Patterns from dried drops as a characterisation and healthcare diagnosis technique, potential and challenges: A review

Patterns from dried drops as a characterisation and healthcare diagnosis technique, potential and challenges: A review

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Abstract

When particulate-laden droplets evaporate, they leave behind complex patterns on the substrate depending on their composition and the dynamics of their evaporation. Over the past two decades, there has been an increased interest in interpreting these patterns due to their numerous applications in biomedicine, forensics, food quality analysis and inkjet printing. The objective of this review is to investigate the use of patterns from dried drops as a characterisation and diagnosis technique. The patterns left behind by dried drops of various complex fluids are categorised. The potential applications of these patterns are presented, focussing primarily on healthcare, where the future impact could be greatest. A discussion on the limitations which must be overcome and prospective works that may be carried out to allow for widespread implementation of this technique is presented in conclusion.

Keywords: sessile drops, Evaporation, pattern formation, diagnosis.

1. Introduction

Droplet evaporation is a complex topic that has been an area of scientific interest for over a century (1). Interest has grown in the last two decades, largely due to the work of Deegan and colleagues (2). In 1997, Deegan *et al*. (3) published a paper which described the ring-like deposit left by the evaporation of particulate-containing droplets (known as the "coffee-ring" effect). There are a number of applications of this phenomenon, including disease diagnosis (4), inkjet printing (5), forensic science (6) and soil characterisation (7).

A considerable amount of literature exists which discuss the mechanisms of droplet evaporation (8-14), which are discussed individually in the following section. This review briefly discusses these fundamentals but will focus on the applications of patterns from dried drops as a means of characterisation and diagnosis technique. Furthermore, the potential and limitations of these applications are assessed.

1.1 History of pure droplet evaporation

The evaporation of sessile droplets was the focus of recent (8) and past (9) reviews. Cazabat and Guena (8) reviewed works from an experimentalist's view, to lay a sound foundation for simulation studies.

Earlier, the first known publication regarding drop evaporation was in 1877 by Maxwell (15), in which the evaporation of a spherical drop in uniform still air was considered (9). A subsequent study was carried out by Sreznevsky (as described in (9)), who extended the work of Maxwell to hemispherical drops on a flat plane, showing that the rate of evaporation was proportional to the vapour pressure of the evaporating liquid.

Additionally, Morse determined experimentally that the rate of evaporation of a spherical drop was proportional to its radius (16). Langmuir considered the analogous nature of mass and heat transfer to confirm theoretically the results of Morse (17). Langmuir further determined that the presence of a plate would reduce the rate of evaporation (18).

In 1959 Fuchs published an extensive review with in-depth criticism of a number of works preceding its publication (19). This article was a key resource for future researchers. He used

the Maxwell and Stefan equations to derive the equations for drop evaporation of a stationary liquid (9).

Deposition patterns in drops during the drying process was studied by Larson (10) and Sefiane (11) and the effect of wetting on evaporation by Brutin and Starov (12), with Zang *et al.* (13) describing the physics of contact line dynamics, phase transition and the formation of patterns.

More recently, several articles have been published covering the mathematical modelling of evaporating droplets and the advances made in this area (9, 20-22); however, this review focusses on the phenomenology of patterning.

1.2 Modes of evaporation

There exist two modes of profile evolution throughout the evaporation of a drop namely the constant radius regime (CRR) and the constant contact angle regime (CCAR) (11) as shown in Fig. 1. In the CRR, the contact area (or radius) remains unchanged but the height of the droplet decreases during the evaporation process. In the CCAR, the contact area reduces with time but the height of the droplet remains fixed.

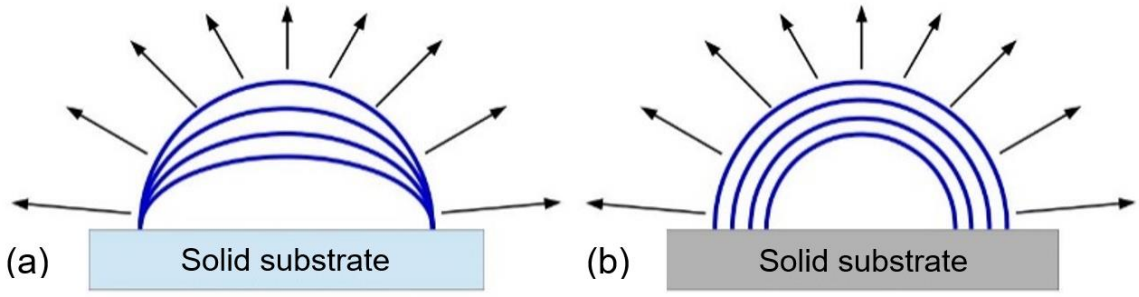


Fig. 1. *Schematic representation of the modes of drying within an evaporating droplet: (a) Constant Radius Regime (CRR) and (b) Constant Contact Angle Regime (CCAR). From (13).*

A combination of these two modes can occur wherein the evaporation slowly switches between the two modes and in some cases both the contact area and angle change with time (1). Alternatively, the drop can evaporate in the CCR mode, with sudden intermittent reductions in the contact area. This is known as the slick-and-slip mode (23).

The mode of evaporation is dependent on the solid substrate upon which the droplet lies. CCR is more common on hydrophilic substrates whereas CCAR is frequent on hydrophobic surfaces

(14). The mode of evaporation is of importance as it can be manipulated to control the deposit left by the drop.

1.3 Flow within an evaporating droplet

A significant amount of research has studied the flow within a drying droplet has been the subject of previous research (1) not least because of the effect the flow regime has on the deposit left by the drop upon its evaporation (11). The two most significant flows within an evaporating drop are Marangoni flow and Capillary flow.

In Capillary flow, the drying operates in the CCR, where the droplet is pinned to the substrate surface (1). Droplets with a contact angle below 90° have evaporative flux greatest at the outer edge (Triple Phase Contact Lines – TPCL) (13). As a result, fluid is required to replace the evaporated liquid at the TPCL. Fluid flows from the centre, radially downwards, to provide this (Fig. 2).

Marangoni flow is caused by a gradient in the surface tension on the external droplet interface (23). The flow of liquid is from areas of low surface tension to areas of higher surface tension (Fig. 2) (1). This gradient in tension can arise from two different factors. The first is a temperature gradient across the droplet surface (thermal Marangoni effect) caused by the changing evaporative flux across the drop surface (24). Additionally, because evaporation is an endothermic process, the bulk liquid is at a higher temperature than the liquid at the surface of the droplet (25). Surface tension increases with decreasing temperature. The second is a change in local composition (solutal Marangoni effect) (24) because of varying concentration of dissolved solute across the droplet. Different solutes have different effects on the surface tension (13).

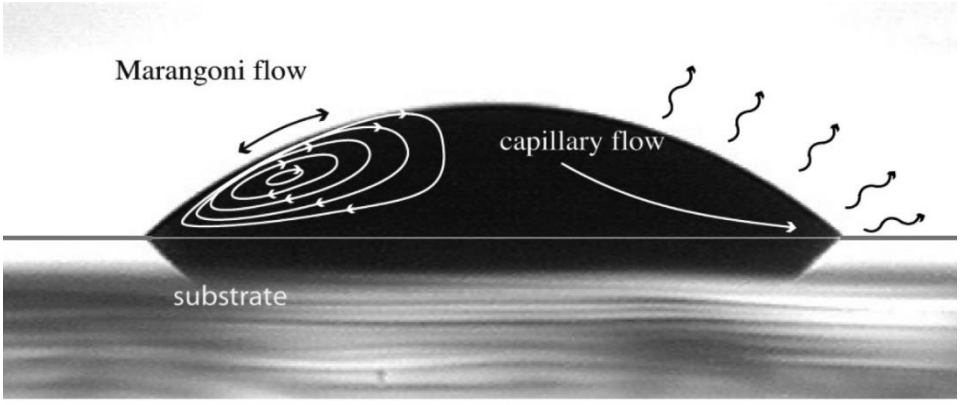


Fig. 2. *Streamline plots of the flow field within an evaporating droplet for Capillary flow and Marangoni flow. The lines represent the direction of the flow. From (24).*

Often a combination of Marangoni and Capillary flows occur within a drop. It was determined by Kim *et al.* (26) that Capillary flow is stronger than Marangoni flow in the case of a heated substrate. Conversely, Marangoni flow is more prevalent on a colder substrate (1). This characteristic allows for the flow regime within the drop to be manipulated (to control the deposited pattern) using the temperature of the drop (11). Resistive micro-heaters or radial heat transfer to the free surface of the droplet can be used for this. Alternatively, to achieve the same outcome, solutes (e.g. solvents or surfactants) can be added to the liquid (25). This is beneficial in cases where a specific deposition pattern is required, such as thin-film coating.

