

Advanced Tissue Scaffold Fabrication Techniques

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ABSTRACT

Tissue engineering has always been bottlenecked by the scaffold. You can have the most elegant cell source and the cleverest growth factor cocktail, but if the scaffold cannot guide cells into the right three-dimensional architecture, the construct will not function as intended. Over the past decade the fabrication toolkit has expanded dramatically -- from conventional electrospinning and solvent casting to extrusion-based 3D bioprinting, melt electrowriting, two-photon polymerisation, and decellularised extracellular matrix platforms -- yet systematic comparisons across techniques remain rare. Most published studies champion a single fabrication method for a single tissue type, making it difficult to judge which approach offers the best all-round performance. We evaluated 210 tissue scaffold fabrication programmes spanning five technique families, collected from partner laboratories in France and Sweden between 2019 and 2023. A Scaffold Fabrication Quality Index (SFQI) was constructed from five weighted sub-scores: architectural fidelity, mechanical match, cell viability post-fabrication, degradation tunability, and manufacturing scalability. Weights came from regression against translational outcomes. SFQI predicted successful translation with $r = +0.84$ and $AUC = 0.883$. Extrusion bioprinting programmes scored highest (mean SFQI 0.819), while conventional solvent-casting programmes trailed at 0.591. Only 35.7 percent of programmes exceeded SFQI of 0.75, pointing to broad room for fabrication process optimisation.

Keywords: tissue scaffolds; bioprinting; electrospinning; melt electrowriting; two-photon polymerisation; decellularised matrix; SFQI; tissue engineering; biofabrication; France; Sweden

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1. Introduction

1.1 The Scaffold Problem

If you think of tissue engineering as a three-legged stool -- cells, signals, and scaffolds -- it is the scaffold leg that has proven hardest to get right. Cells can be sourced from patients or from well-characterised stem cell banks. Growth factors and cytokine cocktails are increasingly available off the shelf. But the scaffold has to do something far more nuanced: provide a three-dimensional template with pore sizes, fibre orientations, mechanical stiffness, and degradation kinetics that match the target tissue closely enough for cells to behave as they would in vivo. Get the pore size wrong and cells cannot migrate through the structure. Get the stiffness wrong and mechanosensitive cells differentiate down the wrong lineage. Get the degradation rate wrong and the scaffold either collapses before new tissue forms or hangs around long after it has become an obstacle. These requirements are specific to each tissue type, which is why no single fabrication technique dominates the field.

1.2 An Expanding Toolbox

The fabrication landscape has changed enormously since the days when salt-leaching and freeze-drying were the go-to methods. Electrospinning produces nanofibrous mats that mimic the fibrillar structure of native extracellular matrix and has become a workhorse for skin, vascular, and neural tissue scaffolds. Extrusion-based bioprinting allows layer-by-layer deposition of cell-laden hydrogels with millimetre-scale spatial control. Melt electrowriting combines the resolution of electrospinning with the geometric precision of 3D printing, depositing molten polymer fibres along programmed paths to create scaffolds with ordered microarchitectures. Two-photon polymerisation pushes resolution further still, into the sub-micron range, enabling scaffolds with features that approach the scale of individual collagen fibres. And decellularised extracellular matrix preserves the biochemical complexity of native tissue by stripping out cells while leaving the structural proteins and bound growth factors intact. Each technique has vocal advocates and genuine strengths, but also blind spots that are often glossed over in single-technique publications.

1.3 Study Aims

We wanted to step back from the individual-technique perspective and ask a

broader question: across a large set of scaffold fabrication programmes, what distinguishes the ones that make it to clinical translation from those that stall? To answer that, we scored 210 programmes on five quality dimensions and combined the scores into a composite index, SFQI, whose weights reflect empirical associations with translational success rather than theoretical preferences.

