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Melt electrowriting with additive manufacturing principles

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Abstract

The recent development of electrostatic writing (electrowriting) with molten jets provides an opportunity to tackle some significant challenges within tissue engineering. The process uses an applied voltage to generate a stable fluid jet with a predictable path, that is continuously deposited onto a collector. The fiber diameter is variable during the process, and is applicable to polymers with a history of clinical use. Melt electrowriting therefore has potential for clinical translation if the biological efficacy of the implant can be improved over existing gold standards. It provides a unique opportunity for laboratories to perform low-cost, high resolution, additive manufacturing research that is well positioned for clinical translation, using existing regulatory frameworks.

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Introduction

Tissue Engineering (TE) is a field of research that aims to safely manufacture implantable materials (scaffold & non-scaffold based) to treat injuries and diseases [1]. It is an inherently multidisciplinary field that promises to deliver a significant benefit to humanity, yet has long-standing limitations, notably in the translation of university-based research through to an implantable product that can be widely accessed by patients. Most recently, the adoption of automated processes in TE has given rise to biofabricated products, which address reproducibility and delivers a capacity to customize medical devices and tissue constructs [2].

There are many challenges in developing TE constructs for treating injury and disease, including for manufacturing methods which have recently trended towards additive manufacturing (AM) approaches [3–6]. This review on electrostatic writing technologies is focused on using polymer melts, since this provides the fastest way to clinically translate research and develop products for TE [5,7]. Most people consider electrospinning (derived from the term "electrostatic spinning") to be a dynamic manufacturing technology that produces ultra-fine diameter fibers in a chaotic deposition pattern [8–10]. Instead, *what if* the placement of every single electrospun fiber could be predetermined? *What if* the manufactured construct could reach milliliter volumes while maintaining accurate fiber placement? And, finally, *what if* the diameter of the electrospun fiber could be automatically controlled by over a magnitude, using the during scaffold manufacture? This review shows that electrostatic direct-writing technologies can deliver all the above, using polymers that have a history of use in clinical settings [11,12] and moreover, can achieve this with a solvent-free manufacturing approach.

Development of electrospinning for TE

Electrospinning was first reported as a method for manufacturing a biomaterial in 2001 by Bowlin and colleagues, on the basis that the small diameter filaments (including those made from collagen) mimic fibrillar structures found in extracellular matrix [13,14]. Since then, the use of electrospinning in TE research as a scaffold has significantly expanded, driven by numerous advantages of the technique [8]. These include the 1) low cost and 2) simplicity of establishing the process within a research laboratory, the 3) diversity of polymers (both synthetic and natural) compatible with the process [15] and 4) capacity to handle the resulting non-woven fabrics manufactured using electrospinning. A strategy, however, is required to induce porosity within a solution electrospun mesh, since randomly depositing sub-micron diameter fibers does not produce a material with sufficient pore size for cell invasion. In 2005, Mikos and colleagues demonstrated that when using a single collector configuration, electrospun fibers needed to be at least 3 μm in diameter, to generate pore sizes (20 μm) sufficient for cell penetration into the material [16].

Electrospinning as a technology that developed quite separately to AM (often described in the media as 3D

printing). In 2008, electrospinning was first used in combination with fused deposition modelling (FDM) to create a "bimodal" scaffold that contained both small diameter and large diameter elements [17,18]. In this instance, the ordered scaffold structure is still provided by the FDM component, while the electrospinning filled up the pores between each deposition layer to aid in cell-seeding. For the most part, electric instabilities that electrospinning researchers rely on to generate sub-micron diameter fibers is fundamentally incompatible with the need for accurate deposition required for AM. The first description of direct-writing using electrospinning was in 2006, where the term "near-field" electrospinning was introduced to the community [19]. In this configuration, the collector distance is very short, and a single layer of fibers could be deposited onto a substrate and controlled using stage movement. As shown later in this review, scaffolds with 200 layers can be direct written when the fluid used is a polymer melt.

