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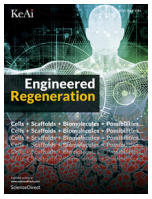

Cell electrowriting: An advanced biofabrication approach for micrometre-scale living tissue fabrication ☆

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ABSTRACT

The precise replication of native tissue microarchitecture remains a key challenge in biofabrication. While extrusion-based bioprinting fabricates multicellular constructs for regenerative medicine and drug testing, its typical resolution (~100 μm) is insufficient to reproduce <50 μm features such as capillaries, aligned myofibres, etc. Electrohydrodynamic (EHD) approaches, such as melt electrowriting (MEW), address this limitation by producing polymer fibres of 1–500 μm in diameter by applying high voltages. Cell electrowriting (CEW) expands this principle to living systems, aiding the direct deposition of cell-laden hydrogel fibres with diameters of 5–40 μm, thereby supporting microscale cell placement and architectures that are unachievable with conventional methods. This review discusses the principles of CEW, strategies for bioink formulation, and assessments of biological performance, with emphasis on recent advances in CEW-based printing approaches. The potential applications, challenges, and outlook of CEW for tissue engineering are also discussed.

1. Introduction

Tissue engineering is an interdisciplinary approach that aims to address the limited availability of donor organs using advanced fabrication approaches. In the early stages, scaffolds were developed using various methods, such as solvent casting, electrospinning, particle leaching, hydrogels casting, etc. Cells were then seeded into these bulk scaffolds [1,2] (Fig. 1A-C). Over the last two decades, several advanced fabrication strategies, such as 3D printing, bioprinting, self-assembled cell-laden materials, organoids, etc., have been developed to closely mimic native tissue architectures [3,4]. Among various bioprinting approaches, extrusion and volumetric bioprinting techniques have shown great promise in developing complex tissues and organs, which have been widely utilised for tissue regeneration and drug testing applications [5,6] (Fig. 1D). However, with a resolution typically limited to approximately 100–200 μm, extrusion bioprinting struggles to precisely develop microvascular structures and mimic the cellular arrangement of native tissues [7]. Therefore, further advances are needed to achieve resolutions below 50 μm to overcome these limitations.

Recently, electrohydrodynamic (EHD) based printing methods, such as melt electrowriting (MEW), have demonstrated the potential for printing polymer fibres with diameters ranging from 1 to 500 μm [8]. Melt electrowriting is a polymer melt-based technique in which the molten thermoplastic polymer is extruded by applied pressure and subsequently deposited on the platform under the influence of a strong electric field between the nozzle and the collector [9] (Fig. 1E). Various thermoplastic polymers, such as polycaprolactone (PCL), poly lactic acid (PLA), polyhydroxyalkanoates (PHAs), poly(L-lactic acid) (PLLA), etc., are commonly used to produce scaffolds using MEW [10–13]. Also, tissues such as cardiac, skeletal muscle, cartilage, bone, and skin have been fabricated with micron-level precision scaffolds, preserving their anisotropy. Further, specific cell types were seeded on these scaffolds to promote cell proliferation and maturation [14,15]. Subsequently, researchers developed composite scaffolds by incorporating cell-loaded hydrogels into MEW scaffolds, utilising the MEW scaffolds for mechanical support [16,17]. Yet, producing live cell-embedded scaffolds is challenging using MEW, as it requires higher temperatures for polymer melting and limited availability of cytocompatible polymers.

Cell electrowriting (CEW) emerged as a potential alternative to MEW, enabling the fabrication of cell-laden, high-resolution structures with living cells through electrically assisted printing (Fig. 1F). CEW utilises cell-laden, hydrogel-based polymers as bioinks [18]. Applied pressure extrudes the bioink through the nozzle, while an electric field between the nozzle and the platform draws it into ultra-fine fibre jets, enabling the deposition of aligned, *in situ* crosslinkable hydrogel fibres with diameters in the tens of micrometres range [7]. CEW facilitates the precise placement of distinct cell types, providing a significant advantage over conventional biofabrication techniques by more