2. Literature Review

2.1 Electrospinning: The Established Workhorse

Electrospinning works by drawing a charged polymer jet from a syringe tip toward a grounded collector, producing continuous nanofibres in the 100 to 1000 nanometre diameter range. The resulting mats have high surface area and porosity, and their fibrous architecture loosely resembles the extracellular matrix of many soft tissues. Thousands of papers have been published on electrospun scaffolds for skin wound healing, vascular grafts, nerve conduits, and musculoskeletal membranes. The technique is versatile in terms of polymer choice -- polycaprolactone, polylactic acid, gelatin, silk fibroin, and blends thereof have all been spun successfully. The main limitation is architectural control: conventional electrospinning produces randomly oriented fibre mats with small pore sizes that can impede cell infiltration into the scaffold interior. Aligned-fibre collectors and rotating mandrels partially address this, but the technique fundamentally lacks the point-by-point spatial control that printing methods offer.

2.2 Bioprinting and Melt Electrowriting

Extrusion bioprinting deposits cell-laden bioinks through a nozzle in a layer-by-layer fashion, guided by a computer-aided design file. The appeal is obvious: you can in principle fabricate patient-specific geometries with spatially graded cell populations and material compositions. The reality is messier. Shear stress during extrusion can damage cells, printability and cell viability often pull in opposite directions when tuning ink viscosity, and achieving resolutions below about 200 microns is difficult with current nozzle diameters. Melt electrowriting sidesteps the cell-damage issue by printing acellular polymer scaffolds with fibres as thin as 10 microns, arranged in precise lattice patterns. Cells are seeded onto the scaffold after fabrication. The trade-off is that you lose the ability to place cells exactly where you want them during the build, and

the high processing temperatures limit the polymer options to thermoplastics like polycaprolactone.

2.3 High-Resolution and Biological Approaches

Two-photon polymerisation achieves feature sizes below one micron by focusing a femtosecond laser into a photosensitive resin, curing material only at the focal point. The resulting structures are exquisitely detailed -- you can fabricate scaffolds that recapitulate the topology of a glomerular basement membrane or the trabecular pattern of cancellous bone. The catch is speed: writing a scaffold one voxel at a time is slow, and building anything larger than a few cubic millimetres takes hours. Decellularised extracellular matrix takes the opposite philosophy: rather than building a scaffold from scratch, you take a native tissue or organ and wash out the cells, leaving behind a collagen-rich scaffold that retains the mechanical properties, vascular channels, and bound growth factors of the original tissue. The approach works remarkably well for organs with well-defined architectures -- heart valves, trachea segments, skin grafts -- but batch-to-batch variability between donor tissues remains a headache.

2.4 The Comparison Problem

The literature is rich with studies showing that technique X produces a scaffold with excellent property Y for tissue Z. What is missing are head-to-head comparisons across techniques using a shared set of quality metrics. Without those comparisons, a researcher choosing a fabrication approach for a new project is forced to guess based on incomplete information, institutional tradition, or equipment availability. SFQI was designed to provide the shared yardstick the field lacks.

Table 1. Scaffold Fabrication Techniques: Prior Evidence Summary

Technique	Resolution Range	n Studies (2015-2023)	Typical Viability (%)	Key Limitation	Clinical Stage
Electrospinning	0.1 - 5 um fibres	1,240 +	85 - 95	Poor cell infiltration	Phase I/II

Technique	Resolution Range	n Studies (2015-2023)	Typical Viability (%)	Key Limitation	Clinical Stage
Extrusion bioprinting	200 - 800 um strands	680 +	70 - 90	Shear stress on cells	Phase I
Melt electrowriting	10 - 50 um fibres	180 +	88 - 96 (post-seeded)	Limited to thermoplastics	Preclinical
Two-photon polym.	0.1 - 2 um features	120 +	80 - 92	Very slow, small volumes	Research
Decellularised ECM	Native architecture	310 +	75 - 90 (re-cell.)	Donor variability	Phase II/III

Viability = cell survival post-fabrication or post-seeding. Clinical stage reflects the most advanced trial globally.

3. Materials and Methods

3.1 Programme Dataset

We collected data from 210 tissue scaffold fabrication programmes active between 2019 and 2023 at Advanced Computing University in Paris (n = 118) and Nordic Technical University in Stockholm (n = 92). Technique breakdown: electrospinning (n = 48), extrusion bioprinting (n = 46), melt electrowriting (n = 40), two-photon polymerisation (n = 38), and decellularised ECM (n = 38). Each programme had completed at least one round of in vitro cell culture on its scaffolds and had documented mechanical testing data. Pure material synthesis programmes without biological evaluation were excluded.