Melt electrospinning is neither a new nor an unknown concept within the electrospinning community [8,9,20], however it remains an area of under-investigation [21]. Melt electrospinning was first described in a 1936 patent [22], in publications from 1981 [23–25], and first described post-1995 by Reneker and colleagues in 2001 [26]. Yet, to date, less than 1% of the electrospinning publications use solvent-free configurations [21,27]. While the first melt electrospinning publications described larger microfibers [23], there have since been numerous reports where sub-micron filament diameters are generated [28–30].

Up to 2015, 20 years after Reneker first published his key paper reintroducing "electrostatic spinning" to the research community [31], over 16,000 peer-reviewed journal articles have been published on this topic. However, even after considerable electrospinning research with polymers that have a history of use in clinical applications, there are a surprisingly low number of medical electrospun clinical products available for implantation (currently only Restorex for heart valves, produced by Xeltis, the Netherlands). While high quality electrospinning devices are now available to manufacture within a controlled environment, the inherent issue of solvent removal (and proving the solvent is removed) results in additional cost for medical device manufacture. As outlined here, switching from a polymer solution to a molten fluid with different electrorheological properties to polymer solutions improves the direct writing performance and stability.

Electrospinning versus electrowriting

The principle underlying controlled direct writing with electrified polymer jets is outlined by Sir Geoffrey Taylor in his seminal 1969 paper [32] on electrically-charged jets. To fully appreciate the distinction between "electrowriting" and "electrospinning", a different starting point to electrospinning is required to describe the method. It is well-known that a non-electrostatically charged falling fluid breaks into droplets – we see this every day, when a water tap is opened (Figure 1A) or honey is allowed to fall from a spoon (Figure 1B). Also well-known is that the location of these (Plateau-Raleigh) instabilities is influenced by the flow rate of the fluid column, and the height at which this non-charged fluid is falling from. In the context of a polymer solution (such as Golden syrup) falling as a column, the flow rate required before Plateau-Raleigh instabilities is significantly lower. However prior to Plateau-Raleigh instabilities, this fluid can be direct-written onto a moving collector (Figure 1C) [33].

What is less appreciated in the electrospinning community, is that the application of a voltage between the nozzle and the landing point of the fluid *stabilizes* the falling fluid (Figure 1D), preventing Plateau-Raleigh instabilities and permits a continuous column of liquid [32]. When the voltage is increased, the electrical instabilities (and corresponding non-predictive path) often associated with electrospinning are achieved (Figure 1D). Interestingly, once an applied voltage has reached a sufficient threshold to stabilize the falling fluid, then the voltage can be reduced, to a level well below the initial threshold (Figure 1E).

While in electrospinning, the electrical instabilities (often termed "whipping") are required to draw out the fiber to its final dimensions, electrowriting uses applied voltage in a different manner – *to permit continuous fluid deposition at low flow rates*. Depending on the configuration and fluid properties, these flow rates can be extremely low, with sub-micron fibers achieved even in the absence of whipping. While the difference between electrowriting and electrospinning is effectively the magnitude of applied voltage, the physical effect that is established is vastly different. Instead of sub-micron diameter electrospun fibers being generated due to "whipping", they are achieved in electrowriting by lowering the fluid flow rate and sustaining this with the application of an applied voltage.

