sorting by a magnetic gradient without labeling." *Analytical and bioanalytical chemistry* 392, no. 7 (2008): 1317-1324. https://doi.org/10.1007/s00216-008-2382-4.
[59] Takayasu, Makoto, D. R. Kelland, and J. V. Minervini. "Continuous magnetic separation of blood components from whole blood." *IEEE transactions on applied superconductivity* 10, no. 1 (2002): 927-930. https://doi.org/10.1109/77.828383.
[60] Spadafora, Carmenza, Lucia Gerena, and Karen M. Kopydlowski. "Comparison of the in vitro invasive capabilities of Plasmodium falciparum schizonts isolated by Percoll gradient or using magnetic based separation." *Malaria journal* 10, no. 1 (2011): 96. https://doi.org/10.1186/1475-2875-10-96.
[61] Strayer, Jacob, Hyeon Choe, Xian Wu, Poornima Ramesh Iyer, Jenifer Gómez-Pastora, Will Moorman, Joseph Cefaratti et al. "Separation of intrinsically magnetic cells using magnetic filters." *Separation and Purification Technology* 368 (2025): 132994. https://doi.org/10.1016/j.seppur.2025.132994.
[62] Jin, Xiaoxia, Stewart Abbot, Xiaokui Zhang, Lin Kang, Vanessa Voskinarian-Berse, Rui Zhao, Marina V. Kameneva, Lee R. Moore, Jeffrey J. Chalmers, and Maciej Zborowski. "Erythrocyte enrichment in hematopoietic progenitor cell cultures based on magnetic susceptibility of the hemoglobin." (2012): e39491. https://doi.org/10.1371/journal.pone.0039491.
[63] Descamps, Lucie, Marie-Charlotte Audry, Jordyn Howard, Samir Mekkaoui, Clément Albin, David Barthelemy, Léa Payen et al. "Self-assembled permanent micro-magnets in a polymer-based microfluidic device for magnetic cell sorting." *Cells* 10, no. 7 (2021): 1734.https://doi.org/10.3390/cells10071734.
[64] Kang, Joo H., Harry Driscoll, Michael Super, and Donald E. Ingber. "Application of a Halbach magnetic array for long-range cell and particle separations in biological samples." *Applied Physics Letters* 108, no. 21 (2016).https://doi.org/10.1063/1.4952612.
[65] Vemulapati, Sasank, and David Erickson. "HERMES: rapid blood-plasma separation at the point-of-need." *Lab on a Chip* 18, no. 21 (2018): 3285-3292. https://doi.org/10.1039/C8LC00939B.
[66] Vemulapati, S., and D. Erickson. "Portable resource-independent blood–plasma separator." *Analytical chemistry* 91, no. 23 (2019): 14824-14828. https://doi.org/10.1021/acs.analchem.9b04180.
[67] Takeuchi, T., T. Mizuno, T. Higashi, A. Yamagishi, and M. Date. "Orientation of red blood cells in high magnetic field." *Journal of Magnetism and Magnetic Materials* 140 (1995): 1462-1463.https://doi.org/10.1016/0304-8853(94)01351-9.
[68] Sharma, Shashi, Uaday Singh, and V. K. Katiyar. "Magnetic field effect on flow parameters of blood along with magnetic particles in a cylindrical tube." *Journal of Magnetism and Magnetic materials* 377 (2015): 395-401.https://doi.org/10.1016/j.jmmm.2014.10.136.
[69] Bhakdi, Sebastian C., Annette Ottinger, Sangdao Somsri, Panudda Sratongno, Peeranad Pannadaporn, Pattamawan Chimma, Prida Malasit, Kovit Pattanapanyasat, and Hartmut PH Neumann. "Optimized high gradient magnetic separation for isolation of Plasmodium-infected red blood cells." *Malaria Journal* 9, no. 1 (2010): 38. https://doi.org/10.1186/1475-2875-9-38.

[70] Kim, Jeongho, Mehrdad Massoudi, James F. Antaki, and Alberto Gandini. "Removal of malaria-infected red blood cells using magnetic cell separators: A computational study." *Applied mathematics and computation* 218, no. 12 (2012): 6841-6850.https://doi.org/10.1016/j.amc.2011.12.057.

[71] Giacometti, Marco, Marco Monticelli, Marco Piola, Francesca Milesi, Lorenzo P. Coppadoro, Enrico Giuliani, Emanuela Jacchetti et al. "On-chip magnetophoretic capture in a model of malaria-infected red blood cells." *Biotechnology and Bioengineering* 119, no. 4 (2022): 1129-1141 https://doi.org/10.1002/bit.28030.