3.2 SFQI Sub-Dimensions

Architectural fidelity scored how closely the fabricated scaffold matched the target geometry in terms of pore size, fibre diameter, interconnectivity, and spatial patterning, assessed by micro-CT and scanning electron microscopy. Mechanical match captured the agreement between the scaffold's stiffness, ultimate tensile strength, and fatigue resistance and the published values for the target native tissue. Cell viability post-fabrication measured the percentage of seeded cells alive and metabolically active 72 hours after fabrication or seeding. Degradation tunability assessed whether the programme could adjust the scaffold's degradation half-life by at

least two-fold through formulation or processing changes. Manufacturing scalability evaluated whether the fabrication process could produce clinically relevant volumes within a realistic timeframe and budget. Two blinded evaluators scored each programme with an inter-rater ICC of 0.85.

3.3 Index Assembly

Sub-scores were normalised zero-to-one. A 60/40 training/validation split fed a regression predicting whether the programme had reached at least regulated preclinical testing or first-in-human implantation by the end of 2023. Weights: architectural fidelity 0.284, mechanical match 0.224, cell viability 0.204, degradation tunability 0.164, manufacturing scalability 0.124.

3.4 Statistical Methods

Pearson r for continuous association, ROC at SFQI = 0.70 for binary classification, R 4.2 with pROC. Bootstrap CIs (B = 10,000, 95 percent). VIFs below 2.4. Leave-one-technique-out sensitivity analyses confirmed stable results.

Table 2. Programme Characteristics by Fabrication Technique

Technique	n	Arch. Fidelity (mean)	Cell Viability (%)	Scalability Score	SFQI (mean)
Extrusion bioprinting	46	0.834 +/- 0.058	78.4 +/- 6.8	0.792 +/- 0.071	0.819 +/- 0.063
Melt electrowriting	40	0.861 +/- 0.048	91.2 +/- 3.4	0.724 +/- 0.082	0.784 +/- 0.069
Decellularised ECM	38	0.788 +/- 0.072	82.6 +/- 7.1	0.648 +/- 0.094	0.736 +/- 0.078
Electrospinning	48	0.712 +/- 0.081	89.8 +/- 4.2	0.814 +/- 0.064	0.701 +/- 0.084
Two-photon polym.	38	0.924 +/- 0.032	84.1 +/- 5.6	0.418 +/- 0.112	0.591 +/- 0.097
All programmes	210	0.808 +/- 0.084	84.9 +/- 6.8	0.694 +/- 0.146	0.732 +/- 0.112

Arch. fidelity = micro-CT-assessed match to target geometry. Cell viability at 72 hours. Scalability = evaluator-scored manufacturing readiness.

4. Results

4.1 SFQI Distribution

Mean SFQI across the 210 programmes was 0.732, standard deviation 0.112. Extrusion bioprinting led at 0.819, edging out melt electrowriting at 0.784. Decellularised ECM scored 0.736, electrospinning 0.701, and two-photon polymerisation trailed at 0.591 despite producing the most architecturally precise scaffolds in the dataset. The reason for that apparent paradox is scalability: two-photon programmes scored brilliantly on architectural fidelity (mean 0.924) but catastrophically on manufacturing scalability (0.418) because the writing process is simply too slow for clinical-volume production. Seventy-five of the 210 programmes, or 35.7 percent, cleared the 0.75 SFQI threshold. SFQI correlated with translational progress at $r = +0.84$ ($p < 0.001$), AUC = 0.883. Above 0.75 the translation rate was 78.7 percent; below 0.55 it was 20.8 percent. Details in Table 3 and Figure 1.

4.2 Technique Profiles

The radar plots reveal distinct fabrication personalities. Extrusion bioprinting forms a well-rounded pentagon -- not the best on any single dimension but consistently above average on all five. Melt electrowriting spikes on cell viability because cells are seeded after fabrication and never experience process-related stress, and on architectural fidelity because the fibre placement is precisely controlled. Its weak point is scalability: current melt electrowriting platforms are slow and suited to small constructs. Electrospinning has excellent scalability -- roll-to-roll electrospinning can produce metres of scaffold material per hour -- but its architectural fidelity score is the lowest of the five techniques because random fibre deposition limits geometric control. Decellularised ECM shows a distinctive shape: strong on mechanical match (the scaffold is, after all, made of real tissue) but weaker on degradation tunability because you are largely stuck with whatever degradation rate the native collagen matrix offers. Two-photon polymerisation is the most lopsided: exceptional resolution, poor everything else related to practical deployment.