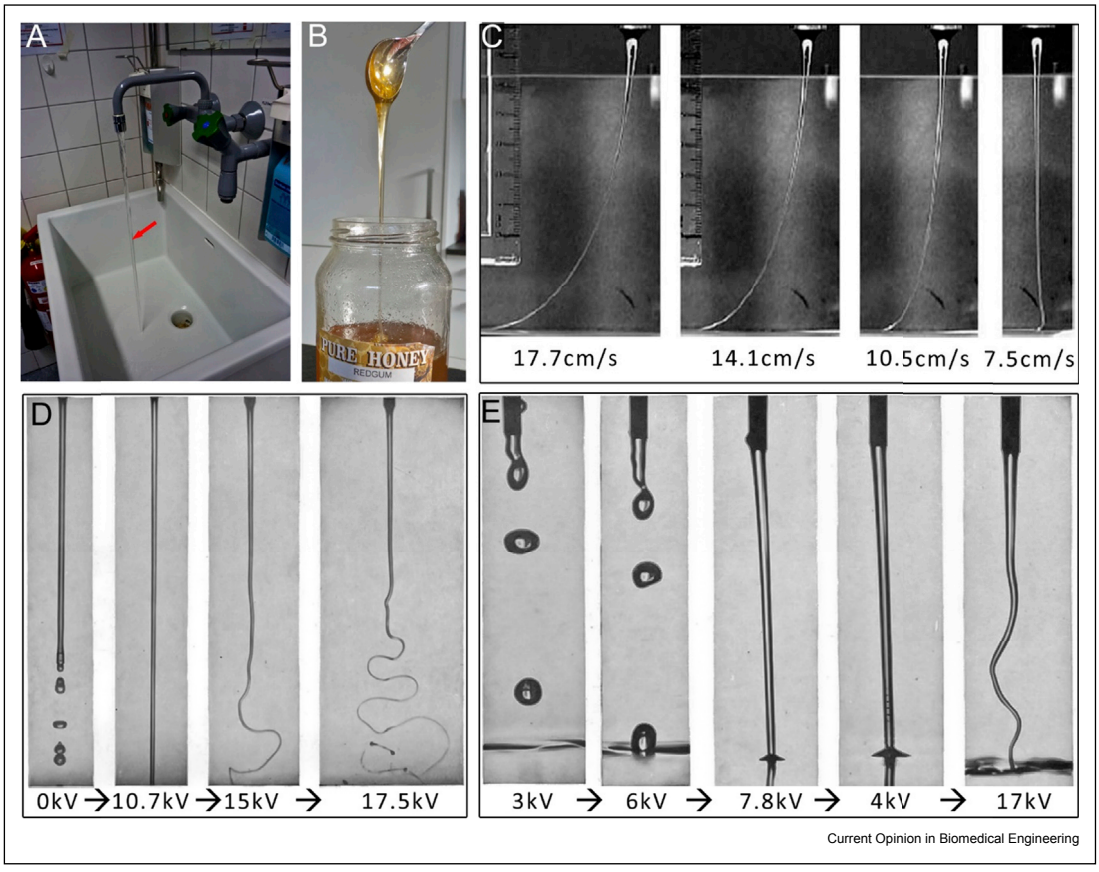
Electrostatic writing today

The underlying principles of controlled fluid deposition at low flow rates can be applied to many liquids, including polymer solutions and melts [34]. However, to generate a fixed structure after the direct writing, this fluid must be solidified. Solvent evaporation, coagulation baths and cooling are three approaches to achieve this fiber solidification that will be described in this review.

Solvent evaporation

First described in 2006, "near-field" electrospinning direct-writes polymer solutions onto a substrate aided

Figure 1



Examples of different non-charged and charged jets. Non-charged jets include A) the column of water (red arrow) that forms when a faucet is opened, or B) when honey is run as a column from a spoon. Due to Plateau-Raleigh instabilities, such jets will break up into droplets, with increasing height or lower flow rates. C) A non-charged Golden syrup jet being deposited onto a moving collector, with the speed indicated. D) Effect of applying a voltage to water when Plateau-Raleigh instabilities are occurring. When applying a voltage, the jet becomes continuous (at 10.7 kV), and then "whips" and breaks up at even higher voltages. E) Once a continuous water column is achieved with a threshold applied voltage (between 6 and 7.8 kV), the voltage can be reduced down to a level (4 kV) well below the threshold for stable jet establishment. Increasing the voltage to 17 kV shows the electrical instabilities associated with electrospinning. C is reproduced from Ref. [33], and D and E from Ref. [32] with permission.

by high voltages (Figure 2A and B) [19,35–37]. While solvent evaporation is excellent at producing a solidified fiber over a larger airborne period, shorter collector distances are more challenging. This is especially the case when electrical instabilities are present (i.e. electrospinning), that results in rapid removal of the volatile solvent. However, one challenge for this approach is to then accurately stack fibers, layer upon layer, so that a scaffold of significant volume can be fabricated. This approach has utility in other application areas such as electronics [38]. For a recent and excellent topical review on this method, you are directed elsewhere [39].

