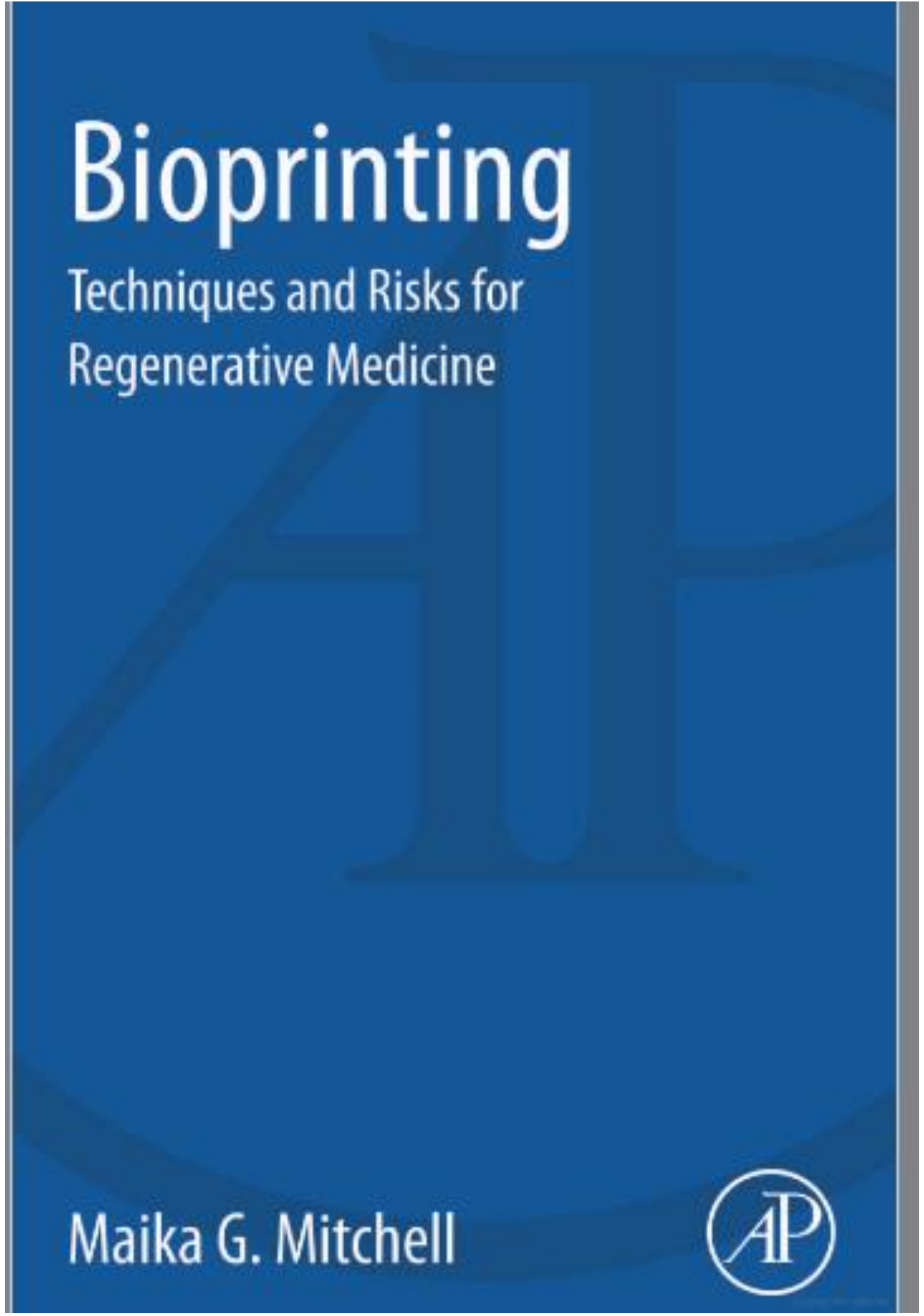
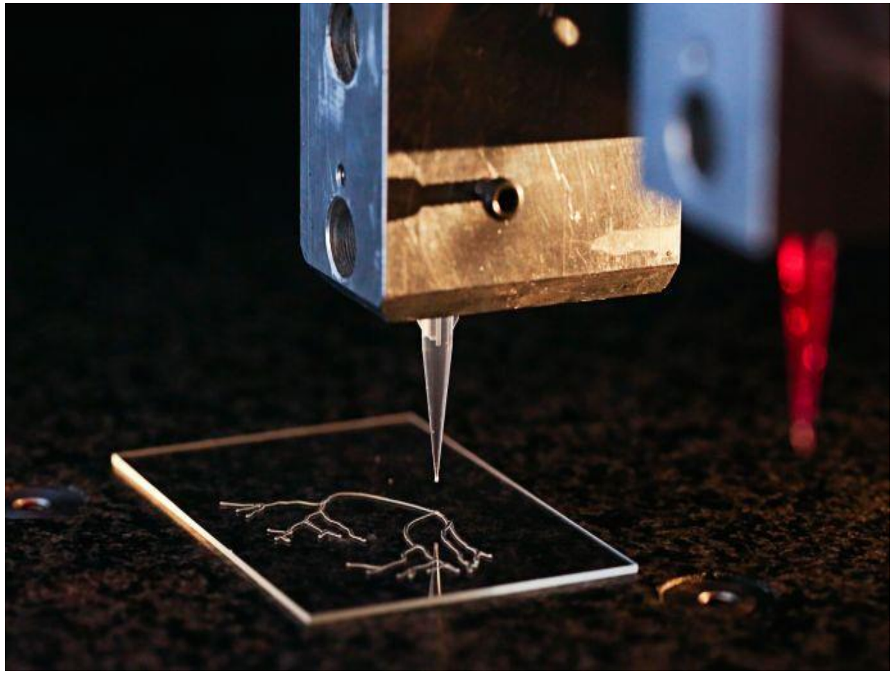
BIO ADDITIVE MANUFACTURING


Bioprinting
Techniques and Risks for Regenerative Medicine
Maika G. Mitchell
AP

Bio-ADDITIVE MANUFACTURING

What is 3d printing?