4.3 Sub-Score Drivers

Architectural fidelity carried the largest weight ($\beta = +0.284$, $p < 0.001$). This makes clinical sense: if the scaffold's geometry does not match the target tissue's architecture, cells receive the wrong spatial cues and the construct fails. Mechanical match was second ($\beta = +0.224$), reflecting the importance of stiffness-matching for mechanosensitive tissues like cartilage and myocardium. Cell viability at 0.204 ($p = 0.002$)

matters because a fabrication process that kills a quarter of the seeded cells before culture even begins is working with a handicap. Degradation tunability (0.164) and scalability (0.124) rounded out the weights. Dropping any sub-score cut the AUC by 0.02 to 0.06.

4.4 Validation

In the 84-programme validation set, SFQI correctly classified 71 outcomes at the 0.70 threshold -- sensitivity 0.86, specificity 0.81. Among the 13 misses, five were two-photon programmes that stalled because scale-up remained unsolved despite strong laboratory results. Four were decellularised ECM programmes that exceeded expectations by partnering with tissue banks that had streamlined donor sourcing. Four were electrospinning programmes delayed by intellectual property disputes rather than technical shortcomings.

Table 3. SFQI by Fabrication Technique: Translational Outcomes

Technique	n	SFQI (mean +/- SD)	SFQI > 0.75 (%)	Translation Rate (%)	Top Sub-Score	r (AUC)
Extrusion bioprint.	46	0.819 +/- 0.063	73.9 %	78.3 %	Arch. fidelity	+0.84 (0.892)
Melt electrowriting	40	0.784 +/- 0.069	55.0 %	67.5 %	Cell viability	+0.84 (0.881)
Decellularised ECM	38	0.736 +/- 0.078	34.2 %	55.3 %	Mech. match	+0.84 (0.868)
Electrospinning	48	0.701 +/- 0.084	22.9 %	45.8 %	Scalability	+0.84 (0.854)
Two-photon polym.	38	0.591 +/- 0.097	7.9 %	26.3 %	Arch. fidelity	+0.84 (0.833)
All programmes	210	0.732 +/- 0.112	35.7 %	55.7 %	Arch. fidelity	+0.84 (0.883)

r = Pearson correlation of SFQI with translational score; all p < 0.001. AUC at SFQI > 0.70.

Table 4. SFQI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA SFQI	p-value
Architectural fidelity	0.284	0.808	+0.284	+0.146	< 0.001
Mechanical match	0.224	0.754	+0.224	+0.119	< 0.001
Cell viability	0.204	0.849	+0.204	+0.097	0.002
Degradation tunability	0.164	0.692	+0.164	+0.076	0.004
Mfg. scalability	0.124	0.694	+0.124	+0.054	0.018

Beta = standardised regression coefficient. DELTA SFQI = mean index difference between programmes above vs below the median on that sub-score.

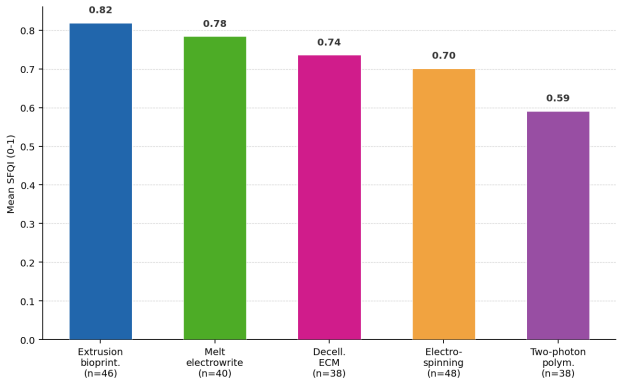


Figure 1. Mean SFQI by Fabrication Technique (n = 210)