An alternative to solvent evaporation to fix a polymer solution jet into shape is with a coagulation bath. The coagulation bath can additionally induce porosity into the fiber, as can be seen in Figure 2C–E. One advantage of this process is that the coagulation bath can be a non-conductive fluid so that there is great flexibility as to what is included within the fluid that is being direct-written. The coagulation bath also permits repeated stacking of filaments, so that a voluminous object can be manufactured. It is a direct-writing approach that will improve with time, including the resolution of the filaments which is above 100 μm, and similar in dimensions to FDM [40].

A polymer melt only requires sufficient cooling to solidify during direct-writing. This happens after, or just prior to, the molten jet touching the collector. This largely depends on the processing parameters, and there is a slight embossing on the underneath of many MEW scaffolds [41] from the collector. In addition, electrohydrodynamic quenching occurs during melt electrospinning, where the movement of charged water vapor induces a cooling effect over the jet [42]. Figure 3F shows "figure of eight" patterns from a molten jet, demonstrating its liquid properties. When the collector

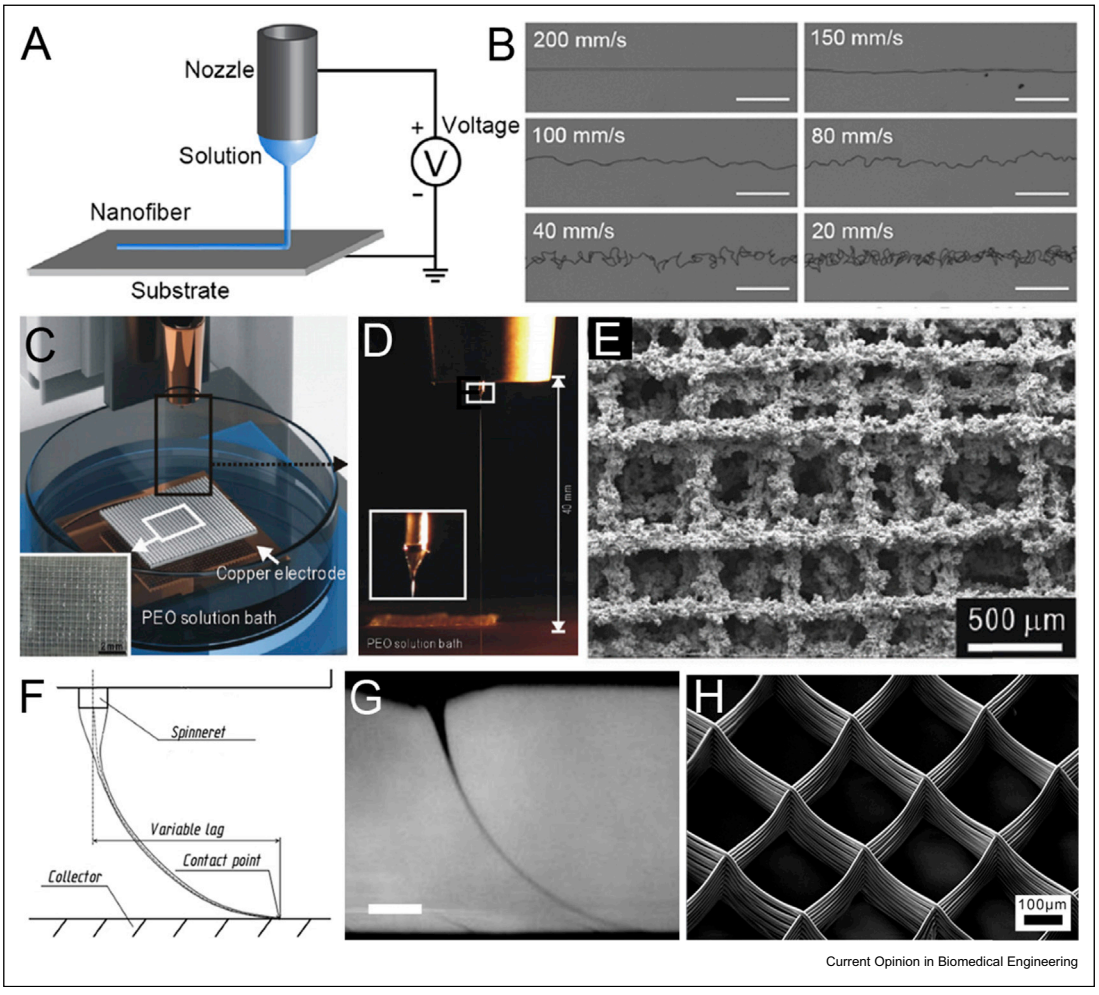
speed is increased further, straight lines of fibers are possible (Figure 3F) that accurately stack upon each other [41,43,44]. One important aspect of MEW is introduced here: the term "critical translation speed" (CTS). The CTS is the speed at which the collector matches the jet and a linear fiber is produced. With this repeated layering approach, a fibrous scaffold with microscale features can be fabricated (Figure 4A–E).