"3D printing or additive manufacturing is a process of making three dimensional solid objects from a digital file. The creation of a 3D printed object is achieved using additive processes. In an additive process an object is created by laying down successive layers of material until the entire object is created. Each of these layers can be seen as a thinly sliced horizontal cross-section of the eventual object".



BIO-PRINTING

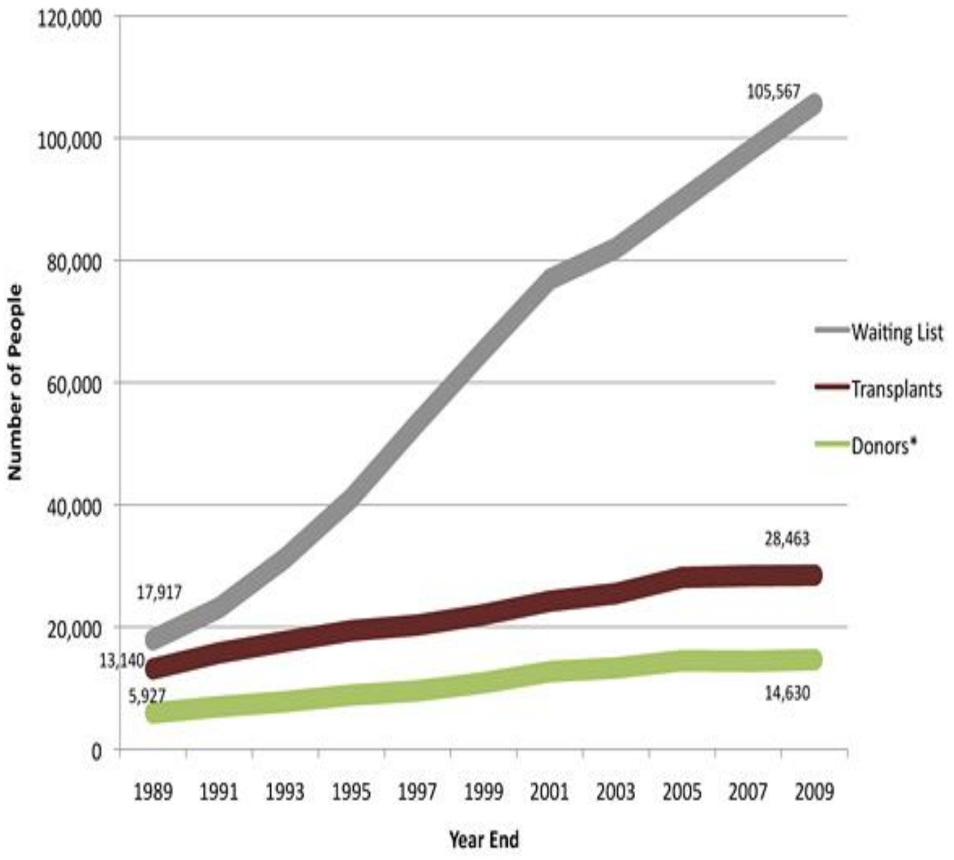
- 3D bio-printing helps constructing living human tissues and organs

- Printing process is made by using printing layer-by-layer approach to generate desired part of the body .

- 3D organs liver, kidney, bones, aortic valve or even heart.

Why..?

- Each day 79 receive organ each day while 18 will die from a lack of one
- Most needed organs are kidneys, livers, lungs, hearts.



How…?

Decreased animal testing

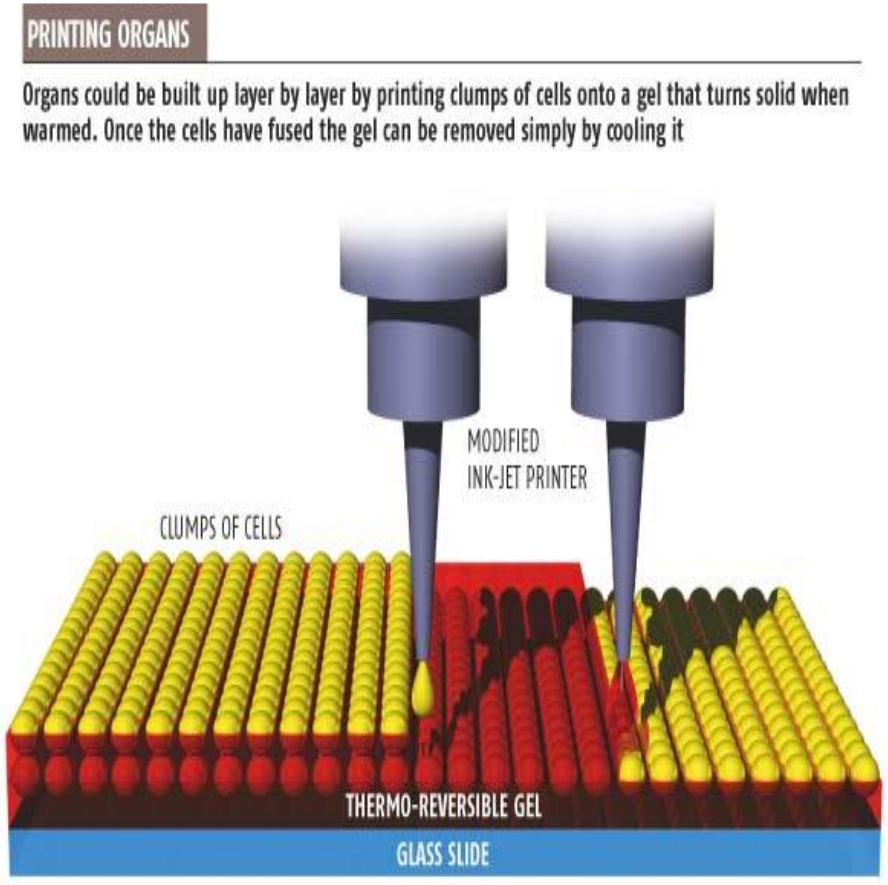
Faster and more precise than traditional methods of building organs by hand