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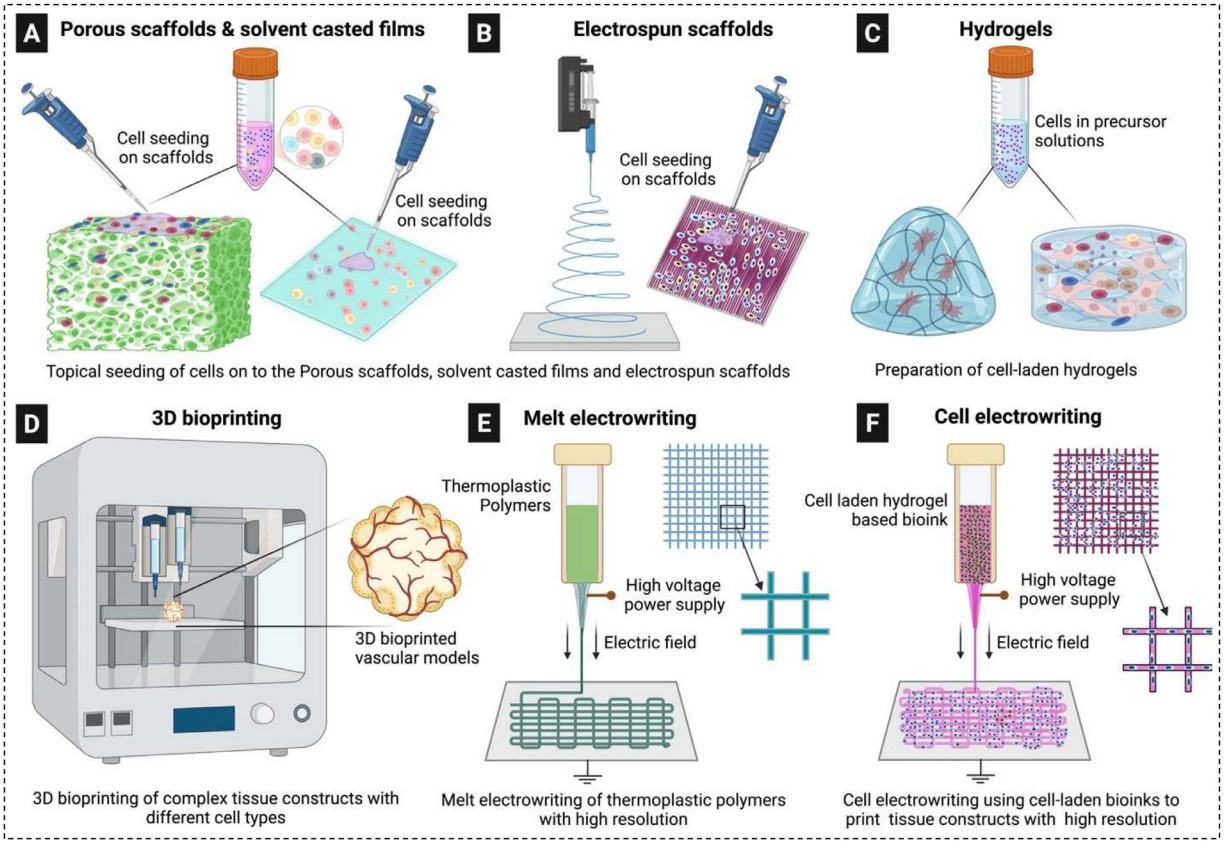

Fig. 1. Progression of tissue engineering strategies. **[A]** Porous scaffolds and solvent-cast films are used for topical cell seeding. **[B]** Electrospun scaffolds provide fibrous networks for cell attachment. **[C]** Hydrogels support encapsulation of cells within precursor solutions. **[D]** 3D bioprinting of complex tissue constructs with multiple cell types and vascular models. **[E]** Melt electrowriting of thermoplastic polymers to produce high-resolution scaffolds. **[F]** Cell electrowriting using hydrogel-based bioinks for high-resolution fabrication of cell-laden constructs.

accurately replicating the heterogeneous cellular architecture of native tissues.

In this article, we compared CEW to extrusion bioprinting and MEW to understand their working principles. We also discussed process optimisation and the materials used in CEW, as well as the impact of printing on cell viability and heterocellular printability. Further, we explored both current and emerging applications of CEW, discussed key technological challenges, and provided an outlook for this advanced platform in fabricating living tissues with high resolution.