MEW for TE applications

There many ways to heat a polymer (electrical, laser, circulating fluids and heated air) [45–47] or deliver the polymer to the nozzle (syringe pump, air pressure, screw-extrusion) [48–50]. Furthermore, a range of configurations have been proposed for the collector (flat plate, rotating tube, parallel collectors, porous mesh) and nozzle (needleless, single- and multi-spinneret). For a full review on melt electrospinning and the configurations another, more comprehensive, review is recommended [27].

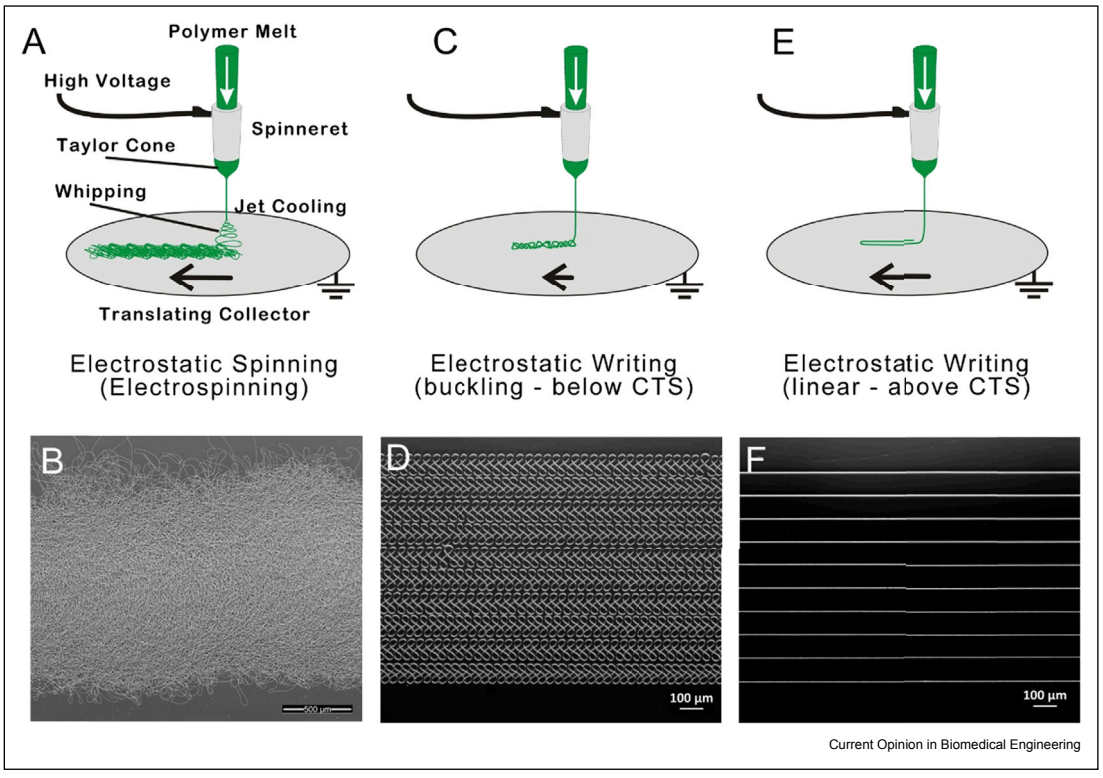
So far a handful of polymers have been processed via MEW including PCL [41], polypropylene [51], poly(L-lactide-co-ε-caprolactone-co-acryloyl carbonate) [52] and poly(2-ethoxy-2-ethyl oxazoline) [53], however it is likely that many more thermoplasts can be manufactured using this technique. This review emphasizes MEW and highlights three important aspects where MEW has potential to advance TE applications: 1) improved resolution, 2) ability to fabricate large volume scaffolds and 3) the ability to integrate multi-modal diameters into a single fabrication step.