Significantly less expensive products created

Decreased waiting times for organ donors

Less liable to human error

How to print an organ

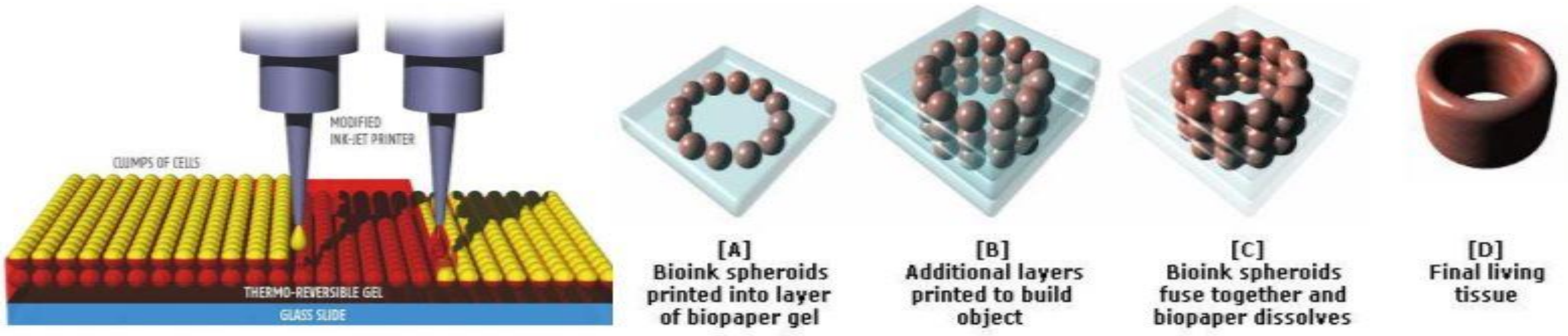


- First, doctors make CT or MRI scans of the desired organ.
- Next, they load the images into a computer and build a corresponding 3-D blueprint of the structure using CAD software.
- Combining this 3-D data with histological information collected from years of microscopic analysis of tissues, scientists build a slice-by-slice model of the patient's organ. Each slice accurately reflects how the unique cells and the surrounding cellular matrix fit together in three-dimensional space.

Bioprinting process flow

Computer model → Printing → Post-processing

3 important components: Bioink, Biopaper, Bioprinter.



Bioink (cells of sp. organ), Biopaper (collagens, nutrients)

Source: organovo.com.

Components Needed for bioprinting

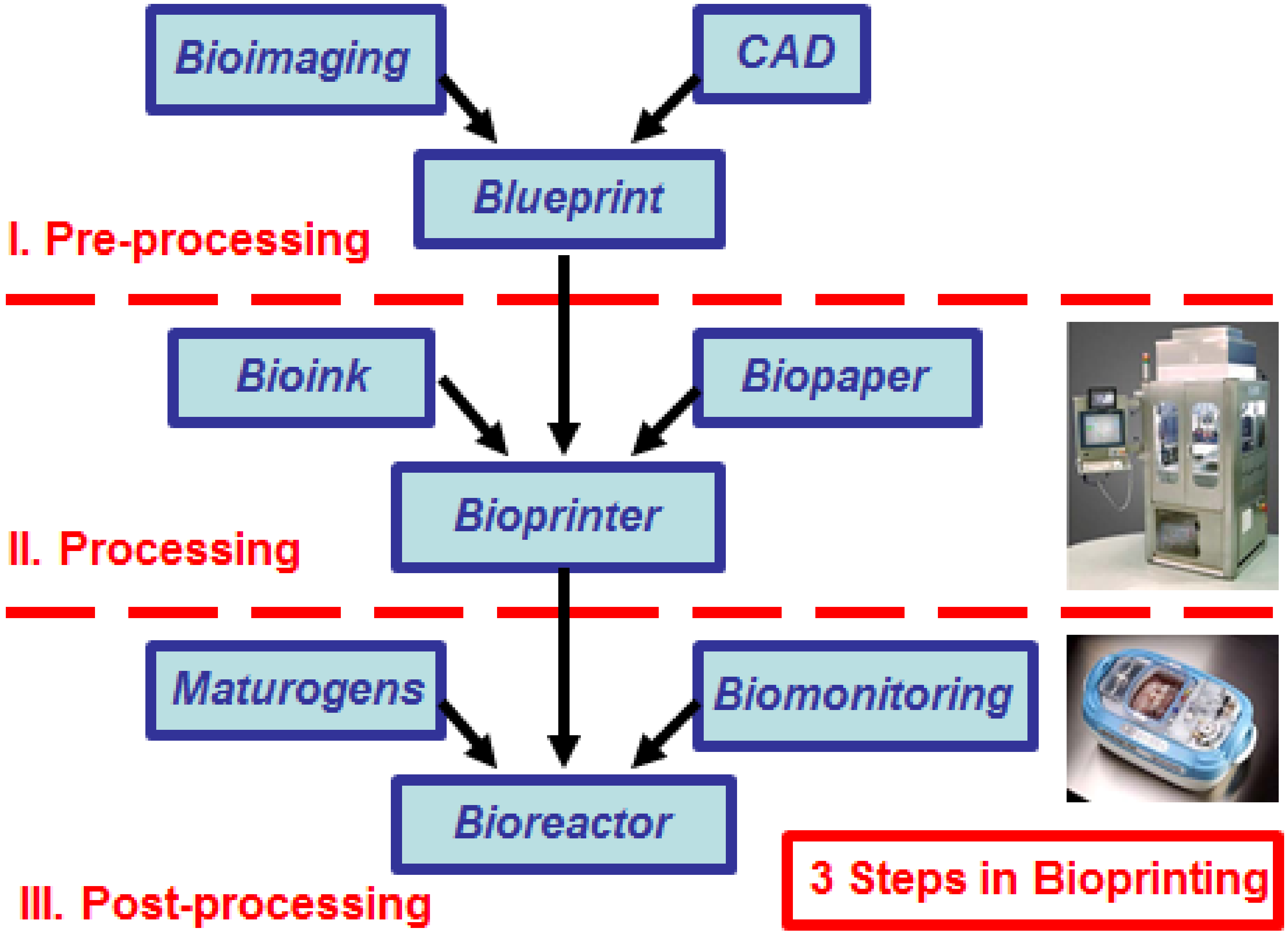
Cells + Hydrogel + Bioprinter = Bioprinted tissue or organ