2. Comparison of extrusion bioprinting, MEW, and CEW

Extrusion bioprinting and melt electrowriting (MEW) represent two contrasting approaches within biofabrication, each with distinct strengths and limitations [17,19]. Extrusion bioprinting is highly versatile, supporting a wide variety of natural and synthetic hydrogel bioinks while enabling centimetre-scale constructs suitable for tissue models and organoid systems. However, its filament diameters typically range between 100–500 μm, which limits microscale fidelity and restricts the recreation of structures at the level of single cells or capillary networks [20,21]. MEW, in contrast, provides unparalleled structural precision, producing fibres as thin as 1–500 μm with excellent reproducibility and mechanical performance. Yet, because it relies on molten thermoplastics, MEW cannot directly incorporate viable cells, and biological complexity must be introduced through post-seeding, which often results in reduced efficiency and poor spatial organisation [22,23].

This technological divide creates a gap between structural precision and biological relevance. Extrusion methods readily generate heterogeneous, cell-laden constructs but lack fine control over alignment and microscale organisation [24]. MEW scaffolds, while mechanically robust and architecturally refined, fall short in replicating the cellular composition and functional heterogeneity of living tissues [25]. As a result, neither extrusion nor MEW alone fully addresses the challenge of engineering constructs that are both biologically functional and structurally biomimetic.

Cell electrowriting (CEW) fills this gap by utilising electrohydrodynamic jet stabilisation for high-resolution deposition while maintaining the bioink compatibility of extrusion-based bioprinting. CEW enables the high-resolution arrangement of viable cells with retained functionality by depositing hydrogel fibres measuring 5–40 μm, which are close to the size of individual cells [26,27]. This hybrid capability allows CEW to achieve a balance between the microscale fidelity of MEW and the biological integration of extrusion, positioning it uniquely as a complementary platform in multimodal biofabrication pipelines. A comparative overview of these techniques is summarised in Table 1.

3. CEW Process optimisation & fundamental

3.1. Bioink design: balancing electroresponsiveness with biocompatibility

Developing bioinks for CEW is a challenge because they must simultaneously perform two crucial functions: respond predictably to an applied electric field and provide a supportive environment for living cells. Hydrogels, such as gelatin methacrylate (GelMA), alginate, Poly(ethylene glycol) diacrylate (PEGDA), silk fibroin, and hyaluronic acid derivatives, are commonly used, but they are rarely used in their pristine form. Instead, they are often blended or chemically modified to adjust viscosity and improve gelation properties, as small changes in

Table 1
Comparative overview of extrusion bioprinting, melt electrowriting (MEW), and cell electrowriting (CEW).

Feature	Extrusion bioprinting	Melt electrowriting (MEW)	Cell electrowriting (CEW)
Printing principle	Pneumatic/mechanical extrusion	Electrohydrodynamic jetting of molten polymer	Electrohydrodynamic jetting of cell-laden bioink
Resolution	100–1000 μm	1–500 μm (typically 10–50 μm)	5–40 μm
Bioinks/biomaterial inks	Natural/synthetic hydrogels, cell suspensions, composite bioinks	Thermoplastic polymers (PCL, PLA, PHAs, PLLA)	Cell-laden hydrogels with electrical conductivity
Construct thickness	Millimetres to centimetres	Hundreds of micrometres to millimetres	Tens to hundreds of micrometres
Cell compatibility	Direct printing of encapsulated/suspended cells; viability affected by shear stress	Acellular scaffolds requiring post-fabrication cell seeding	Direct printing of viable cells in aligned patterns
Cell viability	High (>80 %)	N/A	Moderate to high (70–95 %)
Mechanical properties	Soft hydrogels with limited load-bearing capacity	High stiffness; tunable mechanical performance	Hydrogel-dependent
Stage of development	Mature; widely adopted and commercialized	Advanced; extensively studied for microfabrication	Emerging; proof-of-concept stage
Scalability	High	Low to moderate	Low
Applicability	Tissue models, organ-on-chip devices, drug testing platforms	Bone, cartilage, tendon scaffolds; mechanically demanding tissues	High-fidelity heterocellular constructs; aligned tissue models
Advantages	Versatile, scalable, high throughput	Microscale precision; high mechanical strength	Cellular alignment with microscale resolution; single-cell patterning capability
Limitations	Limited resolution (>100 μm); weak mechanical properties	Acellular (requires post-seeding); limited construct thickness	Narrow processing window; low throughput; limited construct thickness
References	[28,29]	[9,30]	[26,27]