1.4 Deposition patterns on solid substrates

The evaporation of droplets containing non-volatile solutes is found in everyday life, a common example being the drying of a spilt drop of coffee. Such particulate-laden droplets can leave behind a wide range of deposits upon their evaporation, such as uniform patterns, coffee-ring patterns, dot-like patterns and stick-slip patterns (1). A significant amount of work has been carried out to try to deepen the understanding of the mechanisms behind this (1). Various factors have been found to influence the morphology of the pattern left behind by these drying droplets, such as composition, substrate properties and conditions of the local environment (11, 23). In particular, substrate properties play a key role in the morphology of the pattern left behind a dying droplet.

In an experiment by Kim *et al.* (26), the flow fields within drying drops of water solutions with a polymer solute were explored to explain the effect of substrate temperature. The authors observed that the flow within the drop changed direction toward the end of the drying process,

depending on the substrate temperature. As a result of the changing flow dynamics, the deposition pattern was also affected. They reported that on room temperature and heated substrates (surface temperature higher than drop temperature); the outward Capillary flow is more significant than inward Marangoni flow, resulting in the well-known coffee-ring stain. These findings support those of Kajiya *et al.* (11, 27), who saw this pattern on a room temperature substrate. On a cooled substrate, the opposite is true. Therefore, a highly concentrated region is formed in the centre of the drop. The height profiles of the final deposition patterns at three different temperatures can be seen in Fig. 5. This phenomenon can be manipulated to control the deposition pattern left behind by an evaporating droplet.

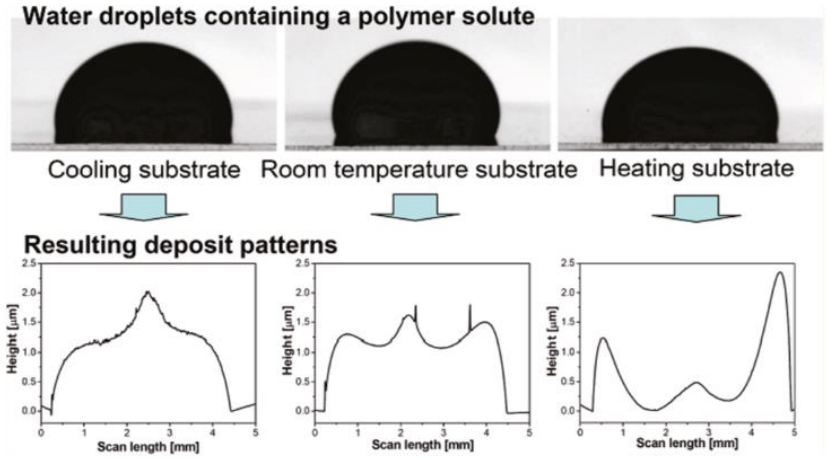


Fig. 3. *Polymer solutions at various substrate temperatures and the height profile of the resulting deposit pattern. From (26).*

Uno *et al.* (28) investigated the pattern formation of evaporating polymer latex solutions on hydrophobic and hydrophilic surfaces. They found that on a hydrophilic substrate, the contact area remained constant through the drying process. Thin clumps of particles adsorbed to the substrate at the periphery causing coffee-ring formation. Conversely, on hydrophobic surfaces, adsorption was not seen at the start of the evaporation. Over time, as concentration within the drop increased, aggregates of particles were formed and these were moved through the particle by convection. Some of these adsorbed to the substrate surface. Upon contact area reduction, the remainder of the aggregates (not adsorbed) moved to the centre of the droplet. This phenomenon is summarised in Fig. 7.

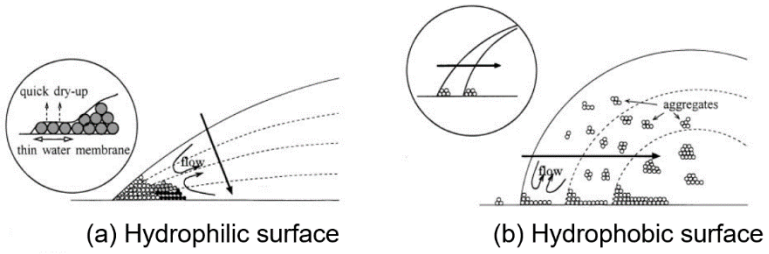


Fig. 4. *Mechanism of drying in polymer solutions on hydrophobic and hydrophilic surfaces. From (28).*

Nguyen *et al.* (29) investigated the effect of added salts on the drying of nanoparticle suspensions on hydrophobic surfaces. Two different nanoparticles were considered: silica (SiO_2) and organic pigment (BI). They found that salt has a significant effect on the pattern left by the evaporation of nanoparticle suspensions as can be seen in Fig. 9. The addition of salt causes the formation of complex structures in the central region of the drop. The authors suggested this was due to the different interactions (interactive and repulsive forces) between the surface and suspended particles, known as DLVO interactions.

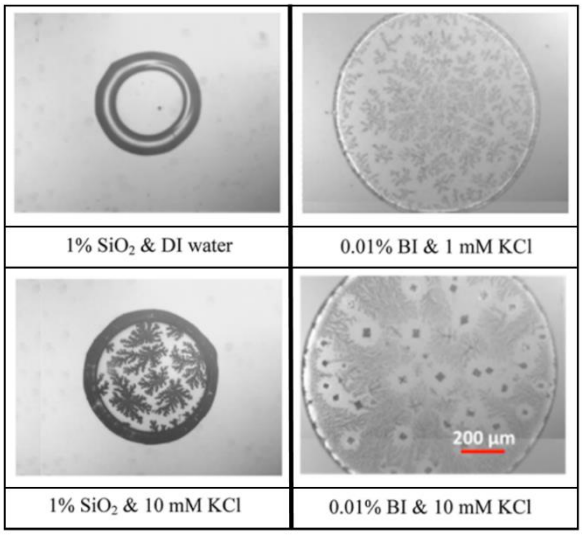


Fig. 5. *Deposit pattern of nanoparticle suspensions with varying concentrations of salt (KCl). Modified from (29).*

Bhardwaj *et al.* (30, 31) and Dugyala *et al.* (32) similarly reported that the patterns left behind by drying droplets were dependent upon these DLVO interactions. The focus of these works was to manipulate the DLVO interactions through the variation of the suspension's pH. It was found that at low and high pH, a coffee-ring pattern was obtained. However, under intermediate pH conditions, a more uniform pattern was observed. Zigelman and Manor (33-35) worked to develop theoretical mass transfer models to assess this theory, considering particle adsorption, pair–limited coagulation and solubility limits during pattern deposition of an evaporating drop. The authors reported similar results. Hence, it can be said that pattern morphology could be regulated through control of the interaction between suspensions and substrate.

1.5 Deposition patterns of complex fluids

As mentioned previously, several factors have been reported to influence droplet pattern morphology. The following subsection will discuss the deposition patterns left behind by some complex fluids and the factors which affect them.

1.5.1 Droplets of biological fluids

Biological fluids (biofluids) can be classified as complex fluids that also contain salts (23). Substantial research has been conducted in the evaporation of various biofluids, such as whole blood, plasma, serum, tears and saliva. However, because of their complex nature, the phenomenon of their drying is not fully understood (36). They contain components such as proteins and electrolytes which alter the mechanism of drying within the fluid and make its behaviour difficult to understand and predict (1).

The drying of drops of these fluids include several physical and physiochemical stages (23). An article by Tarasevich *et al.* (37) reported that upon evaporation, the components within the fluid separate. The constituent salt spreads over the central region of the drop, whilst the proteins migrate to the periphery. Additionally, drops can form cracks during the drying process (23).

Blood plasma is the liquid component within human blood comprising water (90 wt.%), proteins, electrolytes and other components (4). Blood serum is plasma without blood clotting factors. Since many papers use the terms plasma and serum interchangeably, in this paper the term serum will be used exclusively (from this point onwards). A dried drop of blood serum is understood to contain two regions: the central region and the peripheral region. The full span

of the drop contains cracks (radial and orthoradial) with crystalline patterns forming in the central region, as seen in Fig. 3 (4).