(Bioink)

(Biopaper)

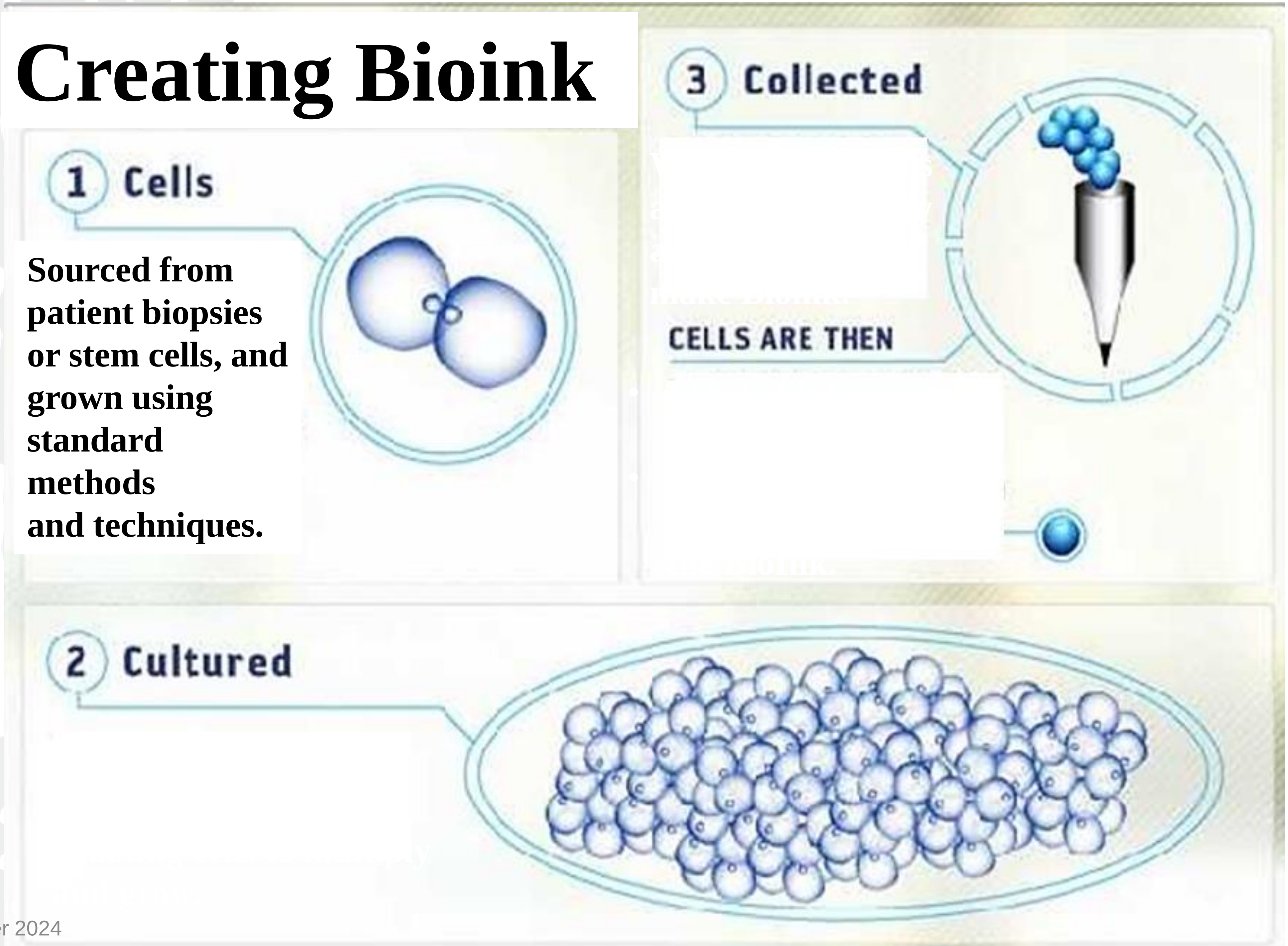
3 phases

- Pre- processing
- Processing
- Post processing


Bioimaging
CAD
Blueprint
I. Pre-processing
Bioink
Biopaper
Bioprinter
II. Processing
Maturogens
Biomonitoring
Bioreactor
III. Post-processing
3 Steps in Bioprinting

Creating Bioink

Sourced from patient biopsies or stem cells, and grown using standard methods and techniques.