Figure 2



Approaches to the direct writing of electrified jets. A) Near-field electrospinning of B) single fiber arrays with $Zn(CH_3COO)_2$/PVP solutions, where the deposited material is later calcined at 500C to obtain ZnO fibers. C–E) Solidification of a jet using a 5% PEO/H_2O coagulation bath. Here, a 4 cm charged jet of 12% PCL in an 80:20 solvent mixture of dimethylformamide and methylene chloride is direct written into the coagulation bath to produce E) a highly porous scaffold. F) shows a schematic of MEW and G) is a photograph of PCL molten jet. H) The electrorheological properties of the PCL melt allow defined scaffolds to be produced with this approach. A and B reproduced from Ref. [38], C–E is reprinted (adapted) with permission from Ref. [40] copyright (2011) American Chemical Society, and F-G is reproduced from Ref. [49] with permission. Figure H is a sample manufactured by Mr Almoatazbellah Youssef and imaged by Dr Claus Moseke (University of Würzburg).

Figure 3



Three different types of writing with polymer melts. When A) the fluid (PCL-*blend*/PCL-*block*-PEG) properties allow whipping, a line (B) of electrospun fibers is observed. When B) there is no whipping, and the speed of the collector is lower than the CTS, mechanical buckling (D) of the melt occurs. When E) there is no whipping and the speed is at CTS or above, a linear fiber (F) is direct-written. A, C and E modified from Ref. [44], B is previously unpublished and D-F are reproduced from Ref. [49] with permission.

Manufacturing resolution

MEW provides an extra manufacturing capability for TE researchers to design and investigate how higher resolution scaffolds interact with cells and tissue. Most MEW scaffolds described to date have a porosity of 87% or higher [54,55], and a fiber diameter typically ranging from 2 µm to 50 µm [27]. With such small diameter fibers (as composed to extruded struts made with FDM), the flexibility and compliance is high, and therefore of particular interest for soft tissue applications. Perhaps counterintuitively, high porosity (93%) MEW scaffolds significantly aid in increasing the mechanical properties of matrices [54], allowing the fiber/matrix composite to undergo high compressive loading which maintaining a "soft" matrix formulation that is compatible with embedded cells (Figure 4F).