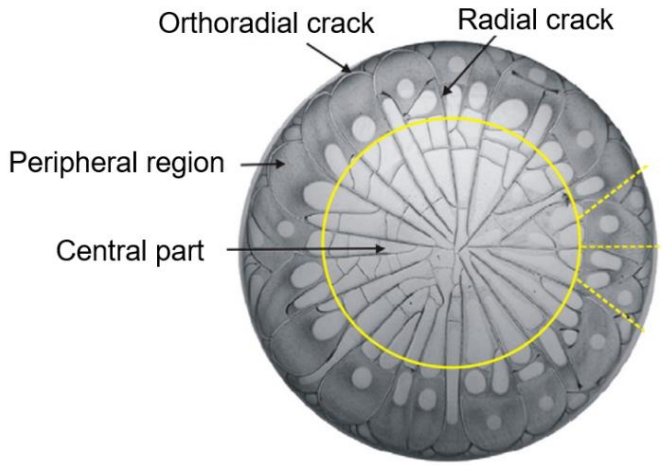


Fig. 6. *The characteristics of a dried drop of human blood serum from a healthy individual. From (4).*

A number of factors can affect the morphology of these serum patterns (38). Several studies by Yakhno *et al.* (39-42) have been published in an attempt to further the understanding of this. One such article observed the change in morphology of drying droplets of model (composition matching that of human blood serum) and real biofluids with varying salt concentrations (42). The investigated fluids were pure water, a 0.9 wt.% salt solution (NaCl), a bovine serum albumin (BSA) solution in water and a 7 wt.% BSA solution in the aforementioned salt solution. BSA is a serum albumin protein isolated from cows and is often used in a range of biomedical applications (11). They reported that the formation of a crystalline pattern within a drying drop of BSA is only possible in the presence of inorganic salts. The study of such model solutions improves the understanding behind the pattern formation within evaporating droplets of more complex biofluids.

Buzoverya *et al.* (43) investigated the effect of varying salt concentrations on the morphology of human serum albumin (HSA) droplets. HSA is a serum albumin that is found within human blood serum. The authors reported that the desiccation pattern of the droplet is dependent upon the concentration of inorganic salt within the drop. Esmonde-White *et al.* reported that the pattern morphology of blood serum and other biofluids was dependent on the substrate upon which the droplet dries (44).

Yakhno *et al.* (45) investigated the morphology of drying drops of various human serum protein solutions. The solutions contained varying amounts of HSA, fibronectin (Fn), immunoglobulin G (IgG) and immunoglobulin M (IgM). Fn, IgG and IgM concentration is found to vary in the blood serum of individuals with certain diseases (46). They found that the concentration of the components within human serum have a significant influence on the final deposition pattern.

The desiccation pattern of other biofluids (e.g. saliva, tears and synovial fluid) has also been investigated. Yakhno *et al.* (47) investigated the drying process of urine and saliva of healthy adults. Pearce and Tomlinson examined the morphology of dried drops of human tears (48). They found that the proteins accumulate at the periphery of the drop upon drying, while the central region of the drop contains crystallisation of salts. López-Solís *et al*. (49) studied the morphology of tear drops and the desiccation pattern they leave behind when drying on a vertical surface (50).

Experiments were carried out by Meloy Gorr *et al.* (51) on the effect of inorganic salts on simplified biofluids. The biofluid was composed of two components: lysozyme and NaCl (varying concentrations). Lysozyme is an enzyme found in a number of biofluids such as saliva and tears. The article concluded that the morphology was dependent upon the concentration of NaCl. However, the general form of the pattern remained the same for all samples: an amorphous ring of lysozyme at the outer perimeter of the drop containing a crystalline structure in the centre. Their results were comparable to those found in literature for dried complex human biofluids (51).

Several works by Chen *et al.* (52-54) have investigated the mechanisms of crack formation within droplets of biofluids. In one such study, Chen *et al.* (54) studied plasma droplets with varying NaCl concentrations to examine the effect of inorganic salts on pattern morphology. The authors reported that increasing NaCl concentration resulted in a reduced number of cracks in the peripheral region of the drop, whilst the region covered by the crystalline patterns in the centre grew.

Few studies have been published on the drying of whole human blood, as research is often focused on other biofluids (12). However, some works by Brutin and colleagues have investigated this. In one article, they describe the three distinctive regions displayed in the deposition pattern of any evaporating droplet of human blood: the central region with

disordered cracks, the corona with large cracks that form plaques and the narrow periphery, as seen in Fig. 4 (55).

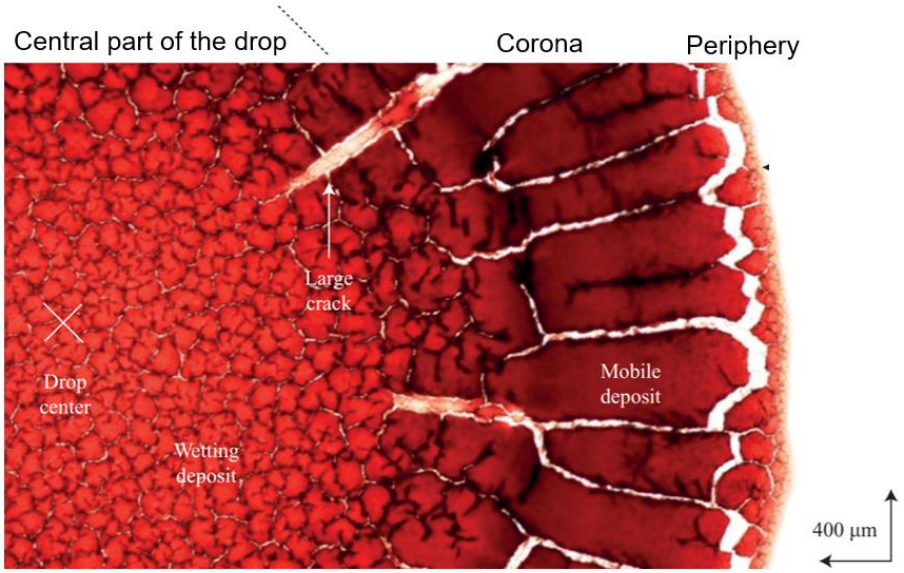


Fig. 7. *The characteristics of a dried drop of whole human blood from a healthy individual. From (55).*

Moreover, Brutin *et al.* (55-61) found that various parameters including substrate properties (including wettability, contact angle and thermal diffusivity), rate of evaporation, droplet size, relative humidity and ambient temperature strongly influence the pattern formed by an evaporating drop of human blood. Based on this, it was determined that the desiccation pattern left from a dried drop of blood is heavily influenced by the environment in which the evaporation occurs. Additionally, it has been reported that individual diet will affect pattern formation in whole human blood (62).

While the works of Brutin et al. examined the influence of various parameters on the pattern formed by an evaporating drop of human blood, the effect of contact angle alone was not investigated. Chen *et al.* (52) reported the important role played by the contact angle on the droplet shape and drying process; particularly the flows within the drop. Moreover, a method for controlling the contact angle was presented in an effort to attain reproducible desiccation pattern.

1.5.2 Droplets of polymer solutions

Polymer solutions are non-Newtonian colloid suspensions, the drying mechanisms of which are not well understood (11). Insight into this would have benefits in the development of

various applications of this phenomenon, such as inkjet printing technologies (5, 63, 64). Often, drying colloidal droplets leave behind a coffee-ring pattern upon their evaporation (27). This phenomenon was first reported by Deegan *et al.* (3), who went on to explain that the only requirements for coffee-ring formation are contact-line pinning and evaporation (65). More recently, Hu and Larson (66) reported that the formation of a coffee stain can be influenced by Marangoni flow.

The formation of a coffee-ring pattern has been further documented by Kajiya *et al.* (27), who investigated the change of concentration within drops of polymer solutions using fluorescent microscopy. They found that during the early stages of drying, polymer concentration was high at the outer edge of the drop, whilst the concentration in the centre of the drop stayed reasonably constant until the later stages of drying. This suggests that the fluid in the central region of the drop is removed by Capillary flow as opposed to evaporation, which explains the thin polymer film formation in this region of the drop. Additionally, the authors found that Capillary flow is proportional to the rate of evaporation.

In an article by Choi *et al.* (67), the drying of polymer solutions with varying particle size was investigated. The experiment was carried out with three different solvents, namely water, polyethylene oxide (PEO) and xanthan gum (XG). The particles added to the polymer solutions were glass beads with a diameter of 9-13 µm, and polystyrene (PS) with diameters of 1 and 6 µm. The patterns left upon evaporation of the dried drops can be seen in Fig. 6. It can be seen that larger particles in XG form a distinct coffee-ring pattern whereas in water and PEO, a more uniform pattern is formed with a distinctive pattern in the central region of the drop. This suggests that both polymer solution and particle size influence the pattern left by a drying drop.