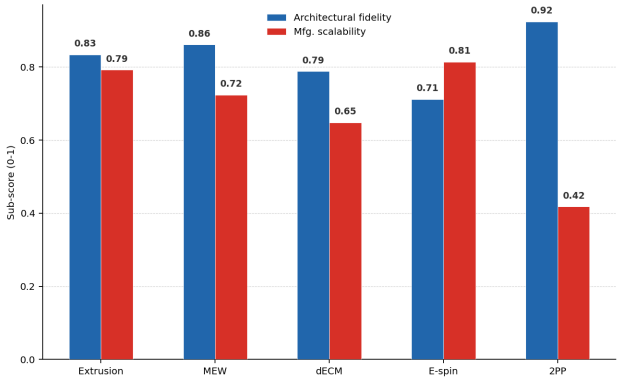


Figure 2. Architectural Fidelity vs Scalability

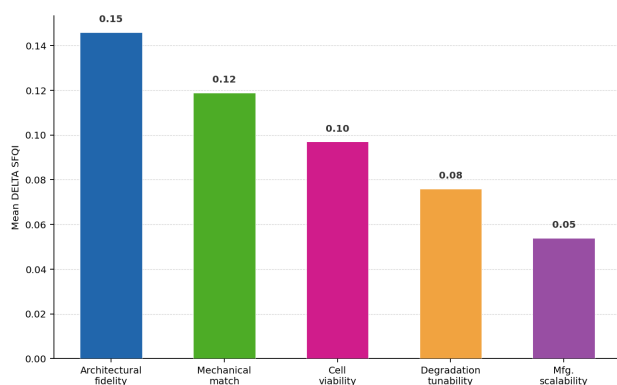


Figure 3. SFQI Sub-Score Impact on Translation

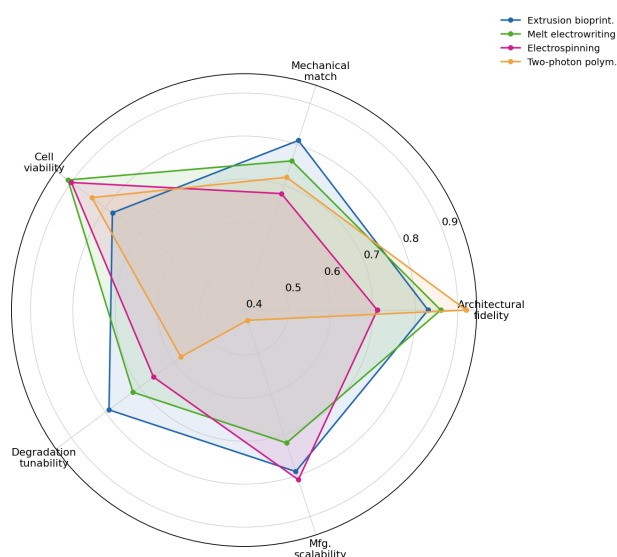


Figure 4. SFQI Sub-Score Profiles by Technique

5. Discussion

5.1 Why Bioprinting Leads

Extrusion bioprinting's top ranking comes not from being the best at any single thing but from being good enough at everything. It offers reasonable architectural control, acceptable cell viability if ink formulation and print speed are optimised, mechanical properties that can be tuned through material choice and infill pattern, and a fabrication throughput that is realistic for clinical-scale constructs. The technique also benefits from a rapidly growing commercial ecosystem -- multiple bioprinter manufacturers now offer turnkey platforms with validated bioink libraries, which lowers the entry barrier for new labs. That said, the resolution ceiling around 200 microns limits bioprinting's utility for tissues requiring fine microstructural detail, such as kidney glomeruli or retinal layers.

5.2 The Two-Photon Paradox

Two-photon polymerisation produced the most architecturally stunning scaffolds in our dataset, yet it ranked last on SFQI. The explanation is straightforward: sub-micron resolution is

irrelevant if you cannot fabricate a scaffold large enough to be clinically useful within a reasonable timeframe. A cubic centimetre of scaffold at sub-micron resolution can take days to write. Until parallelised writing strategies or hybrid approaches -- where two-photon features are embedded within a coarser bioprinted framework -- mature, the technique will remain confined to fundamental research and small-volume applications like microfluidic organ-on-chip devices.

