Current Status and Future Perspectives of 3D Printing and Bioprinting for Regenerative Medicine

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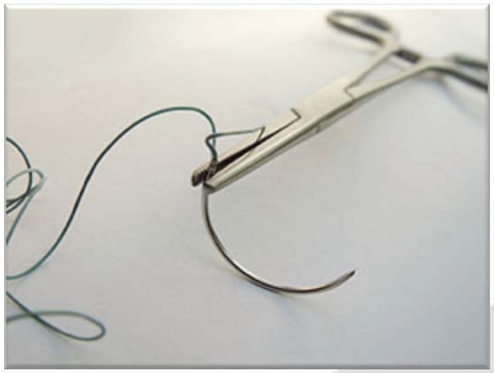
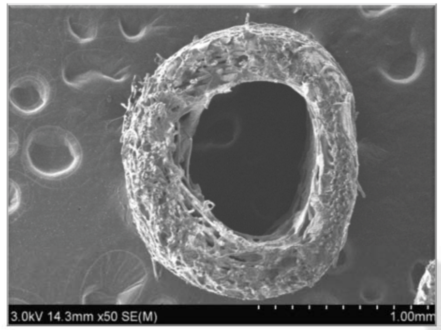
Biomaterials in Medicine

Historical Development of Biomaterials

Contact Lens



Absorbable Sutures



Vascular Grafts

Bioinertness (1970's)

- Minimal interaction with body
- Goal is no immune response

Bioactivity (1980's)

- Control reaction with physiological environment
- Create materials to resorb into natural tissue

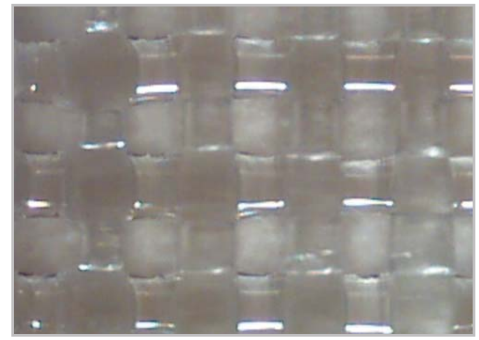
Regenerative Properties (2000's)

- Interact with physiological system
- Stimulate specific cell response at molecular level
- Direct proliferation, differentation, organization

Ratner, B. D. (2012). Biomaterials Science: An Introduction to Materials in Medicine. Amsterdam: Elsevier Academic Press.

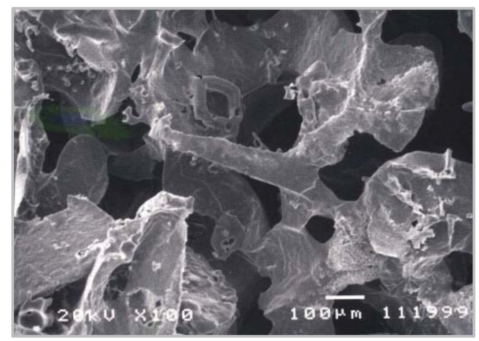
Biomaterials in Medicine

Traditional Fabrication Strategies Remain Limited



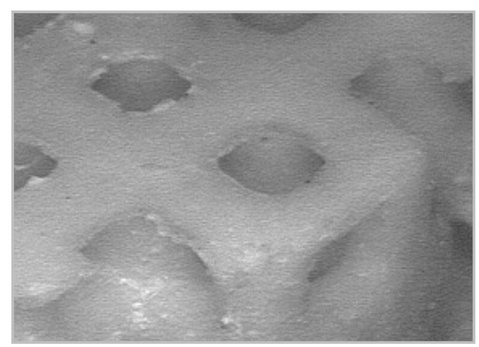
- Fabrication approaches for controlling bulk geometry
  - Shaping
  - Molding
  - Fiber bonding
  - Layered fabrication