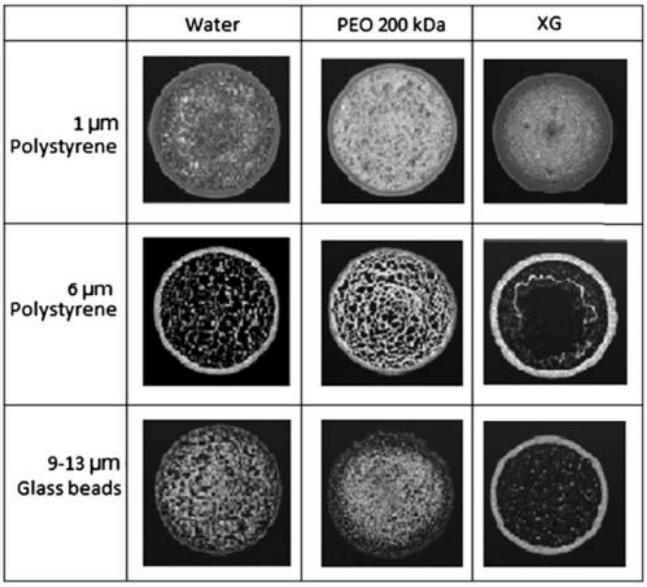


Fig. 8. *Dried drop patterns from three different sized particles dispersed in three different solvents. From* (67).

1.5.3 Droplets of nanoparticle suspensions

Droplets that contain nanoparticle suspensions, or nanofluids, exist as colloidal suspensions. The evaporation of nanofluids, specifically those with metallic nanoparticles, have numerous applications (11). These applications are heavily reliant on the morphology of the patterns left behind by such drying fluids (29), though studies of nanofluid evaporation have been studied more widely (68).

In an experiment by Chon *et al.* (69), the effect of nanoparticle size on pattern morphology was investigated. They examined water with four different nanoparticles suspensions: (a) Au (2 nm), (b) CuO (30 nm), (c) Al_2O_3 (11 nm) and (d) Al_2O_3 (47 nm). The resulting deposit patterns can be seen in Fig. 8. It can be seen that drops containing smaller particles display a more uniform pattern in the central region of the drop. On the other hand, suspensions that contain larger particles leave a more distinct coffee-ring pattern. It is clear that changing the particle size has a significant effect on the pattern formed.

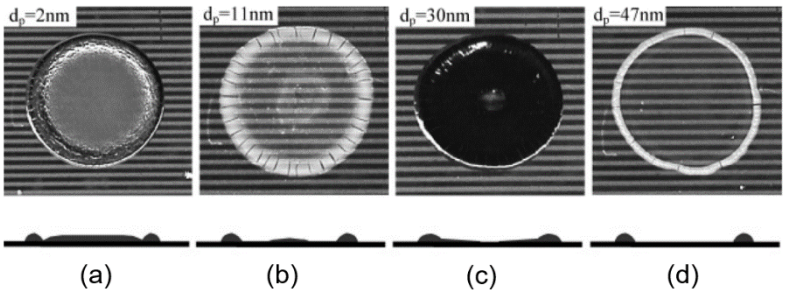


Fig. 9. *Drop patterns and height profiles for evaporated drops of nanofluid with varying nanoparticle size. From (69).*

2. Applications

The patterns formed on a substrate from the evaporation of various complex fluid droplets, as has been discussed previously have given rise in recent years to considerable interest in the applications of this phenomenon, especially in healthcare. This section will identify these uses, as they relate to diagnosis and characterisation.

2.1 Healthcare

The evaporation of biofluids has been of scientific interest in recent years due to its potential as a low-cost, rapid and simple disease diagnosis technique in both humans and animals (13). It requires the comparison of the drop deposition patterns of healthy and ailing patients. This provides benefits in areas where there is little/no access to healthcare.

Consideration of evaporated drops of biofluids as a diagnostic tool began in the 1980s with investigation by doctors in the former Soviet Union (23). This work led to the “Litos” test system, wherein urolithiasis can be diagnosed from the urine drops of suffering patients at a preclinical stage (62). Urolithiasis (or kidney stones) is accompanied by the crystallisation of salts within urine, causing the formation of a unique deposition pattern (62). The development of the Litos test system resulted in a sudden interest in the phenomenon of dried biofluid drops as a diagnostic technique.

Rapis presented the use of deposition patterns for the diagnosis of different types of metastatic cancer (70). The author analysed the final deposit pattern of drying drops of blood serum from individuals with different types of carcinoma: mammary gland carcinoma, neck-of-womb carcinoma, and lung carcinoma. These patterns were compared to serum drops of healthy individuals. The author found that a clear distinction could be made between the drop

morphology of healthy individuals and patients. The micrograph of healthy serum displayed parallel lines and symmetries whereas patterns from diseased individuals showed more irregular shapes. This can be seen in Fig. 10. This work clearly indicates the potential of using this method for the diagnosis of cancer.

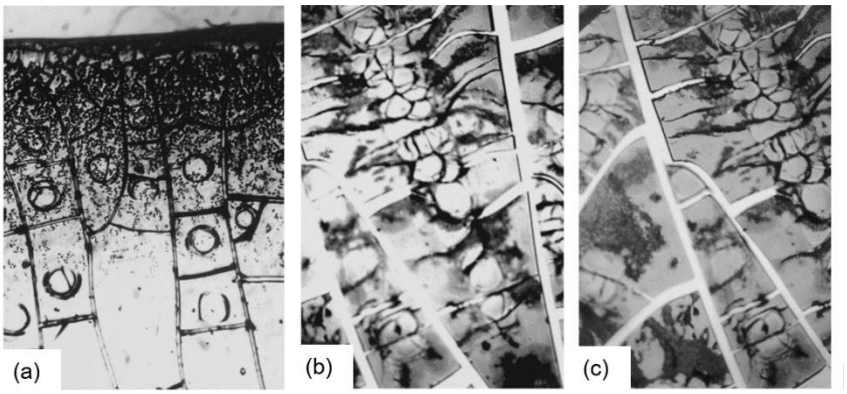


Fig. 10. *Micrograph of blood serum: (a) healthy individual, (b) and (c) patients with cancer. From (70)*

Following this, Yakhno *et al.* (40) studied the blood serum of women who experienced preterm and full-term births, finding that the pattern from a drying drop of blood serum of an individual who experienced a premature birth displayed a thicker ring of larger crystals compared to women who experienced normal childbirth (Fig. 11). In the same article, the group discussed the difference in morphology of a droplet of blood serum of an individual with viral hepatitis B, burn disease and those with good health (40).

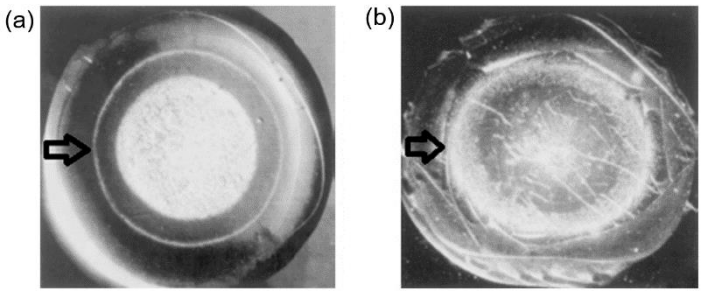


Fig. 11. *The pattern formed from the evaporation of a droplet of blood serum from two different individuals: (a) a woman who experienced full-term childbirth and (b) a woman who experienced preterm birth. The outer ring of crystals is indicated with the black arrow. From* (40).

Further work by Yakhno *et al.* (41) analysed the blood serum of different subjects with various health conditions. The study looked at people with the following conditions: (a) control, (b) breast cancer, (c) lung cancer, (d) paraproteinaemia, (e) normal delivery, (f) preterm delivery, (g) threatened abortion and (h) hepatitis. The patterns for each individual can be seen in Fig. 12. It is clear from this that the morphology of the dried drops noticeably differs from disease to disease. However, it can be also be seen that the test sample of individuals suffering from the same ailment also varies somewhat. For this reason, the certainty of diagnosis is not guaranteed and the method is susceptible to inaccuracies due to subjectivity during analysis.