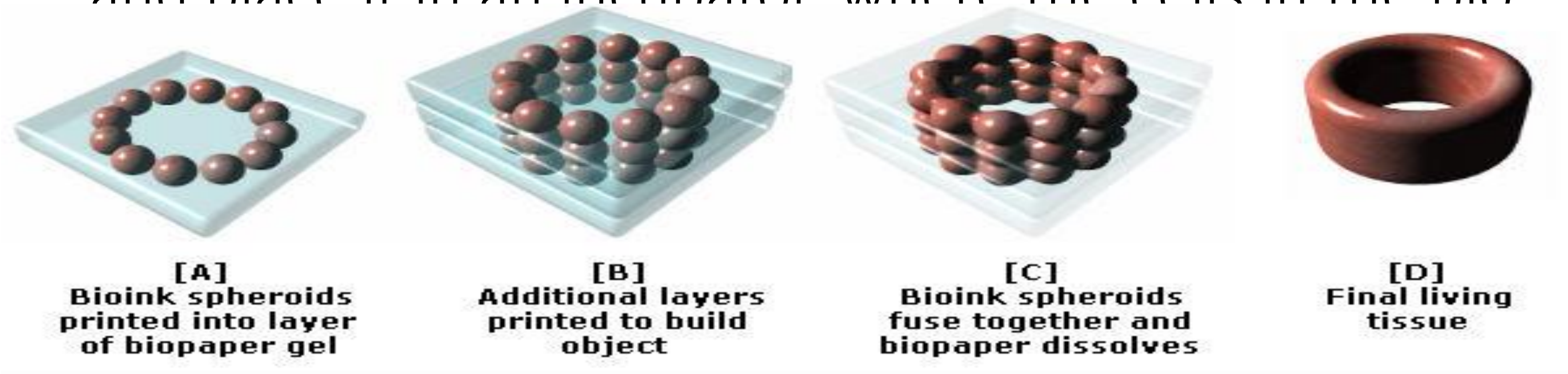


Micro-gel or Hydrogel

Unlike the ink you load into your printer at home, bio-ink is alive, so it needs food, water and oxygen to survive. This nurturing environment is provided by a micro-gel think gelatin enriched with vitamins, proteins and other life-sustaining compounds. Researchers either mix cells with the gel before printing or extrude the cells from one print head, micro-gel from the other. Either way, the gel helps the cells stay suspended and prevents them from settling and clumping.

How do they print an organ.

- After that, it's a matter of hitting File > Print, which sends the modeling data to the bio-printer.
- The printer outputs the organ one layer at a time, using bio-ink and gel to create the complex multicellular tissue and hold it in place.
- Finally, scientists remove the organ from the printer and place it in an incubator, where the cells in the bio-



Last step and the challenging one!

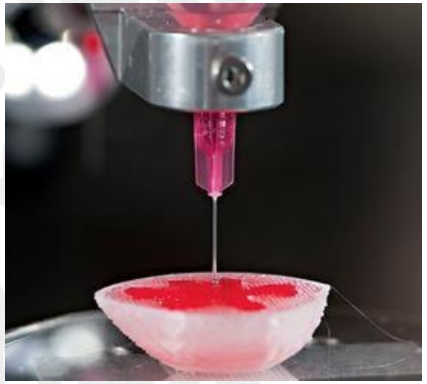
The final step of this process -- making printed organ cells behave like native cells -- has been challenging. Some scientists recommend that bio-printing be done with a patient's stem cells.

After being deposited in their required three-dimensional space, they would then differentiate into mature cells, with all of the instructions about how to "behave." Then, of course, there's the issue of getting blood to all of the cells in a printed organ.

Currently, bio-printing doesn't offer sufficient resolutions to create tiny, single-cell-thick capillaries. But scientists have printed larger blood vessels, and as the technology improves, the next step will be fully functional replacement organs, complete with the vascularization necessary to remain alive and healthy.

Current Progress

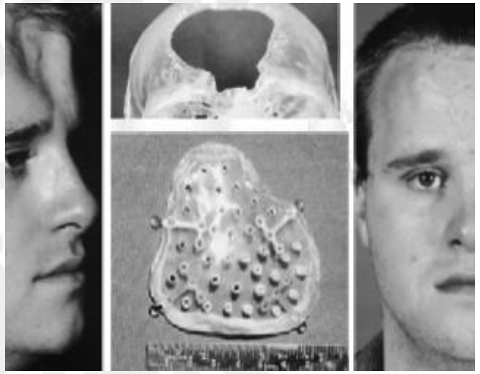
Ear: 250 µm cells and collagen from rat tail make human ear in 15 min. Post-processing 3 months. To serve children with hearing loss due to malformed outer ear.



Kidneys: Layer-by-layer building of scaffold and deposition of kidney cells. Assembly to be transferred into patient

BloodVessels: Rigid but non-toxic sugar filaments form core. Cells deposited around filaments. Subsequent blood flow dissolves sugar.

Skin grafts: laser scan wound to determine depth and area. One inkjet ejects enzymes and second, cells. Layer is finally sealed by human skin cells. Useful in war and disaster zones.



Bones: Print skeleton with ceramic or Titanium powder, incubation of 1 day in culture of human stem cells. Repair of complex fractures in accident survivors.

NUS National University of Singapore

SWOT Analysis

S **Strengths** • All vital organs can be printed by one 3D bioprinter. • Easy to build own custom machine. • Easy to make body parts with desired size and shape. • Huge market potential. • Provides several entrepreneurial opportunities.	**W** **Weaknesses** • Quality of the organs printed. • Production time. • Technolgy is still in prematured state. • Expensive.
O **Opportunities** Improving machine possibilities • larger models. • faster printing. • multi colour prints. • active development of biocompatible materials. • customization of designs based on customer needs.	**T** **Threats** • Technology background of the user. • Time taken for printing an organ. • Cost of organ printing. • In wrong hands, may contribute to fake identity, increase in crime and illegal activities.