  Strategies provide only limited (~1 mm) control over scaffold geometry

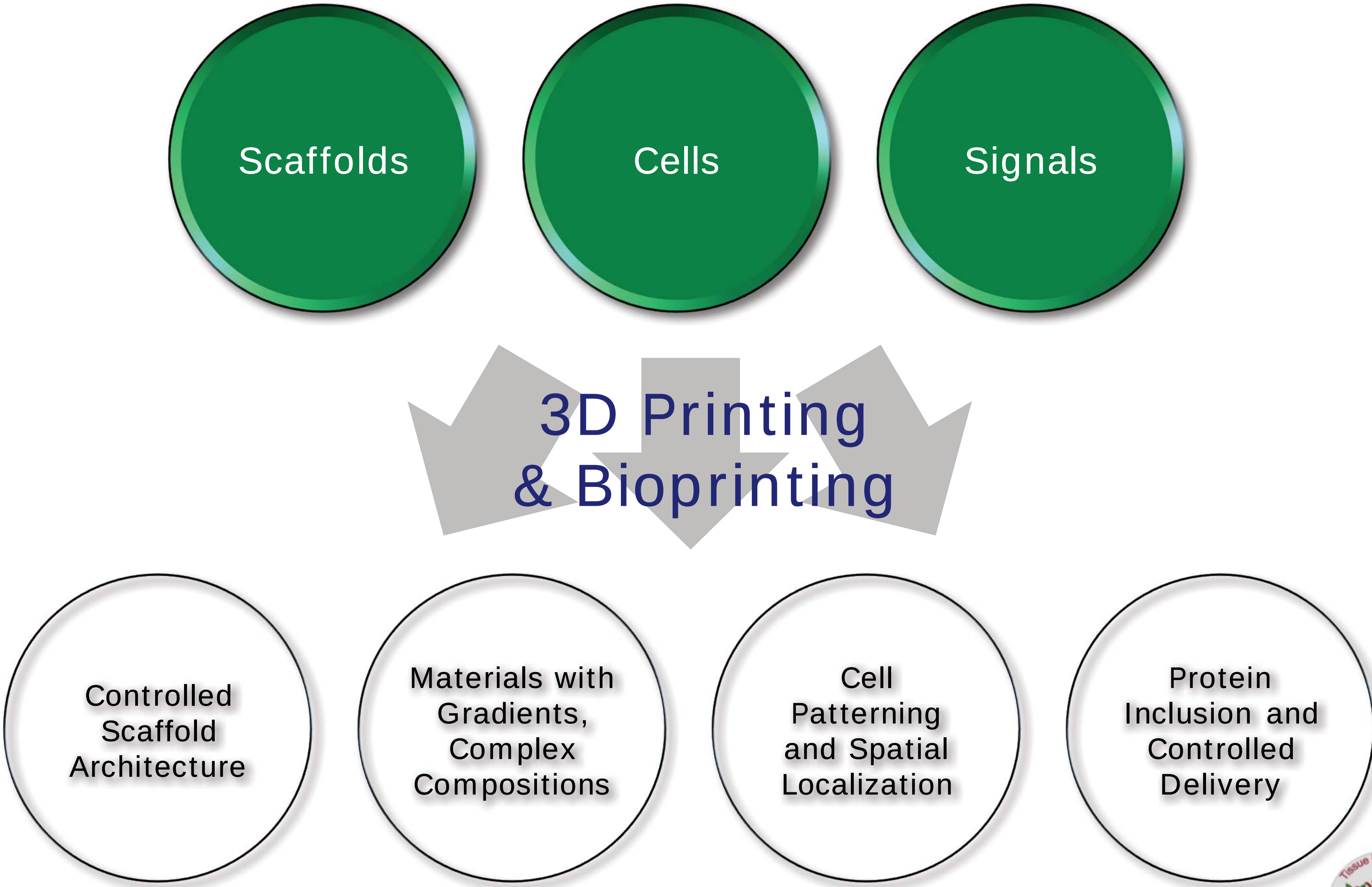


- Fabrication approaches for controlling interior geometry
  - Porogen leaching
  - Phase separation
  - Freeze drying
  - Gas foaming
  - Electrospinning

  Strategies typically provide control over uniform geometry parameters (porosity, pore size, fiber size, interconnectivity), rather than location specific control