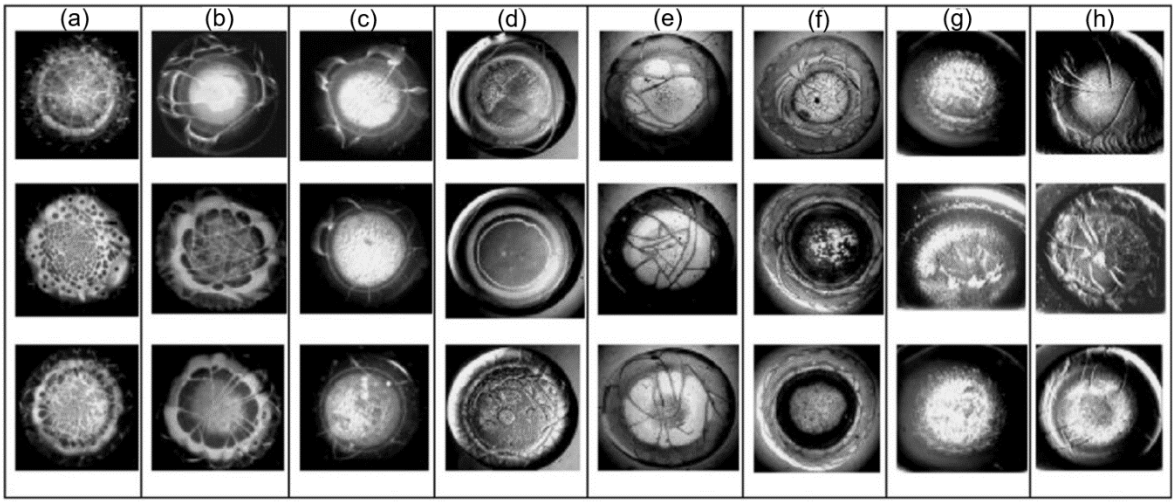


Fig. 12. *Morphology of dried drops of serum from a healthy and seven ailing individuals. From* (41).

Martusevich *et al.* (71) analysed the blood serum of 58 individuals, some of whom were healthy and some suffering from hepatitis B or C. They found that the presence of viral hepatitis affected the crystallisation within a dried drop of blood serum. They suggested that the morphology of the drop varies between individuals depending on their type of viral hepatitis. This can clearly be seen in Fig. 13. Accordingly, they concluded that diagnosis of viral hepatitis B and C from the examination of blood serum drops was possible.

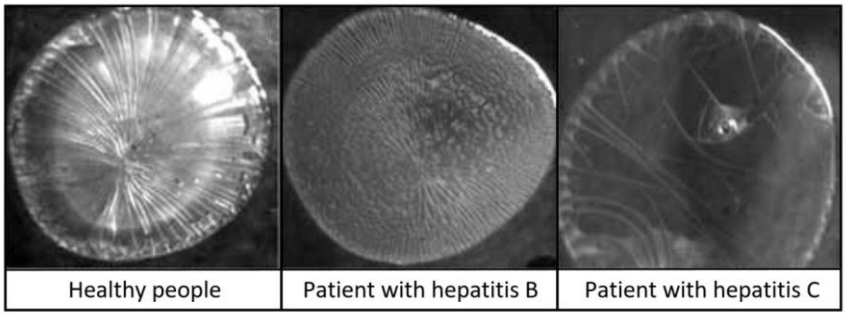


Fig. 13. *Morphology of dried drops of serum from healthy and ailing individuals. From (71).*

The study of the cracking patterns within a dried drop of blood serum and how they relate to various health conditions was carried out by Buzoverya *et al.* (72). The authors determined that some of these crack patterns, seen in Fig 14, are related to certain diseases. For example, triactinal cracks (Fig 14 (a)) are markers for congestive events and disorders in the venous outflow from the cranium. Similarly, tourniquet cracks (Fig 14 (b)) are indicative of chronic hypoxia or inflammation, dashed cracks (Fig 14 (c)) suggest an early stage of discirculatory encephalopathy and wide cracks (Fig 14 (d)) point to dehydration and dysproteinaemia. However, the author advised that there is a lack of fundamental understanding behind crack formation, with patterns being identified through observation (72). While this phenomenon can be utilised in the medical sector (72), more work must be executed to increase reliability.

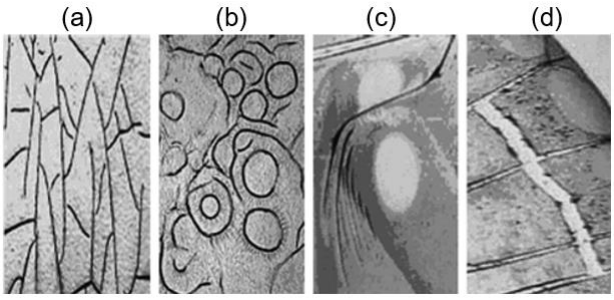


Fig. 14. *Cracking patterns of dried drops of serum. From (72).*

In an article by Muravlyova *et al.* (73), the potential of blood serum pattern analysis as a technique for lung disease diagnosis was examined. Of the 57 people who were involved in the study, 27 patients suffered from idiopathic interstitial pneumonia (IIP), 15 had interstitial lung fibrosis (ILF) and 15 were healthy individuals (used as a control). The author determined that the morphology of serum drops from individuals with interstitial lung diseases differed from healthy individuals. Two factors were suggested as the cause for this: the production of proteins not found in healthy individuals and the accumulation of extracellular nucleic acids.

Brutin *et al.* (74) were the first to investigate dried drops of whole human blood as a means for disease diagnosis, with previous works focusing on blood serum. They investigated the pattern formation from the evaporation of human blood from four different individuals (55), two of whom were in good health and two suffering from different ailments (anaemia and hyperlipidaemia**)**. The patterns from each sample can be seen in Fig. 15. The dried blood pattern of healthy persons (Fig. 15 (a), (c)) display the pattern expected from such healthy individuals (discussed previously). In contrast, in the case of a person with anaemia (Fig. 15 (b)), the drop is lighter at its periphery and the corona contains dark lines and small plaques in its centre. The pattern from the individual with hyperlipidaemia (Fig. 15 (d)) exhibits a thick and 'greasy' corona and similar small plaques in the central region of the drop (55). The patterns of both sick individuals do not have large plaques at the corona of the drop, as is seen in those of healthy persons. It is clear from this that a distinction can be made between the pattern formed by healthy and unhealthy patients. The authors suggested that because of this, blood drops could be used as a reliable means of diagnosing diseases of the blood.

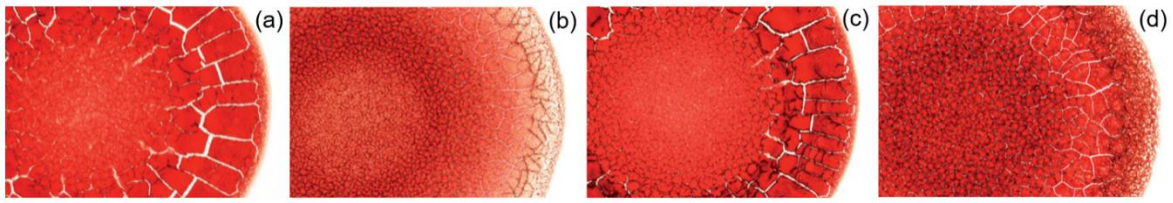


Fig. 15. *The pattern formed from the evaporation of a droplet of blood from four different individuals: (a) a healthy 27-year-old individual (female), (b) an individual with anaemia, (c) a healthy 31-year-old individual (male) and (d) an individual with hyperlipidaemia. From (55).*

Another study by Bahmani *et al.* (75) investigated the desiccation patterns of whole human blood from individuals with thalassaemia and neonatal jaundice. This work sought to deepen the understanding of the underlying mechanisms that result in varying pattern morphology for ailing individuals through the study of the drying process and crack propagation. The patterns left behind by the evaporation of blood from the different groups resulted in distinguishable patterns (Fig. 16). The patterns from healthy individuals and those suffering from neonatal jaundice display clear radial cracks. In contrast, adults with thalassaemia did not show such crack patterns and the corona is thinner compared to the other two groups. It was determined that this was a result of the lower mean cell volume and haematocrit in such patients (75). When comparing the drops of infants with jaundice and healthy individuals, it can be seen that the cracks in the deposition pattern of the former are notably longer. This was found to be due

to a higher bilirubin concentration in ailing infants (75). The authors stated that there is potential for blood pattern analysis as a cost-effective and rapid method for early disease diagnosis

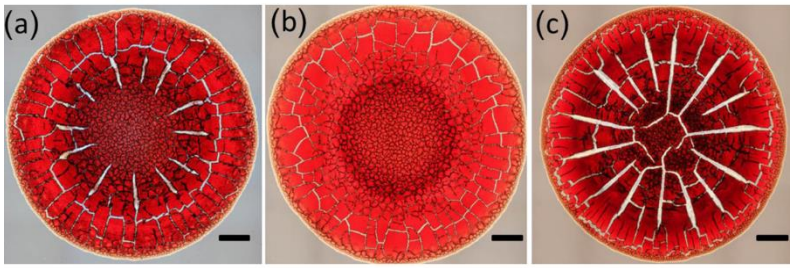


Fig. 16. *The deposition pattern from the evaporation of a droplet of blood from three different persons: (a) a healthy 31-year-old individual (male), (b) a 19-year-old individual with thalassaemia (male) and (c) an infant with jaundice (male). From (75).*

In recent years, pattern formation in drying drops of tears and saliva as a basis for disease diagnosis has been explored. In the case of tears, significant work has discussed the use of drying drop technology to detect issues with ocular health, specifically dry eye disease (48-50, 76, 77). A method for the diagnosis of dry eye is particularly useful as there are currently few tests available for this (78). Dry eye disease is associated with the increase in inorganic salt concentration and changes in the properties of the proteins in tear drops of infected individuals (48). As such, upon drying there is a noticeable difference in pattern morphology between healthy and sick people, as indicated in Fig. 17.