the viscoelasticity of the inks can determine jet stability [26,27]. Additives such as polyethylene oxide are commonly used to enhance shear-thinning behaviour, while controlled ionic components, including salts or polyelectrolytes, are used to tune electrical responsiveness under applied voltage [31]. In this review, cell-laden electrowriting approaches that employ near-field electrohydrodynamic deposition of hydrogel fibres containing living cells are discussed within the broader framework of cell electrowriting (CEW), irrespective of the specific terminology used in the original studies.

Unlike earlier electrohydrodynamic printing studies limited by large nozzle-to-collector distances (>600 μm) and coarse filament widths (>200 μm), Jiankang He et al. demonstrated that insulating substrates combined with a reduced 100 μm gap lowered currents to <10 μA, enabling ~82 μm filaments with >95 % cell viability. However, their alginate-based system relied on calcium diffusion, which restricted multilayer stacking to ~20 layers due to slow gelation [26]. Miguel Castilho et al. advanced CEW by developing protein-based photoresponsive bioinks (gelnor and silk fibroin) that crosslink within seconds under visible light. By incorporating polyethylene oxide (PEO) to adjust viscosity, they achieved stable jetting, fibre diameters of 5–40 μm approaching single-cell dimensions, and improved structural fidelity without fibre spreading [27]. These developments have advanced CEW from a proof-of-concept to a reliable tool for fabricating viable microscale constructs.

Extending CEW bioink design beyond protein-based systems, Han et al. demonstrated that synthetic hydrogel platforms can be rationally tailored to meet the electrohydrodynamic requirements of cell electrowriting. Using polyethylene glycol diacrylate (PEGDA)-based hydrogel blended with extracellular matrix components, they highlighted that relatively lower electrical conductivity can be advantageous for maintaining electric field stability during printing, particularly when compared with more ionically conductive hydrogels. Rapid photocrosslinking preserved fibre morphology during deposition, while the incorporation of ECM provided biological cues without compromising print fidelity [31]. These studies confirmed that CEW supports rational bioink optimisation without sacrificing microscale resolution or direct cell encapsulation, in contrast to extrusion bioprinting and MEW.

3.2. Electrohydrodynamic parameters and stability

Like other electrohydrodynamic (EHD) biofabrication methods, CEW relies on controlled Taylor cone formation and jet stabilisation under near-field electrohydrodynamic conditions, principles that are also fundamental to MEW [32]. Electrostatic forces, surface tension, and fluid mechanics must be finely balanced to sustain continuous jetting; even minor disturbances can cause dripping, whipping, or fibre breakage [33]. Unlike MEW, which processes molten polymers, CEW employs hydrogel bioinks laden with living cells. The biological sensitivity of these systems, combined with the variable rheology of hydrogels, substantially narrows the operational window, demanding stricter process control to ensure both structural fidelity and cell viability.

Experimental studies have begun to define the parameters that support CEW stability. Jiankang He et al. demonstrated that using an insulating substrate with a nozzle–collector distance of ~100 μm reduced electrical currents to the microampere range (<10 μA), enabling the formation of continuous hydrogel filaments as thin as ~82 μm while maintaining greater than 95 % cell viability (Fig. 2A) [26]. In contrast, Miguel Castilho et al. employed a larger nozzle–collector distance (~5 mm) with photoresponsive protein-based bioinks (gelnor and silk fibroin), establishing operating ranges for voltage, pressure, and collector velocity that maintained jet stability while minimising cellular stress [27]. Both studies confirmed that deviations from these conditions produced jet coiling, fibre buckling, or reduced viability, highlighting the tight tolerances of the process. In addition to geometric and electrical parameters, Han et al. showed, using a cell-laden electrowriting approach, that bioink electrical conductivity strongly influences jet stability, with lower-conductivity PEGDA-based hydrogels supporting stable fibre deposition across a wider voltage range than more ionically conductive systems [31]. From these findings, CEW has been reported to operate within approximate ranges of 2–10 kV applied voltage, flow rate range from ten to several hundred microlitres per hour, nozzle–collector distances of 0.1–5 mm, and collector speeds of 10–100 mm/s, depending on the bioink system and cell type used.