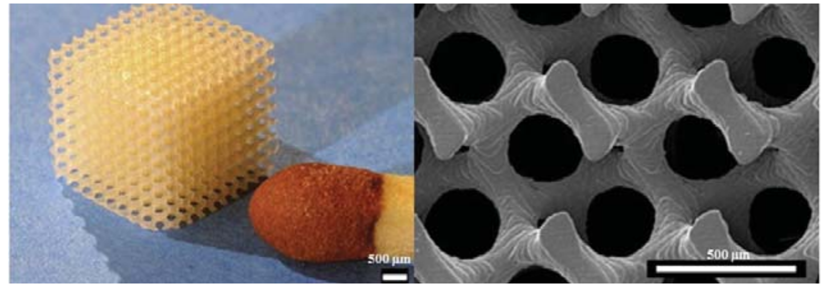
Tissue Engineering

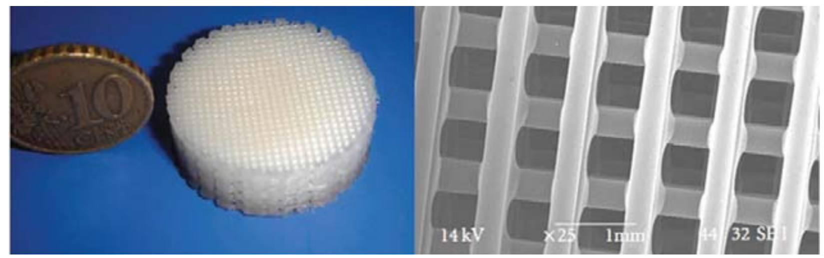


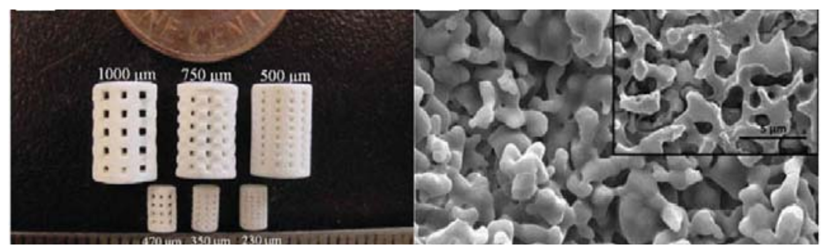
Common Fabrication Techniques

Strategy

- Inkjet Bioprinting
  - Available since the early 2000s, typically a low cost DIY for laboratories
  - Utilizes technology developed for printing on paper for bio-applications
- Extrusion-Based Bioprinting
  - More recent in development, but has been commercially available since the early 2000s
  - Typically driven via pneumatic pressure or a screw drive to extrude the material through a nozzle
- Stereolithography (SLA)
  - One of the oldest 3D printing technologies has been in use since the 1980s
  - Uses a light source (UV, visible, laser, or two-photon) for layer-by-layer curing of photocrosslinkable resins





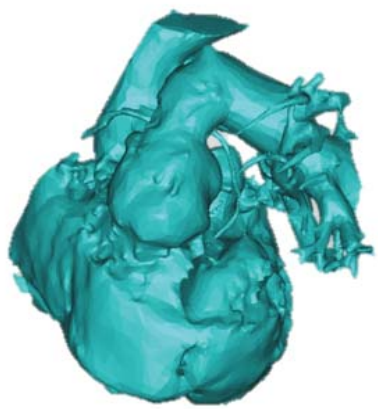


Mota et al, *J Tissue Eng Regen Med*, 2015

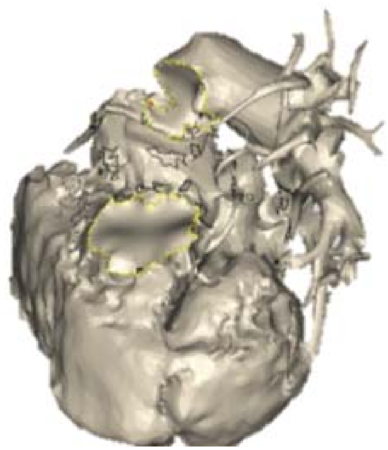
3D Printing and Bioprinting Provides Clear Advantages in Biomaterial and Tissue Engineered Construct Fabrication

- Personalized Medicine
- Cell Patterning
- Standardized Materials
- Advanced Functionality

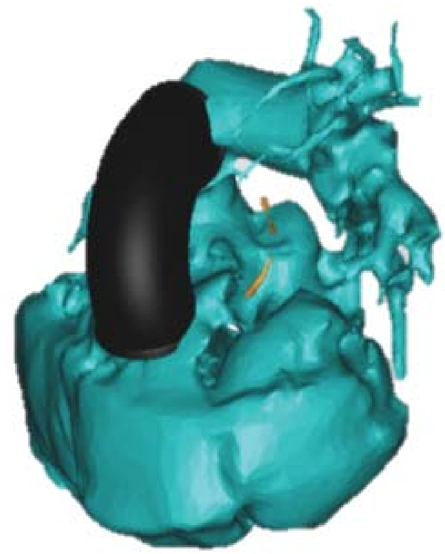
Personalized Medicine



3D Model Based on MRI/CT Images



Isolate Area of Interest

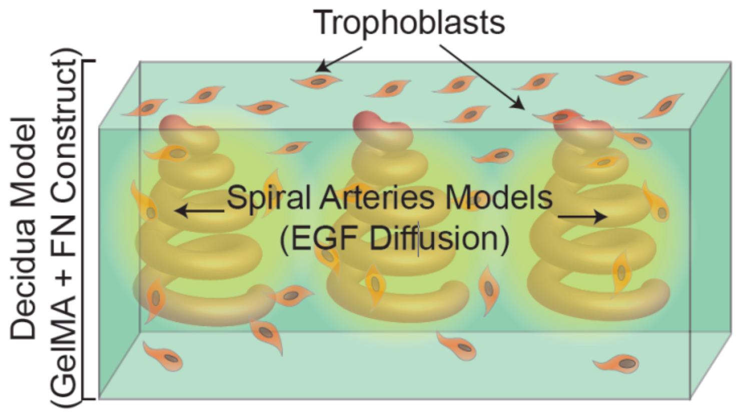


Design Custom Fit Graft

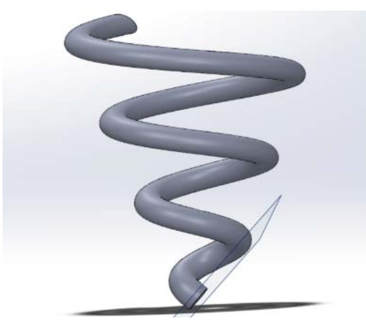
Fabricate Customized Graft

AJ Melchiorri, N Hibino, C Best, T Yi, YU Lee, CA Kraynak, LK Kimerer, A Krieger, CK Breuer, and JP Fisher. 3D Printed Biodegradable Polymeric Vascular Grafts. Advanced Healthcare Materials. 5: 319-325 (2015).