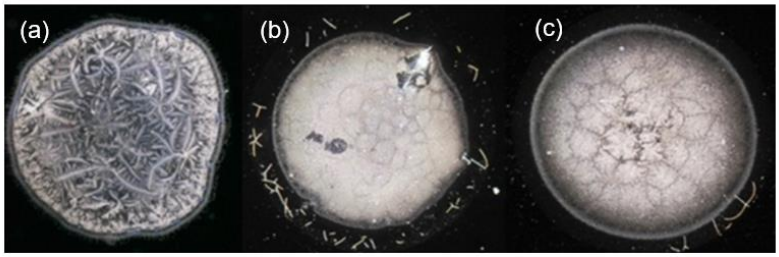


Fig. 17. *The dry tear drops from three different persons: (a) a healthy individual, (b) a 40-year-old individual with moderate dry eye (female) and (c) a 72-year-old individual with severe dry eye (male). From (77).*

The technique of dried drop analysis has been shown to be capable of detecting the diseases mentioned above. However, no data have been reported for accuracy, sensitivity or specificity in these studies. As such, these works are only qualitative. This makes it difficult to determine the feasibility of such a method. Future work should expand these findings with numerical data. They should determine to what degree this method is able to differentiate samples of an unidentified origin (i.e. health status unknown). Additionally, only some of these works have suggested a reason for the dissimilarity in pattern morphology between healthy and ailing individuals. Understanding of this will increase the reliability of this technique.

It is important to note that some variability was seen between samples of persons suffering from the same disease. However, no conclusive account exists of this. Some studies state that variability was seen but provide no further details. Such information is vital to the development of this technique. In cases where repeatability is low, subsequent studies must be carried out to understand the reasons for this. Moreover, the abovementioned works made conclusions based on visual observation alone. This process is subjective to the person who carries out the pattern analysis. As such, incorrect conclusions may be drawn from the samples. To reduce the chance of this, automated image analysis techniques should be employed.

Lebedev-Stepanov *et al.* (79) presented the use of computerised image analysis of dried saliva drops to detect the degree of endogenous intoxication (EI). This automated method of analysis removed previous issues of subjectivity as conclusions were made through comparison with an expert electronic database. They were able to reach a sensitivity to degree of EI of 80%. This indicates the promise of automated comparison of saliva drops as a diagnosis technique of EI. This work could be extended beyond just EI to automate the diagnosis of some of the diseases mentioned previously.

Recently, several have been carried out to investigate the use of vibrational spectroscopy for disease diagnosis (36). Generally, Raman spectroscopy is used for this analysis (36). Raman spectroscopy is cheaper and faster than traditional methods used in hospitals (80). It can be used for the analysis of a number of biofluids, including synovial fluid, tears and serum (81). A study by Esmonde-White *et al.* (82, 83) investigated the use of Raman spectroscopy on dried drops of synovial fluid to diagnose osteoarthritis (OA). The authors established that individuals with OA experienced changes in synovial fluid chemical composition which can be related to protein secondary structures. Raman bands could be used to describe these protein structures and therefore to detect OA. They reported a classification sensitivity of 74% and a selectivity

of 71%. Filik and Stone (84) presented a method for diagnosis of ocular infection using Raman spectroscopy of dried tear fluid. The authors suggest that issues with ocular health cause a change in protein levels within the tear fluid. These findings are qualitative. In another article, Taleb *et al.* (85) reported the potential of using micro-Raman spectroscopy to analyse dried serum drops as a tool for the diagnosis of hepatocellular carcinoma (HCC). HCC is the most common type of liver cancer. It must be diagnosed early to ensure the patient receives treatment in time. They reported an accuracy of 84.5 – 90.2% for dried serum drops and 86 – 91.5% for freeze-dried serum drops.

While these articles only consider using Raman spectroscopy, the composition change associated with the diseases suggest that there is a possibility of using dried drop comparison methods for diagnosis. Raman spectroscopy requires equipment that is sophisticated, bulky and expensive. The method proposed in this review for dried drop analysis can be used as a first screening step since it is easy and does not require such complicated equipment. Following this, if ill health is suspected, Raman spectroscopy can be used for secondary screening. Samples can be sent by post to a laboratory from home. As a final step, a hospital visit can be scheduled. The proposed three-step screening method would be beneficial to those who do not have access to a local hospital. Unnecessary travel to see a doctor could be reduced.

Yakhno *et al.* (86) first introduced the concept of using dried drop analysis for disease detection in animals. The article suggested the use of pattern analysis as a technique for leukaemia and tuberculosis detection in cattle. Tests were carried out on blood, serum and milk drop samples from cows. The resulting deposit patterns can be seen in Fig. 18. A clear distinction can be seen between the three groups considered. The study concluded that there is real potential for this technique. The proposed analysis would reduce diagnostic time from 3-15 days to 20 minutes (86). Moreover, such a technique is not limited to cattle and can be extended to other animals. However, work in this area is still in its preliminary stages and some aspects of the process require further investigation. For example, the seasonal effect on pattern morphology is not known. Additionally, the specificity and sensitivity of the method are unknown. Understanding of this is crucial to evaluate the feasibility of this technique. As such, more work must be done before widespread use of this technique can begin.

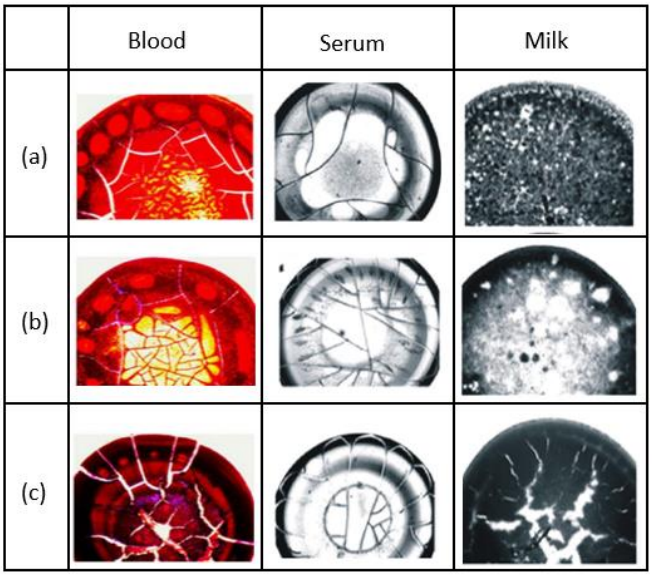


Fig. 18. *Deposition pattern of various biological fluids from different cattle groups: (a) a control, (b) bovine leukaemia virus positive and (c) bovine tuberculin positive. Modified from (86).*

2.2 Other application areas

The use of drying drop technology has been proposed in the food industry for evaluating the quality of various foodstuffs, such as alcoholic drinks.

Yakhno *et al.* (39) investigated the possibility of using a technique based on drying drops for quality analysis of alcohol. The patterns left behind by fresh beer, aged beer and spirits were analysed. It was found that the different samples underwent an intrinsically different drying process and consequently produced dissimilar patterns which need to be related to quality.

González-Gutiérrez *et al.* (87) used drop analysis to assess differences between pure and adulterated alcoholic beverages, more cheaply and possibly faster than previous methods. A clear difference can be observed between the resulting patterns for four adulterants (see Fig 19).

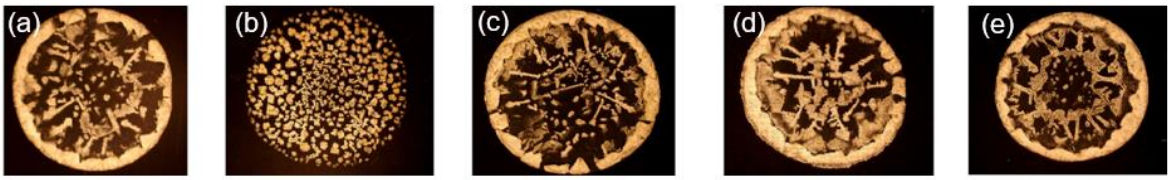


Fig. 19. *Dried drop patterns from tequila adulterated with four different substances: (a) a control, (b) MEG (5 %v/v), (c) EtOH (10 %v/v), (d) Water (10 %v/v) and (e) MeOH (40 %v/v). From (87).*

Busscher *et al.* (88) attempted quality analysis of carrot samples was proposed. The group extended this method to milk and milk products (89) to identify milk products deriving from cows with dissimilar feeding regimes finding that some distinction could be made but repeatability issues arose.