At low collector speeds, thicker filaments with increased local cell density were obtained whereas high collector speeds led to jet instability, filament discontinuity, and reduced cell density. Furthermore, this approach also supported the deposition of multilayered constructs up to 20 layers, confirming the suitability of electrowriting under optimised conditions (Fig. 2B). Another study found that stable, straight fibres were obtained at around 3.0 kV, while higher voltages (≥5.0 kV) caused jet coiling and morphological instabilities. Collector velocity further showed fibre alignment, with insufficient speeds causing buckling and optimal values producing uniform filaments. At the scaffold level,

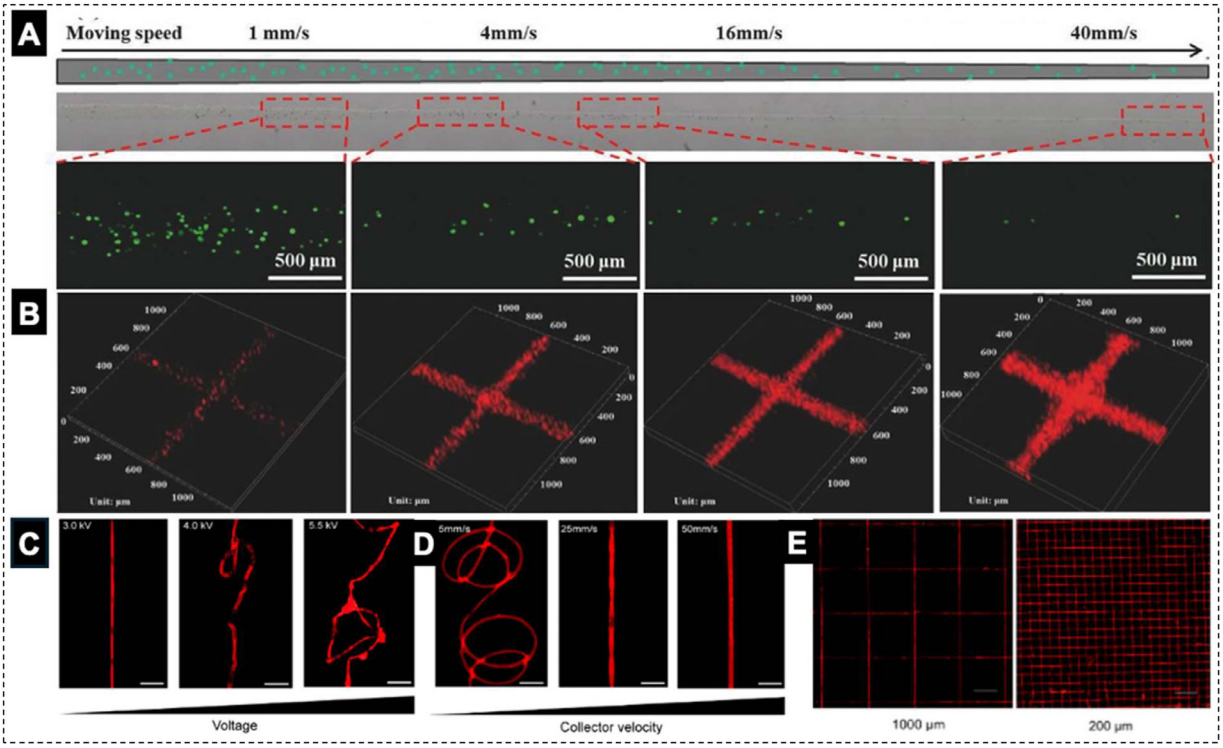

Fig. 2. Influence of processing parameters on CEW fibre formation, cell distribution, and scaffold architecture. **[A]** Effect of collector moving speed (1–40 mm/s) on cell distribution and alignment within printed hydrogel filaments. Fluorescent microscopy images (green: live cells) show reduced cell density with increasing speed, while corresponding 3D reconstructions confirm continuous filament deposition at higher speeds (scale bar: 500 μm). **[B]** Confocal 3D projections demonstrating the fidelity of cross-shaped constructs fabricated under varying collection conditions (single, five, ten and twenty-layer alginate filaments). Reproduced with permission from [26], Copyright 2017, WILEY-VCH Verlag GmbH & Co. **[C]** Effect of applied voltage (3.0–5.5 kV) on fibre morphology, illustrating transition from straight to unstable/coiled jets at higher voltages. **[D]** Influence of collector velocity (5–50 mm/s) on fibre straightness, showing coiling at low speeds and uniform fibres at optimal conditions. **[E]** Representative CEW scaffolds with square pore architectures (1000 μm and 200 μm), highlighting the ability to fabricate ordered microstructure constructs with high resolution and reproducibility. Reproduced under the terms of the CC-BY-NC–ND from [27], Copyright 2021, American Chemical Society.

these optimised conditions enabled the fabrication of ordered lattices with pores as small as 200 μm, demonstrating CEW's capacity for reproducible, high-resolution, cell-laden architectures (Fig. 2C-2E).

3.3. Cell viability under electrical stress

In CEW, the key optimisation lies in balancing jet stability with the protection of cells from the forces essential to fibre formation. Higher applied voltages can stabilise the jet but may increase the risk of cellular damage through mechanisms such as electroporation, joule heating, or oxidative stress if not accompanied by appropriate current control. Jiankang He et al. showed that fibroblast survival dropped sharply at 4 kV, highlighting