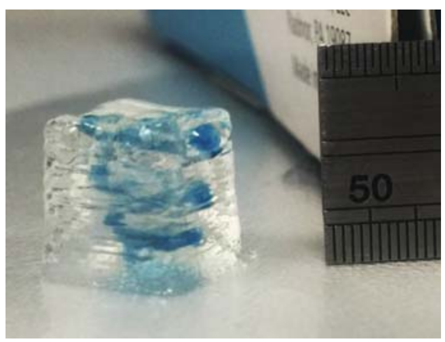
Cell and Biomaterial Patterning



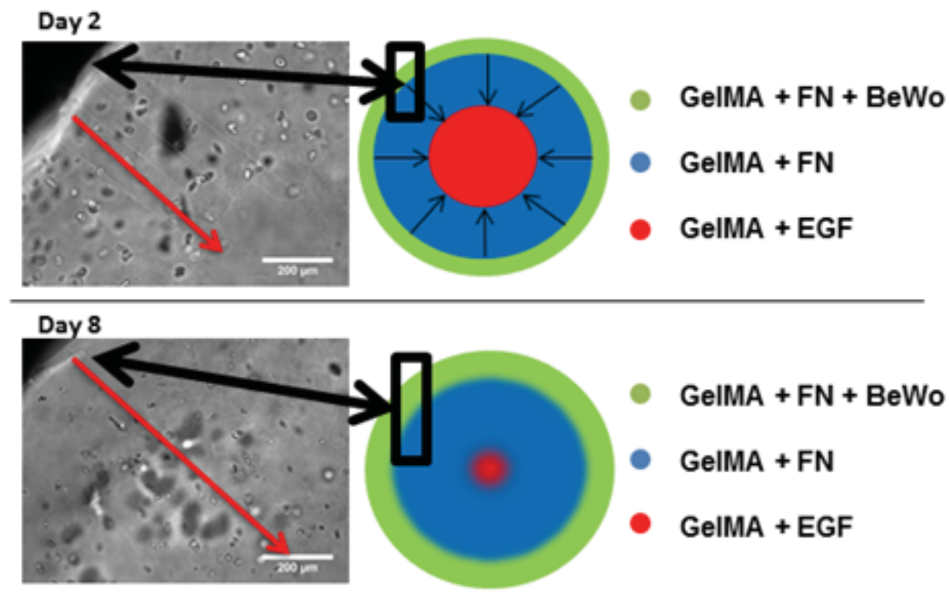
Bioengineered Placenta Model



Solid-Works Model



Bioprinted Spiral Artery Model



Migration of Trophoblast Towards Growth Factors in Bioengineered Placenta Model

In Preparation.

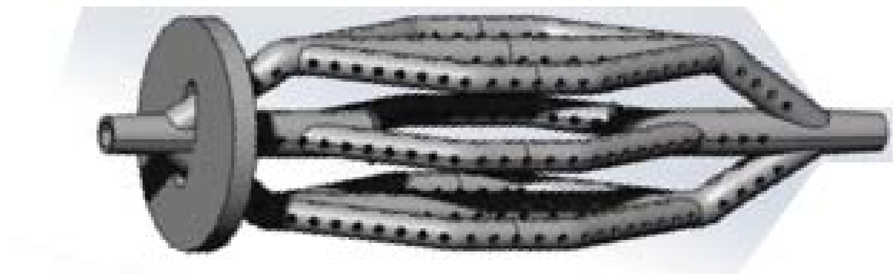
Precise Manufacturing Capabilities

Modular Cylindrical Scaffolds Where Pore Size and Porosity are Determined by the Geometry of the Repeating Annulus /Column Unit

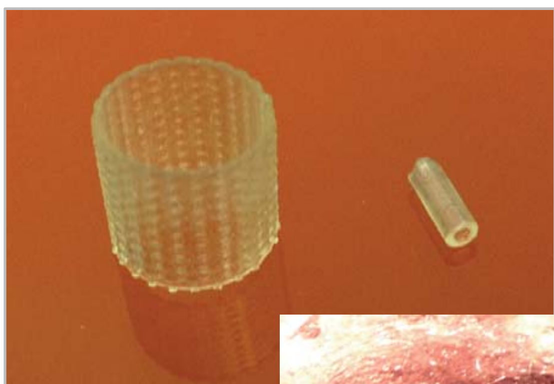
MO Wang, CE Vorwald, ML Dreher, EJ Mott, MH Cheng, A Cinar, H Mehdizadeh, S Somo, D Dean, EM Brey, and JP Fisher. Evaluating 3D Printed Biomaterials as Scaffolds for Vascularized Bone Tissue Engineering. Advanced Materials. 27: 138-144 (2015).