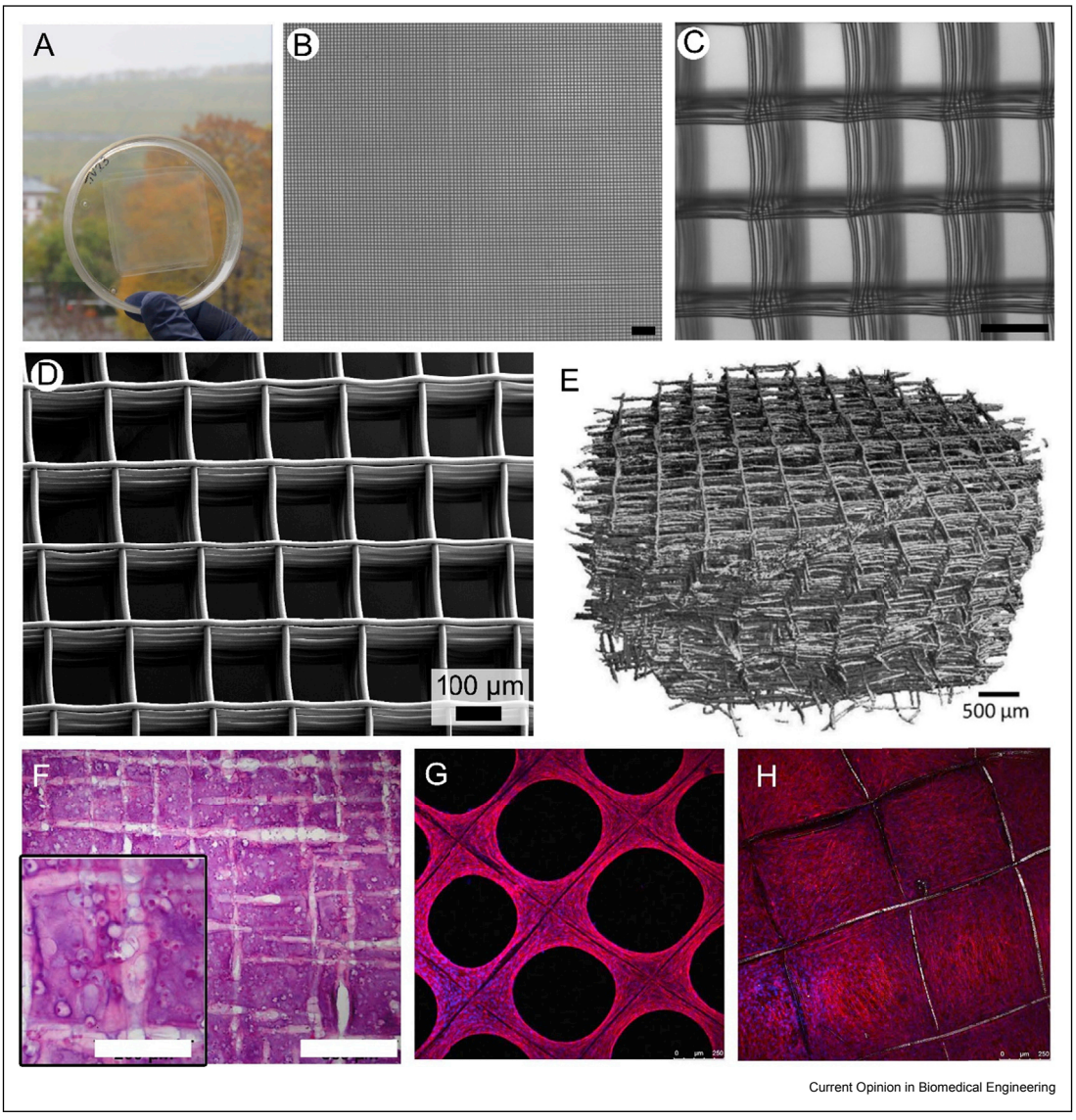
Voluminous scaffolds

Another major challenge facing TE is the manufacture of highly resolved scaffold morphologies in large volume (milliliter) dimensions [56,57]. Most tissues and organs have these volumes, and contain fine, complex ultrastructures. The incorporation of complex morphologies, that are anisotropic (and ideally patient customizable) into a TE scaffold is one area that AM is attempting to address. However, there are resolution levels that still require attaining to replicate the "delicate" morphologies of natural tissue. Therefore, AM improves on many conventional TE scaffold manufacturing technologies, including porogen leaching, which are isotropic in morphology. This capacity to fabricate scaffold anisotropy, however, must also be met with further improvements in resolution for AM technologies. In this context, MEW fibers are well defined, positioned and can stack upon each other to (currently) millimeter heights. While the literature has described mm thick MEW scaffolds [43,54], I have personally held and observed 7 mm thick constructs that were accurately manufactured within the Hutmacher laboratory. One restriction on an exhaustive study on the volume limits of MEW scaffolds is the time required to manufacture such samples. As mentioned later, scale-up manufacturing is the greatest current challenge for the technology.

Multi-modal scaffold design

One compelling aspect of MEW is that the flow rate to the nozzle largely determines the fiber diameter of the

Figure 4



MEW scaffolds made from PCL. A) With translucent, macroscopic properties, stereomicroscopy shows B) cm-range order with C) micron-scale precision. Quantitative SEM studies on MEW scaffolds show a low coefficient of variation (4%) for 15.4 ± 0.6 μm diameter deposited fibers. Depending on the "box" size, millimeter heights while maintaining accurate printing are achievable (E), shown here in a microCT scan. When MEW scaffolds are embedded within chondrocyte-containing matrices, the composite can be mechanically loaded. When large pore MEW scaffolds (98% porosity) are seeded with dividing and ECM-producing cells, a circular morphology is typically first observed (G), that later completely fills the scaffold (H). When (I) the flow rate is altered, different diameter fibers can be generated as shown here with PCL. Such different diameter fibers can be layered upon each other, shown in (J) with a false-colored SEM image. Figure A is previously unpublished, B and C reproduced from Ref. [27], D is reproduced from Ref. [49], E reproduced from Ref. [43], F reproduced from Ref. [54], G and H reproduced from Ref. [45]. All figures reproduced with permission.