the narrow safe operating window. Importantly, they also demonstrated that cell safety is dictated more by electrical current than voltage alone; by using insulating substrates to reduce current from milliamperes to microamperes, viability above 95 % was maintained even at 3 kV [26]. Miguel Castilho et al. extended this biological perspective by showing that equine MSCs encapsulated in gelatin- and silk-based CEW fibres not only survived but spread and aligned, benefiting from protein-rich bioinks that promote adhesion compared to alginate [27]. Nevertheless, cell survival rates above 70 % are often reported in CEW studies, which is broadly comparable to extrusion-based printing.

One of the key benefits of CEW lies in its capacity to direct cell alignment along the axis of deposited fibres. On the other hand, MEW commonly produces acellular scaffolds; however, subsequent cell seeding rarely achieves comparable alignment [34,35]. While extrusion printing exposes cells to mechanical shear forces within the nozzle and generally results in thicker fibres (100–1000 μm), it often lacks the refined guidance cues characteristic of CEW [36–38].

3.4. Heterocellular constructs & demonstrated applications

The ability to fabricate complex tissue architectures and non-linear geometries is crucial for replicating the hierarchical organisation of native organs. Many tissues, such as myocardium, skeletal muscle, and neural networks, depend not only on the presence of multiple cell types but also on their precise alignment and spatial arrangement within intricate three-dimensional structures [39–42]. Achieving such precision requires techniques that combine high resolution with multi-material flexibility.

As illustrated in Fig. 3, CEW addresses this need by producing highly ordered microfibrous scaffolds that differ sharply from extrusion-based constructs. Extrusion printing of GelNOR or silk generates relatively thick filaments and large pores (Fig. 3A). Conversely, CEW produced finer, well-aligned fibres with hexagonal pore geometries and higher architectural fidelity (Fig. 3B). Moving beyond single-material systems, multi-material CEW enables the deposition of alternating bioinks within the same lattice, creating heterogeneous constructs (Fig. 3C). Miguel Castilho et al. confirmed that these CEW-printed scaffolds not only had superior structural resolution but also exhibited improved stiffness due to enhanced fibre alignment, while maintaining high post-printing viability of encapsulated mesenchymal stromal cells (>70 %) demonstrating clear cytoskeletal organisation and alignment along fibre axes, a feature that distinguishes CEW from conventional extrusion approaches where cellular orientation remains largely random [27].