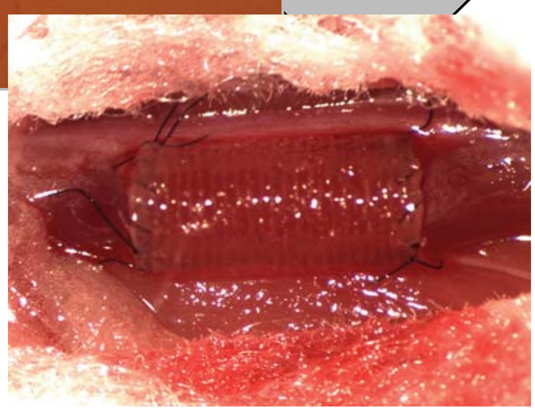
Advanced Biomaterial Functionalities

3D Printed Vascular Network



3D Printed Template of a Vascular Network that Allows the Perfusion of a Surrounding Cell Population





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The Future of 3D Printing and Bioprinting – and the Widespread Clinical Translation of these Technologies – Will Require Considerable Technical Development

- Printable Biomaterials
- Bioreactors
- Manufacturing Standards
- Manufacturing Sites

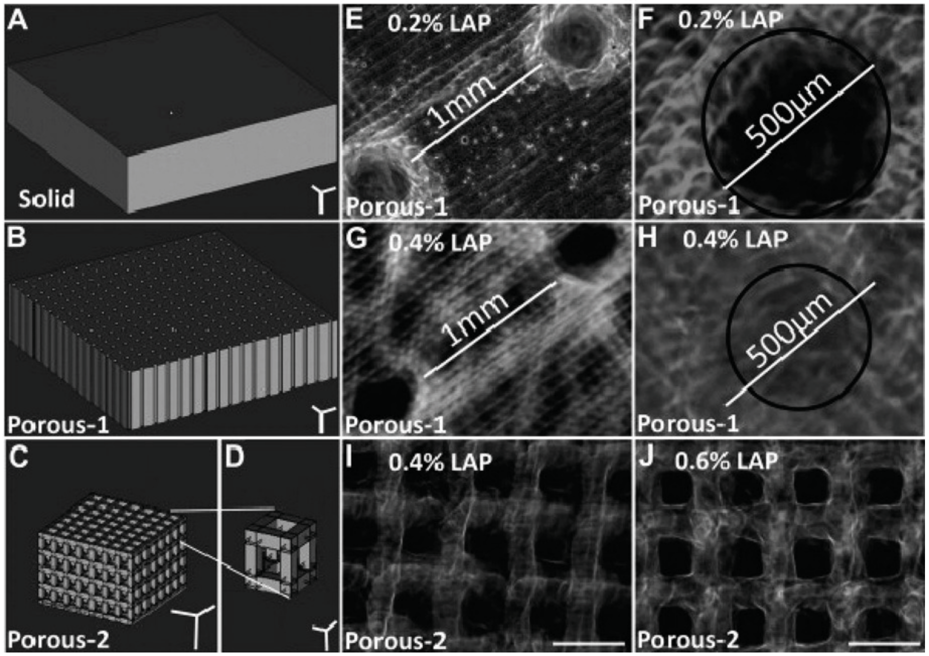
Stereolithography-Based 3DP Biomaterials

Material Choices and Resolution

- Some biocompatible and biodegradable materials used in SLA include
  - PLGA (PLLA/PGA)
  - PEG
  - PPF
  - ECM / Proteins

- Few light responsive components (photoinitiators and photoinhibitors) that are suitable for biological applications

There is a lack of SLA suitable materials that may be translated for tissue engineering and regenerative medicine applications

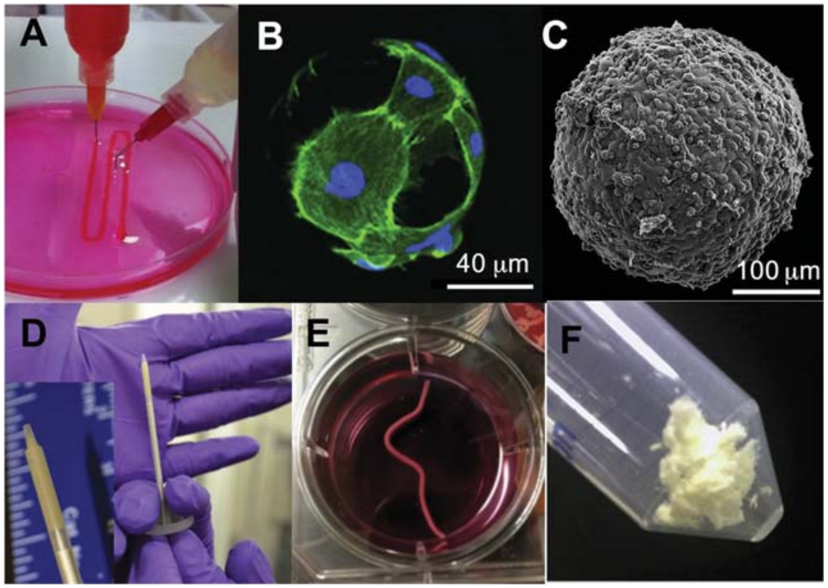


Chia HN, Wu BM. Journal of Biological Engineering 2015

Extrusion-Based 3DP Biomaterials

Material Choices and Resolution

- Shear thinning materials are often utilized due to the decrease in viscosity with increasing shear
- However, viscosity and cell viability/function concerns persist
- Examples of extrusion suitable, biocompatible materials
  - Gelatin
  - Alginate
  - Ceramics
  - PCL
  - PLGA (PLLA/PGA)