Kokornaczyk *et al.* (90) presented a preliminary study for a method of wheat quality analysis using the pattern left behind from common wheat grain cultivar leakages. The authors found that each of the different cultivars that were analysed displayed different crystallisation patterns with varying levels of complexity. These promising patterns can be seen in Fig. 20, but work is preliminary and sensitivity and specificity are still to be assessed.

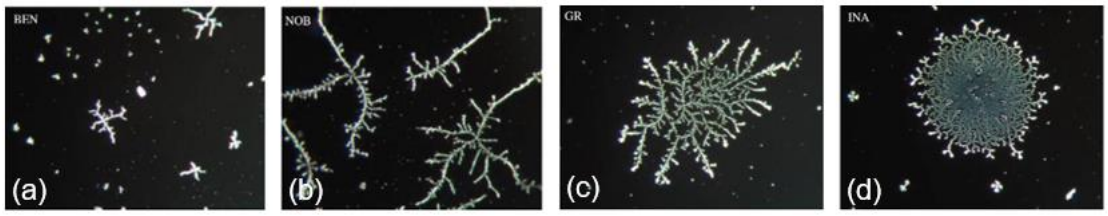


Fig. 20. *Dried drop crystallisation patterns within drops of 4 different wheat cultivars: (a) Benco (BEN), (b) Nobel (NOB), (c) Gentil Rosso (GR) and (d) Inallettabile (INA). From (90).*

In the environmental sector, Chambers *et al.* (7) presented the first investigation into a method for characterisation of soil properties centred around drying drop technology. An experiment was carried out on agricultural soil/water solutions to investigate the impact of fertiliser on pattern morphology. For each type of soil, four different fertiliser mixtures were considered: (a) pure soil, (b) soil and calcium phosphate fertiliser, (c) soil and potassium sulphate fertiliser and (d) soil and magnesium sulphate, the dried drop patterns of which are in Fig 21. The dried drop deposition patterns for agricultural soil can be seen in Fig. 21. In Fig. 22, drop patterns

from city soil are seen. While the correlation between fertiliser and pattern remains, there is some ambiguity when classifying different soils and some attempt was made to lessen this by filtration. The authors found it difficult to analyse these mixtures and recommended further work with advanced image processing software.

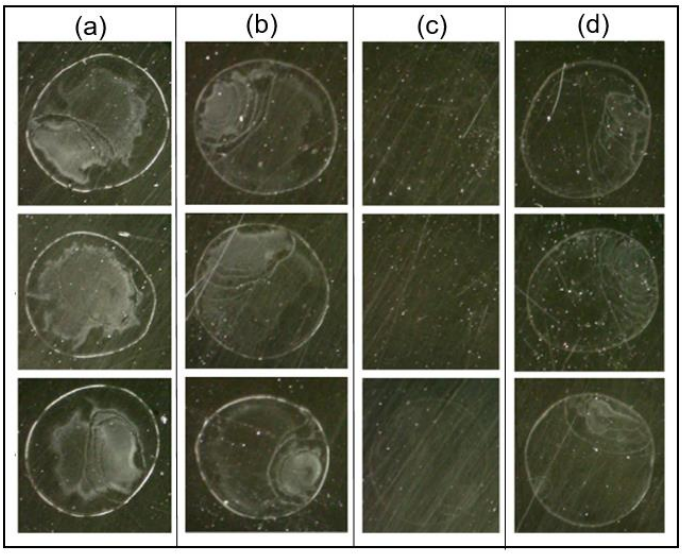


Fig. 21. *Dried drop patterns for soil with different fertilisers. From (7).*

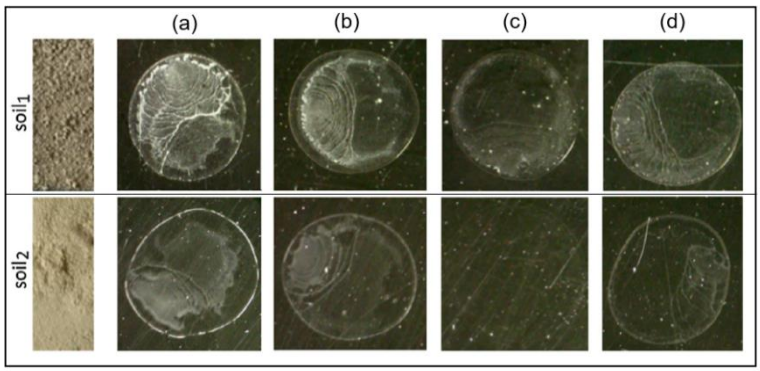
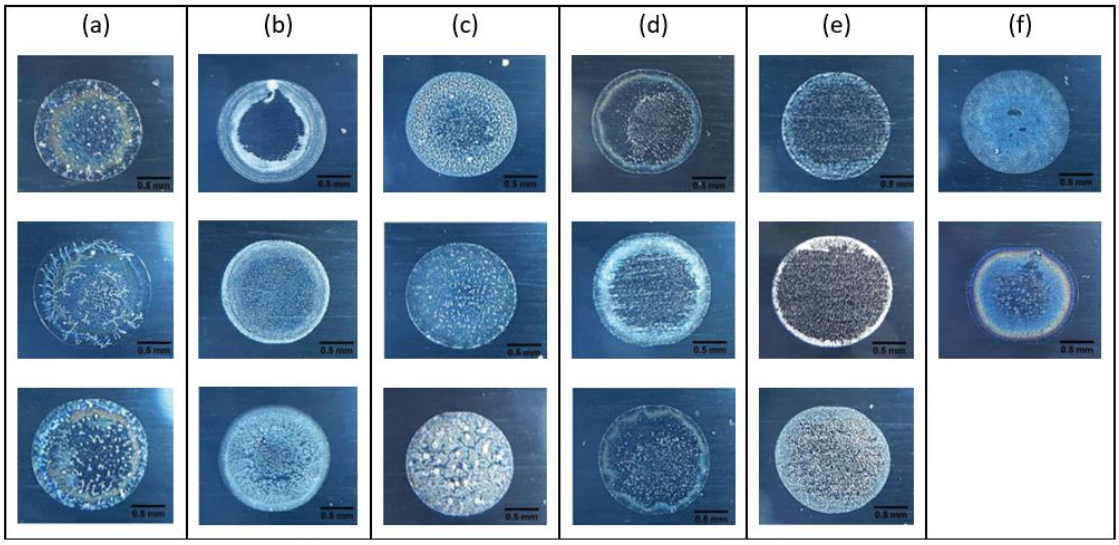


Fig. 22. *Dried drop patterns from different soils with different fertilisers. From (7).*

Water quality analysis is also possible using this method Li *et al.* (91), obviating negative effect on human health (92) of contaminated water and improves on tested methods which detect only specific contaminants (91). Tap water samples were collected from across Michigan, each having underwent different water treatments. These samples were to be deposited on an aluminium substrate and the resulting pattern to be photographed on a smartphone camera fitted with a magnification lens. A convolution neutral network (CNN) model was established for the classification of the images into groups of similar composition. The patterns left from different treatments can be seen in Fig. 23. Minimally treated ground water (a) displayed rings within

which was dispersed particles and ion exchange samples (c) show large crystals spread across the drop. The CNN classified the images into groups (of similar chemistry) with an accuracy of 80%. The accuracy could be improved by expanding the limited dataset and using it to train the model. As such, this technique has great promise and should be further investigated.

Fig. 23. *Dried drop patterns from tap waters that underwent different treatments: (a) minimally*



treated groundwater, (b) lime softened, (c) ion exchange, (d) surface water source, (e) untreated groundwater and (f) reverse osmosis. Modified from (91).

3. Discussion

This section provides a critique of these abovementioned techniques especially for healthcare, and some commentary on the nascent applications in food and environmental areas.

The use of biofluid deposit patterns for disease diagnosis would be revolutionary. The method is quick, low cost and minimally-invasive. This technique is especially useful in areas with no access to hospitals in the local area (e.g. in low resource countries). It can indicate the likelihood of a specific disease and suggest if a person should go to the hospital for further evaluation. Furthermore, it can allow for the early detection of diseases traditionally difficult to diagnose.