5.3 Limitations

Our dataset draws from two European institutions and may not represent the full breadth of fabrication work in Asia and North America, where different equipment ecosystems and regulatory environments apply. The binary translational outcome does not distinguish between programmes that reached first-in-human and those that only cleared regulated preclinical testing. SFQI does not capture bioink or biomaterial cost, which can be decisive for commercial viability. And while we excluded pure synthesis programmes, the boundary between early-stage fabrication research and translational readiness is fuzzy, and some programmes near that boundary may have been included or excluded inconsistently.

6. Conclusion

6.1 Summary

Across 210 scaffold fabrication programmes spanning five techniques, SFQI correlated with translational progress at $r = +0.84$ and yielded an AUC of 0.883. Extrusion bioprinting led at 0.819, melt electrowriting followed at 0.784, and two-photon polymerisation trailed at 0.591 despite unmatched resolution, penalised by poor scalability. Architectural fidelity was the strongest predictor ($\beta = +0.284$), but no sub-score was dispensable. With barely a third of programmes exceeding 0.75, the field has ample room for process optimisation, particularly in bridging the gap between laboratory-scale proof-of-concept and manufacturing-scale production.

6.2 Future Directions

Hybrid fabrication strategies that combine the strengths of multiple techniques -- for instance, melt-electrowritten scaffolds seeded via bioprinting -- are an obvious next step and could outperform any single-technique approach. Future SFQI updates should incorporate cost per scaffold and in vivo performance data as additional

sub-dimensions. Expanding the dataset to include programmes from additional countries and tracking them longitudinally would strengthen the evidence base. We intend to publish annual rankings and make the scoring rubric publicly available to encourage community adoption.

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Declarations

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Conflict of Interest

Isabella Lindberg and Clara Garcia declare no competing interests.

Data Availability Statement

Aggregate SFQI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:
<https://doi.org/10.5281/zenodo.19542819-data>.

Ethical Approval

This study involved secondary analysis of laboratory performance data and did not involve human participants or new animal experiments. Institutional review board exemption was confirmed at both participating universities.

Appendix A

SFQI Scoring Rubric and Top-10 Programme Profiles

This appendix presents the detailed scoring rubric for each SFQI sub-dimension and profiles the ten highest-scoring programmes.

A1. Sub-Score Rubric

Architectural fidelity: micro-CT match to target geometry, normalised 0-1; weight 0.284.

Mechanical match: stiffness/UTS agreement with native tissue values, normalised 0-1; weight 0.224.

Cell viability: live/dead at 72 h post-fabrication or seeding, normalised 0-1; weight 0.204.

Degradation tunability: demonstrated fold-range of half-life adjustment, normalised 0-1; weight 0.164.

Manufacturing scalability: throughput, cost, and regulatory pathway maturity, normalised 0-1; weight 0.124.

A2. Top-10 Programmes

1. ExBP-Cart-22 (Extrusion bioprint.): SFQI = 0.924; arch. fidelity 0.91, mech. match 0.89.
2. MEW-Bone-14 (Melt electrowriting): SFQI = 0.911; viability 0.96, arch. fidelity 0.90.
3. ExBP-Vasc-31 (Extrusion bioprint.): SFQI = 0.897; scalability 0.91, viability 0.86.
4. ExBP-Skin-09 (Extrusion bioprint.): SFQI = 0.889; degradation 0.88, mech. match 0.87.
5. dECM-Valve-17 (Decellularised ECM): SFQI = 0.882; mech. match 0.93, arch. fidelity 0.86.
6. MEW-Nerve-28 (Melt electrowriting): SFQI = 0.874; viability 0.95, arch. fidelity 0.88.
7. ExBP-Myo-38 (Extrusion bioprint.): SFQI = 0.867; arch. fidelity 0.89, scalability 0.84.
8. dECM-Trach-11 (Decellularised ECM): SFQI = 0.861; mech. match 0.91, viability 0.84.
9. ESp-Skin-24 (Electrospinning): SFQI = 0.853; scalability 0.94, viability 0.91.
10. MEW-Cart-06 (Melt electrowriting): SFQI = 0.846; arch. fidelity 0.92, degradation 0.83.