There is a lack of extrusion suitable materials that may be translated for tissue engineering and regenerative medicine applications

Murphy SV, and Atala A. Nat. Biotech 2014
Ozbolat IT, Hospodiuk M, Biomaterials 2016
Dababneh AB, Ozbolat IT, J Manufacturing Science and Engineering 2014

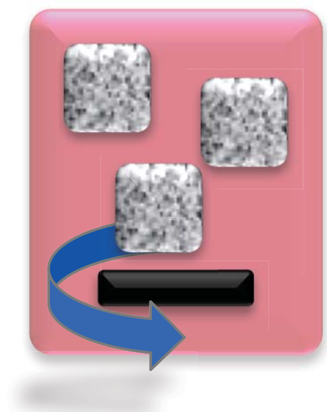
Bioreactors

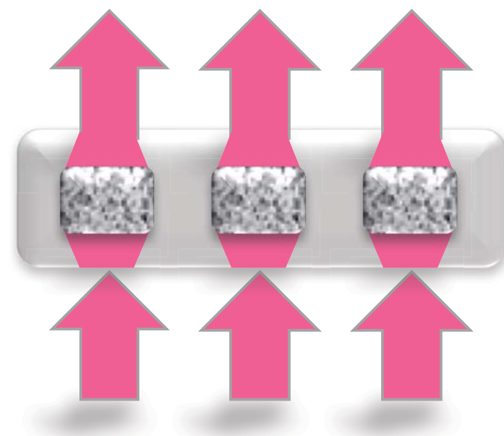
Bioprinting Often Needs Bioreactors

- Bioprinting allows for the simple fabrication of large, cell-laden constructs
- However, these cell laden constructs often require a dynamic environment for the efficient delivery of oxygen and nutrients, as well as the removal of carbon dioxide and waste

Bioreactor development needs to continue so as to provide a mechanism to support the viability and proliferation of these nutrient demanding cell constructs

spinner flask





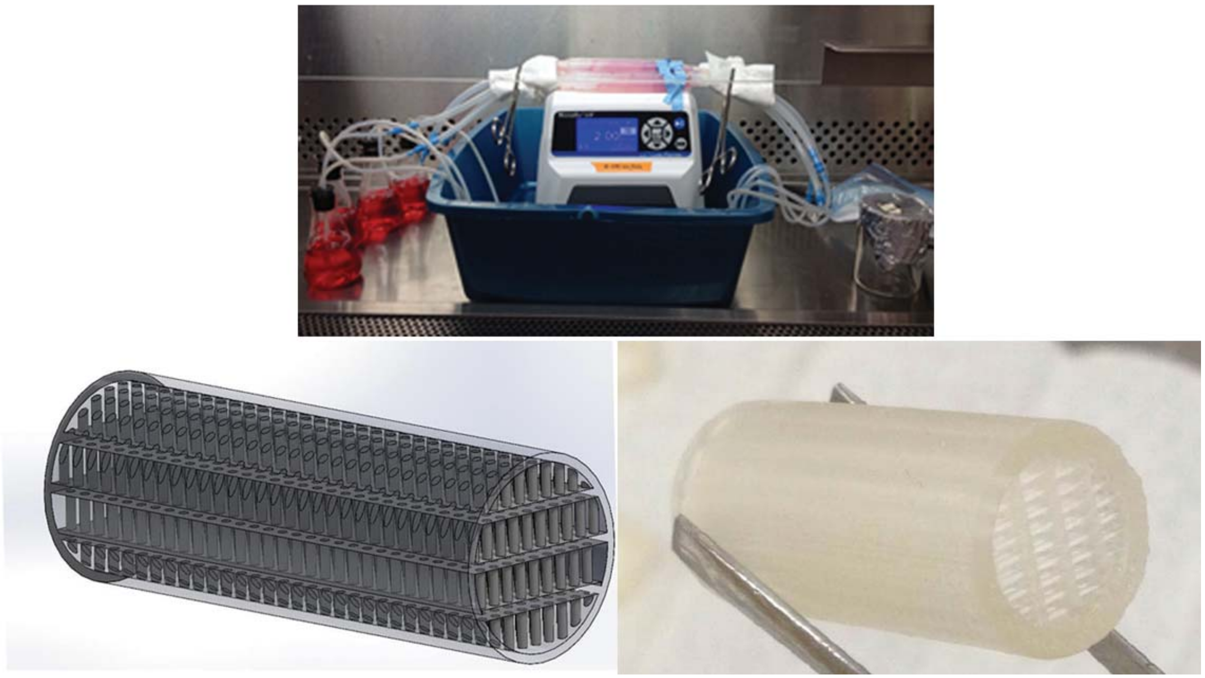
perfusion chamber

BNB Nguyen, H Ko, RA Moriarty, JM Etheridge, and JP Fisher. Dynamic Bioreactor Culture of High Volume Engineered Bone Tissue. Tissue Engineering Part A. In Press.