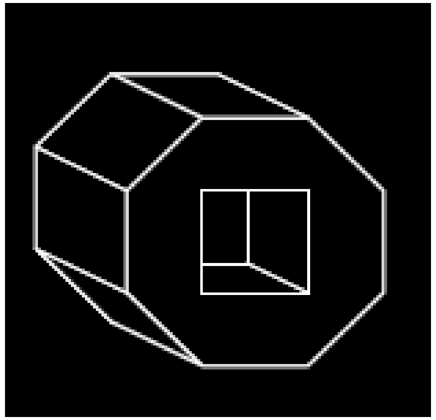
Advantages

- The waiting list for transplant can be reduced considerably.
- Offers high precise resolution scan can be obtain and software can calculate the exact size of the desired replacement.(eg bones)
- Quick process ,10 days to print an average sized liver and lobe. Time will be reduced considerable as the technology advances.
- Artificial organ personalized using patients own cells
- No DNA rejection

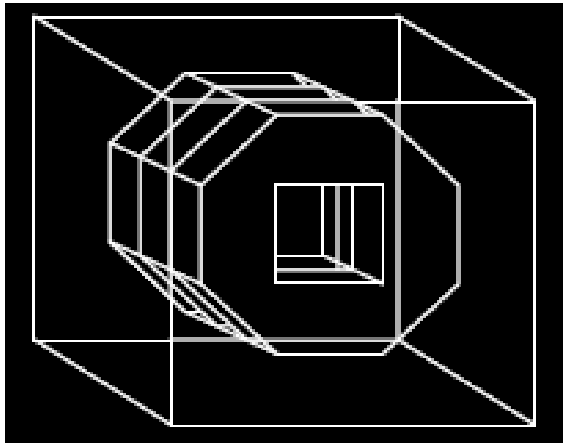
Disadvantages

- It will bring a major ethical and moral debate on its use .
- Implanted organ can be rejected as body cant accept them as functional tissue.
- The cost of printers are very expensive.
- Possibly more expensive than regular organ transplant
- Cost of using stem cells
- Not successfully created yet

Direct Shell Production Casting (DSPC)

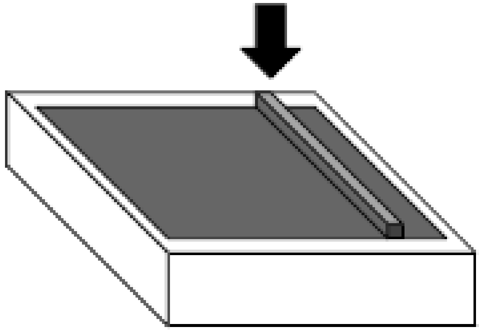


Step 1: CAD design

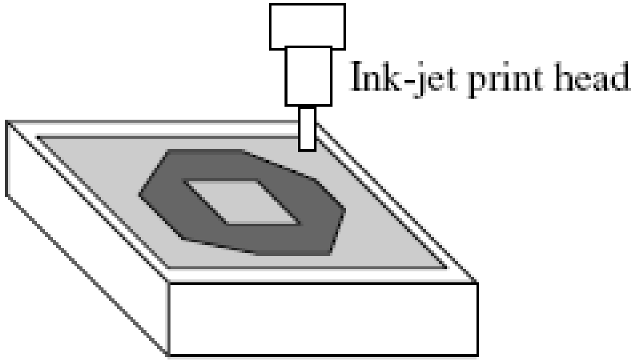


Step 2: Soligen software designs casting mold

casting mold

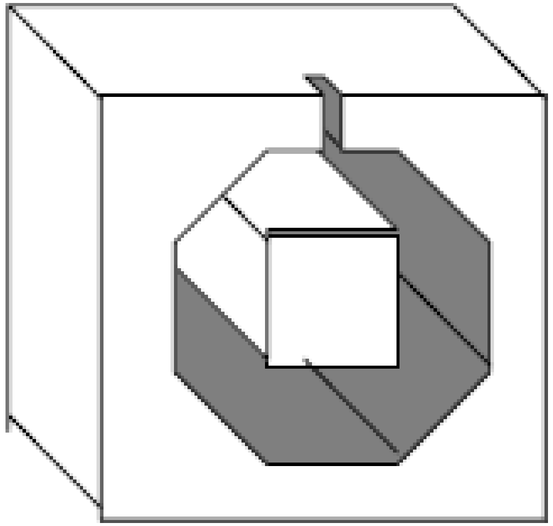


Step 3: The machine deposits thin layer of powder

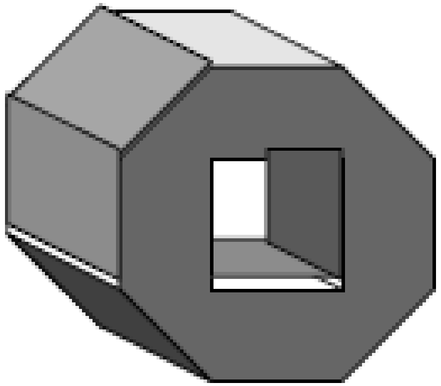


Step 4: Ink-jet print head deposits binders to solidify powder

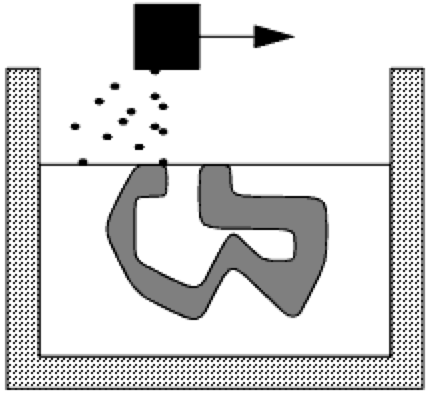
Step 5: The process repeats Steps 3 and 4 until all layers of the mold are formed