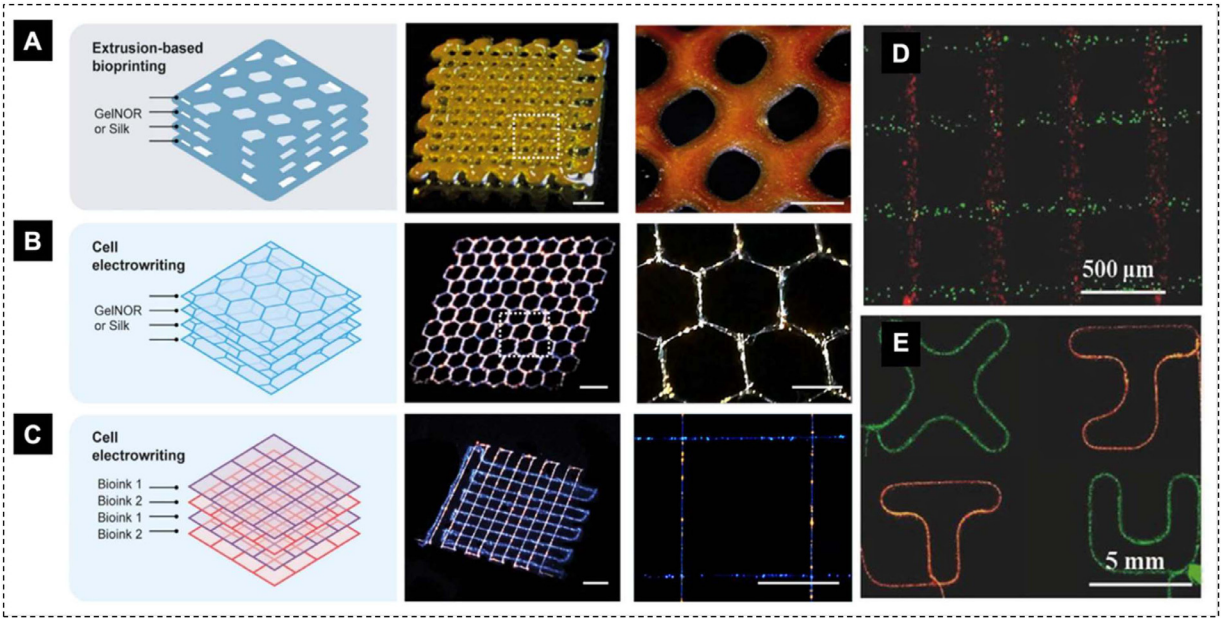

Fig. 3. Comparison of extrusion-based bioprinting and cell electrowriting (CEW) for protein-based hydrogel constructs. **[A]** Extrusion-based bioprinting of GelNOR and silk fibroin hydrogels results in relatively large filament diameters and pore sizes, with limited resolution (brightfield and stereomicroscopy images, scale bars: 1 mm). **[B]** CEW enables fabrication of highly ordered microfibrous hydrogel scaffolds with significantly finer features and hexagonal pore geometries, demonstrating improved resolution and architectural fidelity (scale bars: 500 μm). **[C]** Multi-material CEW using alternating hydrogel bioinks allows spatial patterning of distinct bioinks within the same construct, illustrating the potential for heterogeneous architectures (scale bars: 500 μm). Reproduced under the terms of the CC-BY-NC–ND from [27], Copyright 2021, American Chemical Society. **[D]** Confocal fluorescent images of CEW-printed cell-laden fibres (live cells in green, dead cells in red), showing high post-printing viability and ordered distribution within the lattice (scale bar: 500 μm). **[E]** Multi-material CEW constructs with curved geometries, highlighting the versatility of CEW for complex design fabrication (scale bar: 5 mm). Reproduced with permission from [26], Copyright 2017, WILEY-VCH Verlag GmbH & Co.

Confocal images further confirm that CEW-printed cell-laden fibres maintained high viability, with live cells (green) distributed uniformly along the lattice (Fig. 3D). Furthermore, CEW has the ability to fabricate complex, curved geometries with distinct bioinks (fluorescently labelled), showcasing its versatility in producing non-linear, heterocellular designs (Fig. 3E) that mimic the features of vascular bifurcations, neural tracks, or layered skin tissues [26]. Han et al. demonstrated that CEW-printed PEGDA/ECM hybrid scaffolds could support post-printing cell migration, spatial reorganisation, and tissue-specific matrix formation. Applied to cartilage tissue engineering, the microscale fibre organisation and ECM supplementation promoted chondrogenic matrix deposition, underscoring the relevance of CEW for load-bearing, anisotropic soft tissues [31].