One of the main issues with using dried biofluid drops for disease diagnosis is the subjectivity of this technique. The fundamentals of their drying, and how patterns relate to various diseases, is not fully understood. An increasing number of repeating patterns have been identified experimentally, some of which have been associated with specific diseases (11). However, the

diagnosis of a disease from pattern recognition alone is very difficult and there exists only a limited number of very experienced individuals who, after years of research, are able to identify such patterns from dried drops (79). Herein lies another issue due to the subjective nature of such analysis. Conclusions are dependent upon the interpretations of such personnel. Additionally, the process can become tiresome and costly if a large number of patterns need to be analysed. To overcome these issues, automation of the pattern recognition process has been suggested using computer software (79). The development of such a software would allow for the widespread use of this diagnostic technique. In the long run, the hope would be to have an automated image analysis method available that is compatible with smartphone use to make this method of diagnosis available to almost everyone.

Kim *et al.* (93) proposed a novel method of computerised pattern recognition. This involved the classification and clustering of drops using pattern recognition algorithms. They reported an accuracy of 80-94% for classification algorithms. The clustering algorithm achieved a slightly lower accuracy of 62-80%. These results are promising for disease diagnosis. Some works have made use of CNN and PCA for image analysis. However, this type of image analysis has high computational costs and requires experienced individuals for its tuning (94). Automation is underdeveloped and requires further study for improvement to improve the accuracy and sensitivity.

The dependency of pattern morphology on drying conditions (e.g. relative humidity and substrate properties) must also be considered (4). Tests would require a standard set of drying conditions to allow for repeatability and fair comparison to set a standard, and to identify best practice in disparate climates. Similarly, individual diets can result in pattern dissimilarities. The effects of this must be understood to aid in pattern analysis. There should be further research to understand fully the influence of both environmental and dietary factors in order to accurately analyse samples. Otherwise, researchers can draw incorrect conclusions from their analysis.

Dried drop technology can be used in combination with Raman spectroscopy and more traditional diagnostic techniques. The proposed drop drying method would act as a preliminary screening step. This would be followed by Raman spectroscopy analysis and finally a visit to the hospital if disease was suspected. The ease of using dried drop analysis would allow for widespread medical aid in countries where hospitals are not easily available, saving numerous lives.

Animal disease detection is in its very early stages. Some preliminary work has been carried out by Yakhno *et al.* (86), revealing the depth of the possibility in this area. The issues of this technique are similar to those of human drop analysis methods. There is still work to be done before this can be used as a tool for real-world biological testing.

Pattern-based disease diagnosis has good potential but it is still in its conceptual stage and requires some development before being implemented. Work must be carried towards deepening the understanding of the mechanisms of pattern formation within drying drops of biofluid. This will allow researchers to determine, with more certainty, which patterns are associated with which diseases, thereby increasing the reliability. Furthermore, it will remove the ambiguity linked to the environmental conditions during the drying process and human diet. The establishment of automation methods is necessary to remove any subjectivity when analysing drop patterns.

The application of the drop drying method for food quality analysis and environmental usage is in its infancy. Issues of e.g. repeatability need work, and applicability to wider classes is not yet established; however, the method is promising, especially the wheat quality analysis. For all of these proposed applications, automation is required to remove subjectivity of analysis. Pattern analysis is slow and requires expert personnel to carry it out. As discussed previously, an automated pattern analysis technique would remove such issues. Indeed, pattern formation from certain types of drops may be affected by aggregation or (in biofluid drops) protein crystallisation mechanisms, but this is beyond the scope of this work.

Likewise, environmental applications are in the early stages of development. Soil characterisation is proving promising with regard to rapidity, low-cost, simplicity and selectivity to particular soil components. This method can also be used alongside already-established techniques such as electrical sensors, which have a sensitivity to fertiliser concentration but are not able to make a distinction between soil components (95). A method of controlled drying must be established to mitigate the effect of drying conditions on the pattern left by the evaporating droplet. Soil patterns contain significant information which can be utilised and implemented as a component of a multi-sensor instrument once the effect of soil texture and analysis of mixed soils is assessed. The preliminary work of Li *et al.* (91) indicated clear potential for a water quality analysis method that would provide a cheap blanket test for all contaminants instead of just one. To increase the accuracy of this model, a bigger database is needed for CNN training. Furthermore, pattern morphology is influenced by various

factors (e.g. temperature, humidity and droplet volume), which would need to be controlled for successful testing. Additionally, substrate selection, effect of pH and organic matter need investigation.

4. Conclusions

Over the past two decades, there has been significant interest in applications based on the interpretation of the deposit patterns of dried drops of complex fluids. A review of these different applications in healthcare has been presented in this paper.

Numerous studies have been published concerning the use of dried drop analysis in the healthcare sector, proposing it as a tool for disease diagnosis. This technique has good potential as a preliminary screening method but it is still in its conceptual stage and requires some development before being implemented. (The use of dried drops in food quality and environmental analysis is more limited. However, the few works proposed show great potential and the findings can be extended.)

However, there remains a significant amount of work that must be carried out before widespread use of this technique in any sector. In particular, it is hoped that future works will address two critical issues associated with these applications: repeatability of pattern formation and subjectivity of pattern analysis. Methods for automation of pattern image analysis have been presented to overcome the issue of subjectivity; however, these works are in very early stages and further development is necessary. Further research is required to understand the reason for variance in patterns. Of significance is the effect of the drying conditions on final pattern morphology. Work should be done to establish a standardised drying method to lessen the effects of these drying conditions.

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Figure Captions

Fig. 1. Schematic representation of the modes of drying within an evaporating droplet: (a) Constant Radius Regime (CRR) and (b) Constant Contact Angle Regime (CCAR). From (13).

Fig. 2. Streamline plots of the flow field within an evaporating droplet for Capillary flow and Marangoni flow. The lines represent the direction of the flow. From (24).

Fig. 3. Polymer solutions at various substrate temperatures and the height profile of the resulting deposit pattern. From (26).

Fig. 4. Mechanism of drying in polymer solutions on hydrophobic and hydrophilic surfaces. From (28).

Fig. 5. Deposit pattern of nanoparticle suspensions with varying concentrations of salt (KCl). Modified from (29).

Fig. 6. The characteristics of a dried drop of human blood serum from a healthy individual. From (4).

Fig. 7. The characteristics of a dried drop of whole human blood from a healthy individual. From (55).

Fig. 8. Dried drop patterns from three different sized particles dispersed in three different solvents. From (67).

Fig. 9. Drop patterns and height profiles for evaporated drops of nanofluid with varying nanoparticle size. From (69).

Fig. 10. Micrograph of blood serum: (a) healthy individual, (b) and (c) patients with cancer. From (70)

Fig. 11. The pattern formed from the evaporation of a droplet of blood serum from two different individuals: (a) a woman who experienced full-term childbirth and (b) a woman who experienced preterm birth. The outer ring of crystals is indicated with the black arrow. From (40).

Fig. 12. Morphology of dried drops of serum from a healthy and seven ailing individuals. From (41).

Fig. 13. Morphology of dried drops of serum from healthy and ailing individuals. From (71).

Fig. 14. Cracking patterns of dried drops of serum. From (72).

Fig. 15. The pattern formed from the evaporation of a droplet of blood from four different individuals: (a) a healthy 27-year-old individual (female), (b) an individual with anaemia, (c) a healthy 31-year-old individual (male) and (d) an individual with hyperlipidaemia. From (55).

Fig. 16. The deposition pattern from the evaporation of a droplet of blood from three different persons: (a) a healthy 31-year-old individual (male), (b) a 19-year-old individual with thalassaemia (male) and (c) an infant with jaundice (male). From (75).

Fig. 17. The dry tear drops from three different persons: (a) a healthy individual, (b) a 40-year-old individual with moderate dry eye (female) and (c) a 72-year-old individual with severe dry eye (male). From (77).

Fig. 18. Deposition pattern of various biological fluids from different cattle groups: (a) a control, (b) bovine leukaemia virus positive and (c) bovine tuberculin positive. Modified from (86).

Fig. 19. Dried drop patterns from tequila adulterated with four different substances: (a) a control, (b) MEG (5 %v/v), (c) EtOH (10 %v/v), (d) Water (10 %v/v) and (e) MeOH (40 %v/v). From (87).

Fig. 20. Dried drop crystallisation patterns within drops of 4 different wheat cultivars: (a) Benco (BEN), (b) Nobel (NOB), (c) Gentil Rosso (GR) and (d) Inallettabile (INA). From (90).

Fig. 21. Dried drop patterns for soil with different fertilisers. From (7).

Fig. 22. Dried drop patterns from different soils with different fertilisers. From (7).

Fig. 23. Dried drop patterns from tap waters that underwent different treatments: (a) minimally treated groundwater, (b) lime softened, (c) ion exchange, (d) surface water source, (e) untreated groundwater and (f) reverse osmosis. Modified from (91).