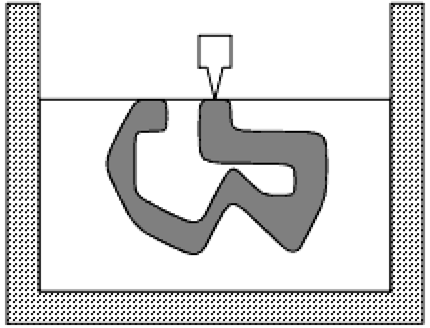
Step 6: Loose powder is removed from the completed mold



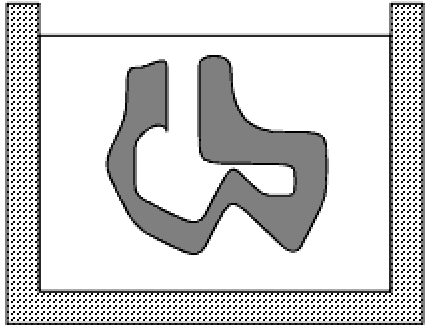
Step 7: Molten metal is poured into mold to create the finished product



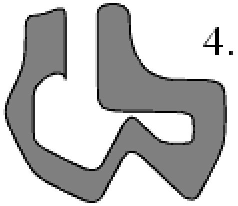
1. powder distribution
   - Aluminum powder is distributed and compressed by a roller



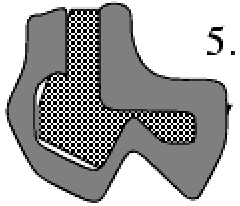
2. Adhesive fusing by printhead
   - operates like a printer, but uses colloidal silica



3. Part complete



4. Part removed



5. Part cast in shell

Advantages

(1) Patternless casting.

Direct tooling, thus eliminating the need to produce any patterns.

(2) *Functional metal parts*.

As a result, functional metal parts (or metal tooling, such as dies for die casting) could be made directly from the CAD data of the part.

(3) *Net-shaped integral molds*.

No parting lines, core prints or draft angles are required. Integral gatings and chills can be added to optimize mechanical properties.

.

Disadvantages

1. Limited materials**.**

   The DSPC only focuses on making ceramics molds primarily for metal casting

2. Rough surface finish: details down to 0.175mm; tolerance +/- 0.05mm

3. Unbound powder can clog in hidden cavities

4. not commercially available yet

5. small work envelope

Applications

The DSPC Technology is used primarily to create casting shells for production of parts and prototypes. It aims to be a premier “one-stop shop” for functional cast metal parts produced directly from a CAD file, and with no need for pre-fabricated tooling to produce the first article. DSPC has been used in the following areas:

(1) Automotive industry.

(2) Aerospace industry.

(3) Computer manufacture.

(4) Medical prostheses.

Water Cooled Marine Exhaust Manifold

Ford Cobra R - Intake Manifold

Race cars intake manifold - GM Motorsports

Parts Pilots Metal Parts for Caterpillar

Caterpillar needed to prototype a complex engine component within a week .

They sent the design file of the component via a modem to Parts (a division of Soligen Inc.) on Wednesday evening.

By Friday, Parts had completed two casting shells with the DSPC systems.

On Monday, the foundry poured the shells with A356 aluminum.

On Tuesday, the parts were heat treated and machining finished on Wednesday. On the same day, the fully functional parts were shipped to Caterpillar for installation on the engine, thus completing the order from Caterpillar.

This is very much faster than any traditional fabrication process could deliver.

Current materials in Rapid /Additive Manufacturing

Materials in AM today

- Thermoplastics (FDM, SLS)
- Thermosets (SLA)
- Powder based composites (3DP)
- Metals (EBM, SLS)
- Sealant tapes, paper (LOM)
- Starch and sugar (3DP)

Functional/structural parts

FDM (ABS and Nylon)
SLS (thermoplastics, metals)
EBM (high strength alloys, Ti, stainless steel, CoCr)

Non-functional/structural parts

SLA (resins): smoothest surface, good for casting
LOM (paper), 3D Printing (plaster, sand): marketing and concept prototypes, sand casting molds

As new materials are introduced, more functional components will be manufactured (perhaps 30-40% by 2020).