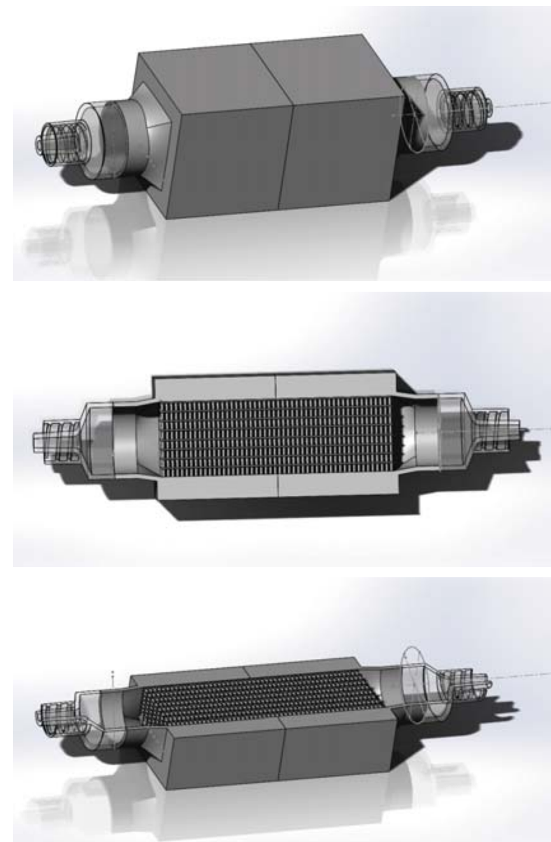
AB Yeatts and JP Fisher. Bone Tissue Engineering Bioreactors: Dynamic Culture and the Influence of Shear Stress. Bone. 48: 171–181 (2011).

3DP Bioreactors

Bioreactor Setup



Top: Bioreactor with 4 growth chambers
Bottom Left: CAD rendering of 3DP scaffold
Bottom Right: 3DP scaffold



In Preparation.

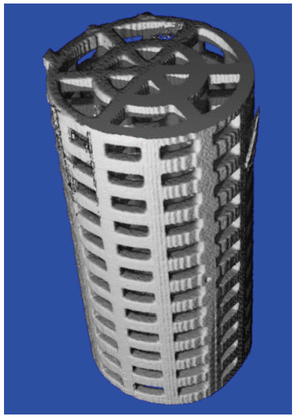
Manufacturing Standards

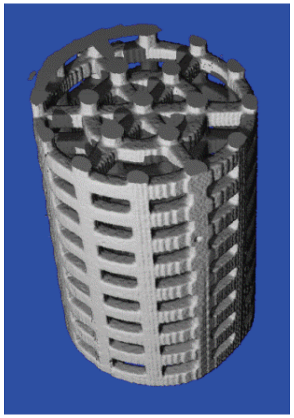
Effect of Printing on Material Properties

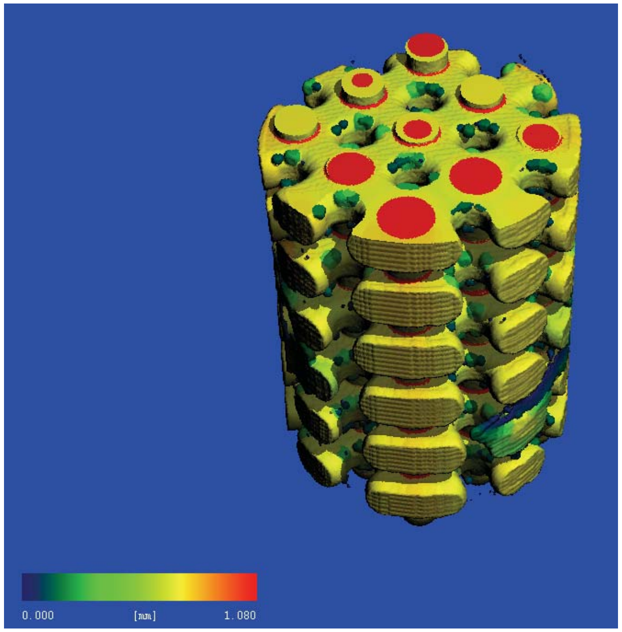
- The additive manufacturing approach provides immense flexibility in the ability to create diverse biomaterial with precise structures