printed material [41,49]. Air (or nitrogen) pressurization of the dispenser is the most effective and recommended method of dispensing, since this pressure can be electronically regulated within the printing script. MEW fibers have a range of diameters that are typically one (but sometimes two) magnitude different in diameter. Therefore, a pressure calibration curve can be generated and direct-writing can occur using any diameter within this range. The ability to change diameter so significantly during a print is one feature that neither solution electrospinning nor FDM can achieve. This adds an extra element capability that could significantly affect scaffold design.

Future directions

MEW provides the TE community with an additional option for the *reproducible* fabrication of materials at micro-scale resolutions in a manner that is likely

compatible with medical device regulatory processes [7,58]. The historical success of melt processing for medical devices (hernia meshes, fixation screws, sutures) over numerous decades is clear [59,60]. The more recent development of melt-extruded calvarial implants via FDM also establishes operating procedures and protocols for additive manufactured porous implants [61]. From a regulatory point of view, when MEW is compared to FDM, the key difference is the application of a voltage, which does not fundamentally alter the polymer composition. With melt processing providing the most rapid path to medical device translation, MEW is uniquely positioned to play a role in the translation of TE applications.

While MEW has similar complexities to FDM, it is significantly more difficult to establish than conventional solution electrospinning. For this AM technology to become widely adopted, it must be accessible to both researchers and the end user. Indeed, both FDM and electrospinning are low-cost technologies, and MEW is an extension of these two manufacturing classes. While MEW printers have always been custom-built in my laboratory, there are numerous private companies working to fill this "access" gap. The Hutmacher laboratory at the Queensland University of Technology, however, has constructed MEW printers for other laboratories. There are, to the extent of my knowledge, only three companies that are in the process of establishing, or already advertise, a MEW printer: RegenHU (Switzerland), GeSIM (Germany) and Spraybase (Ireland). To make such a technology accessible, low-cost options for MEW printers, as well as software to aid in the design and manufacturing of the TE scaffold, are required.

Similarly, for TE to really entrench itself within global healthcare, low-cost methods that reduce the price of an implantable construct are required. While it may appear to be contradictory, the ability to deliver an implantable material that is both further improved and inexpensive over existing gold standards is one challenge that AM technologies could provide. Even using medical-grade polymers for MEW, the material cost of manufacturing a tube, for example, via MEW is less than 1 cent.

While many of the fundamental aspects of MEW (reproducibility, control) are excellent, there remain challenges for the technology to expand into wider use. Probably the greatest limitation is the manufacturing time using a single nozzle. Since each filament is direct-written, samples can take time to be completed — typically numerous hours, depending on the processing parameters and size/layers of the print. Mitigating this challenge is that MEW printers can operate for long periods — overnight or over multiple days. While this is suitable for a research laboratory, developing scale-up approaches to significantly increase the manufacturing output is essential.

At essence, the principle of MEW is simple: a molten jet can be stabilized with an applied voltage so that low flow rates are achieved. This jet can then be direct-written onto a surface, and can be done so with minimal fluctuations or changes in manufacturing tolerances. There are a multitude of TE applications where MEW scaffolds have utility, such as 1) reinforcement structures for cartilage repair [54], 2) artificial ligaments/tendons [52], 3) periosteum TE [62] or 4) as nerve guidance conduits. Furthermore, the defined MEW morphology permits *in vivo* analysis of the foreign body reaction [63] and the establishment of humanized mouse models for cancer research [64,65]. One fabricated, a MEW scaffold is ready to be used or prepared for the next stage of the manufacturing process. One concluding remark needs to be made on this emerging AM process; the capability of MEW is constantly improving, and current research has barely scratched the surface on what will be a potent and reliable manufacturing technology.

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Conflicts of interest

None declared.

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