4. Challenges & future directions

CEW is an advanced biofabrication approach that can create precise, micro-scale tissue structures with its ability to replicate the cellular organisation of native tissues. However, several significant challenges need to be overcome to fully utilise CEW for clinical applications. Firstly, CEW is highly sensitive to a combination of environmental conditions and process-related factors, both of which directly influence printing fidelity and cell viability. Fluctuations in temperature and humidity can alter charge distribution and disturb the delicate balance required for a stable jet, while even minor variations in laboratory airflow or ambient vibrations may deflect its trajectory and reduce reproducibility. At the same time, process-related factors intrinsic to CEW further complicate fabrication outcomes. Jet instability remains a major challenge, often triggered by imbalances in applied electric field strength, flow rate, nozzle-to-collector distance, or bioink viscosity, leading to uneven fibre deposition, compromised resolution, or structural discontinuities. The behaviour of bioinks under electric fields adds another layer of complexity, as properties such as conductivity, gelation kinetics, and charge accumulation dictate whether a jet remains stable or collapses prematurely. Future progress in CEW is therefore likely to depend on the integration of real-time monitoring and feedback-controlled systems capable of dynamically adjusting electrical and mechanical parameters to stabilise jet behaviour.

The current reliance on single-nozzle configurations restricts the architectural complexity of CEW constructs, resulting in tissues that are relatively uniform in composition. This limitation contrasts with clinically relevant tissues, such as myocardium or skeletal muscle, which require precise spatial organisation of multiple cell types, anisotropic microstructures, and coordinated integration of supporting components, including vasculature and innervation. Meeting this level of biological complexity will likely depend on the development of multi-nozzle and coaxial printing systems capable of co-depositing different bioinks and cell populations with spatial precision. At the same time, balancing resolution with scalability remains a major hurdle, as CEW can achieve fine features but struggles to build centimetre-scale, vascularised constructs.

A further limitation of CEW lies in the narrow selection of bioinks that are truly compatible with the technique. Formulations are often difficult to balance, since parameters such as gelation speed, electrical conductivity, and cell compatibility interact in ways that are not always predictable. This restricts the diversity of tissues that can currently be engineered, making it difficult to consistently reproduce outcomes across laboratories.

In recent years, combinational approaches, such as integrating MEW scaffolds with extrusion inkjet bioprinting, have been used to deposit cell suspensions [43,44]. However, these workflows face inherent challenges: MEW and hydrogel deposition occur as separate, sequential processes, resulting in imperfect interfacial integration and limited control over cell positioning relative to fibrous structures. Furthermore, inkjet bioprinting, though capable of single-cell resolution, struggles with hydrogel viscosity constraints and lacks the continuous fibre formation required for aligned tissue architectures. CEW has been explored as an

alternative approach by depositing cells within aligned hydrogel fibres, thereby reducing the need for post-seeding and enabling more precise spatial control over cellular organisation.

5. Conclusions

Cell electrowriting (CEW) has progressed beyond its initial role as a technical demonstration and is emerging as a platform that redefines the interplay of resolution, cell viability, and functional relevance in biofabrication. Positioned between extrusion bioprinting and melt electrowriting, CEW reflects a broader paradigm shift: the advancement of the field relies less on individual technologies and more on their integration within complementary biofabrication strategies. CEW demonstrates the potential for biologically relevant microscale control, yet critical limitations remain in process robustness, bioink development, and construct scalability. Key unmet needs include standardised bioink libraries, predictive models for electrohydrodynamic stability, and approaches to fabricate thicker, mechanically reinforced constructs without compromising cell health. CEW offers promising opportunities in heterocellular tissue models and related biofabrication systems but requires substantial optimisation prior to clinical and industrial translation. Future advances in bioinks, hardware integration, and automation are expected to play a crucial role in enhancing process reliability and facilitating the progression of CEW toward clinically and industrially relevant applications.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare they have no conflicts of interest.

CRediT authorship contribution statement

Harshavardhan Budharaju: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing.

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