- However, the additive manufacturing approach can lead to materials with anisotropic properties

The relationship between manufacturing approach and resulting material properties needs to be fully understood and characterized





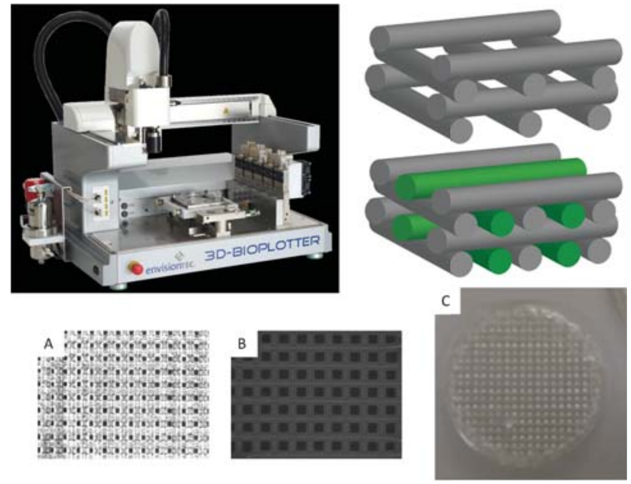


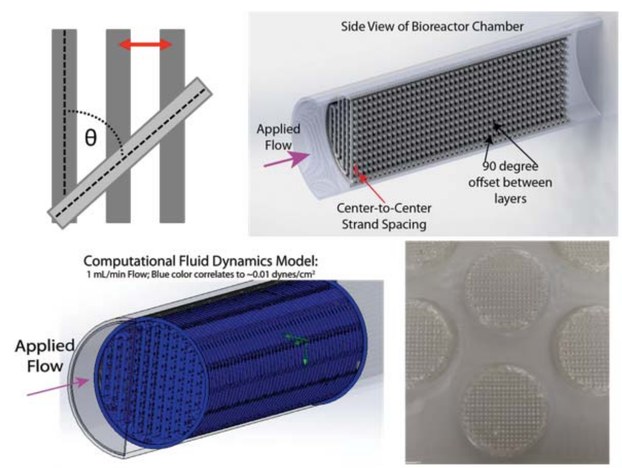
Biomanufacturing Sites

Centers for Excellence in Printing Complex Tissues

- The establishment of hospital specific clinical printing centers has already begun nationwide
- However, the ability to support these facilities at each institution is unclear
- Further, the regulation – and standardization - of these facilities nationwide may be a considerable challenge

The establishment of regional centers of excellence in 3D printing and bioprinting may be a reasonable option for the efficient and widespread dissemination of these therapeutic technologies

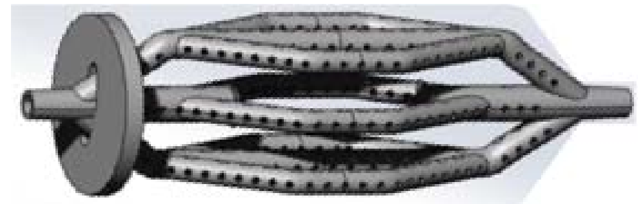




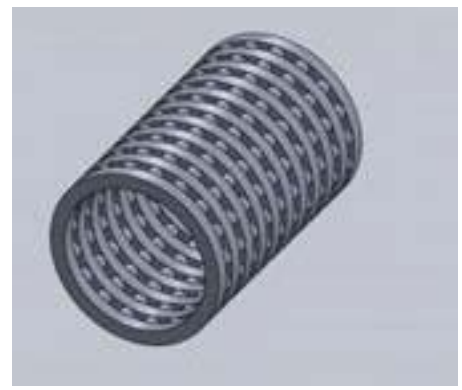
3D Printing and Bioprinting in TE/RM

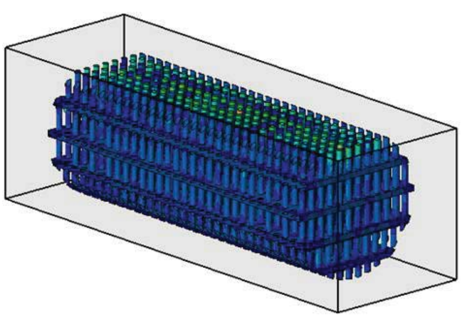
Summary

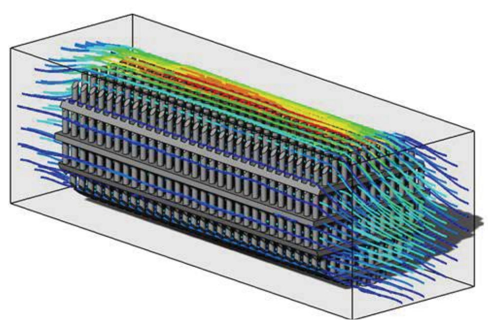
- 3D printing and bioprinting show incredible promise in tissue engineering



However, both technical hurdles and translational barriers must be overcome so that the promise of the technology can become clinical realities for a broad population of patients







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