[72] Winoto-Morbach, S., W. Müller-Ruchholtz, and V. Tchikov. "Magnetophoresis: II. Quantification of iron and hemoglobin content at the single erythrocyte level." *Journal of Clinical Laboratory Analysis* 9, no. 1 (1995): 42-46.https://doi.org/10.1002/jcla.1860090108.

[73] Kim, James, Jenifer Gómez-Pastora, Christopher J. Gilbert, Mitchell Weigand, Nicole A. Walters, Eduardo Reátegui, Andre F. Palmer, Mark Yazer, Maciej Zborowski, and Jeffrey J. Chalmers. "Quantification of the mean and distribution of hemoglobin content in normal human blood using cell tracking velocimetry." *Analytical chemistry* 92, no. 2 (2019): 1956-1962. https://doi.org/10.1021/acs.analchem.9b04302.

[74] Strayer, Jacob, Xian Wu, Hyeon Choe, Mitchell Weigand, Payal C. Desai, Kristina Landes, and Jeffrey Chalmers. "Magnetic Fractionation of Red Blood Cells Based on Oxygen Saturation in Sickle Cell Disease." (2022): 8560-8561. https://doi.org/10.1182/blood-2022-171010.

[75] Darrow, Michele C., Yujin Zhang, Bertrand P. Cinquin, Elizabeth A. Smith, Rosanne Boudreau, Ryan H. Rochat, Michael F. Schmid, Yang Xia, Carolyn A. Larabell, and Wah Chiu. "Visualizing red blood cell sickling and the effects of inhibition of sphingosine kinase 1 using soft X-ray tomography." *Journal of cell science* 129, no. 18 (2016): 3511-3517. https://doi.org/10.1242/jcs.189225.

[76] Weigand, Mitchell, Jenifer Gomez-Pastora, Jacob Strayer, Xian Wu, Hyeon Choe, Shuwei Lu, Eric Plencner et al. "The unique magnetic signature of sickle red blood cells: a comparison between the red blood cells of transfused and non-transfused sickle cell disease patients and healthy donors." *IEEE Transactions on Biomedical Engineering* 69, no. 12 (2022): 3582-3590. https://doi.org/10.1109/TBME.2022.3172429.

[77] Byeon, Yeongje, Chang-Seok Ki, and Ki-Ho Han. "Isolation of nucleated red blood cells in maternal blood for Non-invasive prenatal diagnosis." *Biomedical microdevices* 17, no. 6 (2015): 118.. https://doi.org/10.1007/s10544-015-0021-3.

[78] Karakukcu, Musa, Cigdem Karakukcu, Ekrem Unal, Ahmet Ozturk, Zahid Ciraci, Turkan Patiroglu, and Mehmet Akif Ozdemir. "The importance of nucleated red blood cells in patients with beta thalassemia major and comparison of two automated systems with manual microscopy and flow cytometry." *Clin Lab* 61, no. 9 (2015): 1289-1295. https://doi.org/10.7754/Clin.Lab.2015.141250.

[79] Büsch, J., P. Huber, E. Pflüger, S. T. Miltenyi, J. Holtz, and A. Radbruch. "Enrichment of fetal cells from maternal blood by high gradient magnetic cell sorting (double MACS) for PCR-based genetic analysis." *Prenatal diagnosis* 14, no. 12 (1994): 1129-1140. https://doi.org/10.1002/pd.1970141206.

[80] Feng, Chun, Zhaobo He, Bo Cai, Jianhong Peng, Jieping Song, Xuechen Yu, Yue Sun, Jing Yuan, Xingzhong Zhao, and Yuanzhen Zhang. "Non-invasive prenatal diagnosis of chromosomal aneuploidies and microdeletion syndrome using fetal nucleated red blood cells isolated by nanostructure microchips." *Theranostics* 8, no. 5 (2018): 1301. https://doi.org/10.7150/thno.21979.

[81] Simchen, Michal J., Gad Barkai, Ayala Lusky, and Esther Guetta. "Fetal hemoglobin-expressing nucleated red blood cell frequencies in pregnancies with intrauterine growth restriction." *Prenatal diagnosis* 21, no. 1 (2001): 31-35.

[82] Tripathi, Siddhartha, YV BalaVarun Kumar, Amit Agrawal, Amit Prabhakar, and Suhas S. Joshi. "Microdevice for plasma separation from whole human blood using bio-physical and geometrical effects." *Scientific reports* 6, no. 1 (2016): 26749.https://doi.org/10.1038/srep26749.

[83] Sheybanikashani, Sana, Jian Zhou, and Ian Papautsky. "Blood microfluidics: progress and challenges." *Lab on a Chip* (2026).https://doi.org/10.1039/D5LC00059A

.