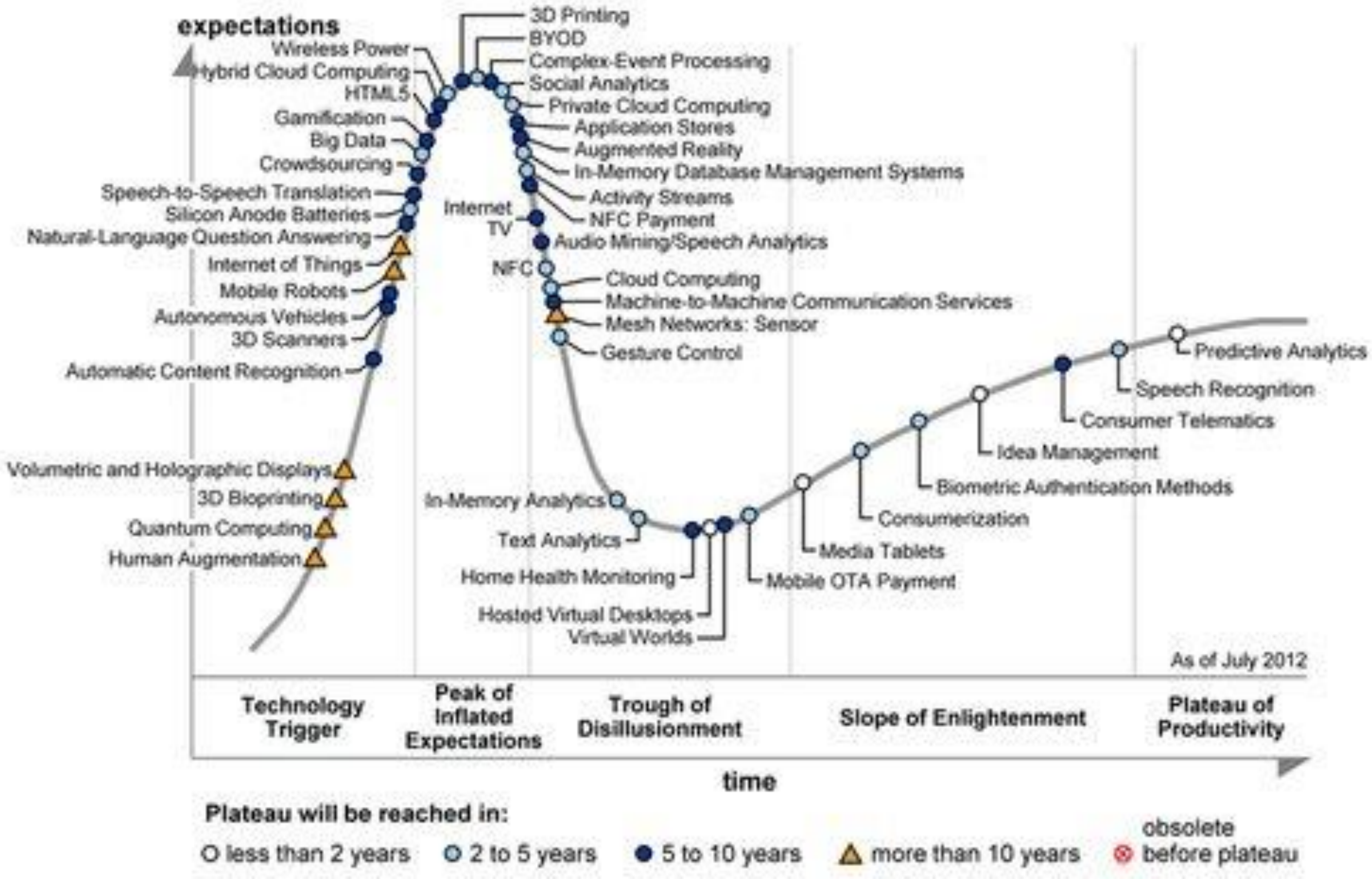
Importantly AM is one of the best approaches for complex architected materials.

Challenges in AM materials properties predictions

- Most AM processes introduce anisotropy in mechanical properties (z different from x,y)
- Local differences in laser/EB power (e.g., perimeter vs center) introduce heterogeneity in mechanical properties
- Laser fluctuations might result in embedded defects that are difficult to identify
- All existing machines are open-loop: temperature sensors have been introduced in some processes, but the readings are not used to optimize the processing parameters on the fly.

A word of caution

Tech Consultancy Puts 3D Printing at Peak of "Hype Cycle"



Bio-CAD modeling and its applications in computer-aided tissue engineering

Hamza Riaz

UW-14-ME-BSC-045

Layout

- Use of CAD in Bio-Medical engineering
- Overview of computer-aided tissue engineering
- Bio-CAD modeling in CATE
- Different structures of unit cells

Use of CAD in Bio-Medical Engineering

Cad is being used in Bio-Medical Engineering as

- In Clinical medicine
- In tissue engineering
- In Customized medical implant design

Overview of CATE

CATE embraces three major applications in tissue engineering

- computer-aided tissue modeling, including 3D anatomic visualization, 3D reconstruction and CAD-based tissue modeling
- computer-aided tissue scaffold informatics and biomimetic design, including computer-aided tissue classification and application for tissue identification and characterization at different tissue hierarchical levels

Overview of CATE

- Bio-manufacturing for tissue and organ regeneration, including computer-aided manufacturing of tissue scaffolds, bio-manufacturing of tissue constructs, bio-blueprint modeling for 3D cell and organ printing

Overview of CATE

Computer Aided Tissue Engineering

Computer-Aided Tissue and Bio-Modeling

CT/MRI Image

Anatomic and Biophysics Modeling
- Geometry/Morphology
- Volumetric representation
- Mechanics/Deformation/Kinematics

CAD-based Modeling
- Contour-based model
- Surface extraction
- Solid model

Biomedical Physical Modeling
- Physical model by rapid prototyping
- Biomodeling for surgical planning

Scaffold Informatics and Biomimetic Design

Scaffold Informatics & Modeling
- Tissue morphology classification
- Morphology property characterization
- Biological intent
- Informatics database and modeling

Biomimetic Design
- Design for Multi-constraints
- A framework for biomimetic design

Multi-scale Modeling for Biological System
- Asymptotic homogenization for both spatial and temporal degradation

Bio-Manufacturing for Tissue and Organ Regeneration

Bio-manufacturing of Tissue Scaffolds
- Bio-conductive scaffold fabrication
- Multi-material hybrid scaffold
- "Smart" scaffold with micro/nano sensors

Bio-manufacturing of Tissue Constructs
- Scaffold with automatic cell seeding
- Cellular tissue threads
- Cell-embedded tissue constructs

3D Cell and Organ Printing
- Cell pattern, printing and deposition
- Bio-blueprint and organ modeling
- Organ printing

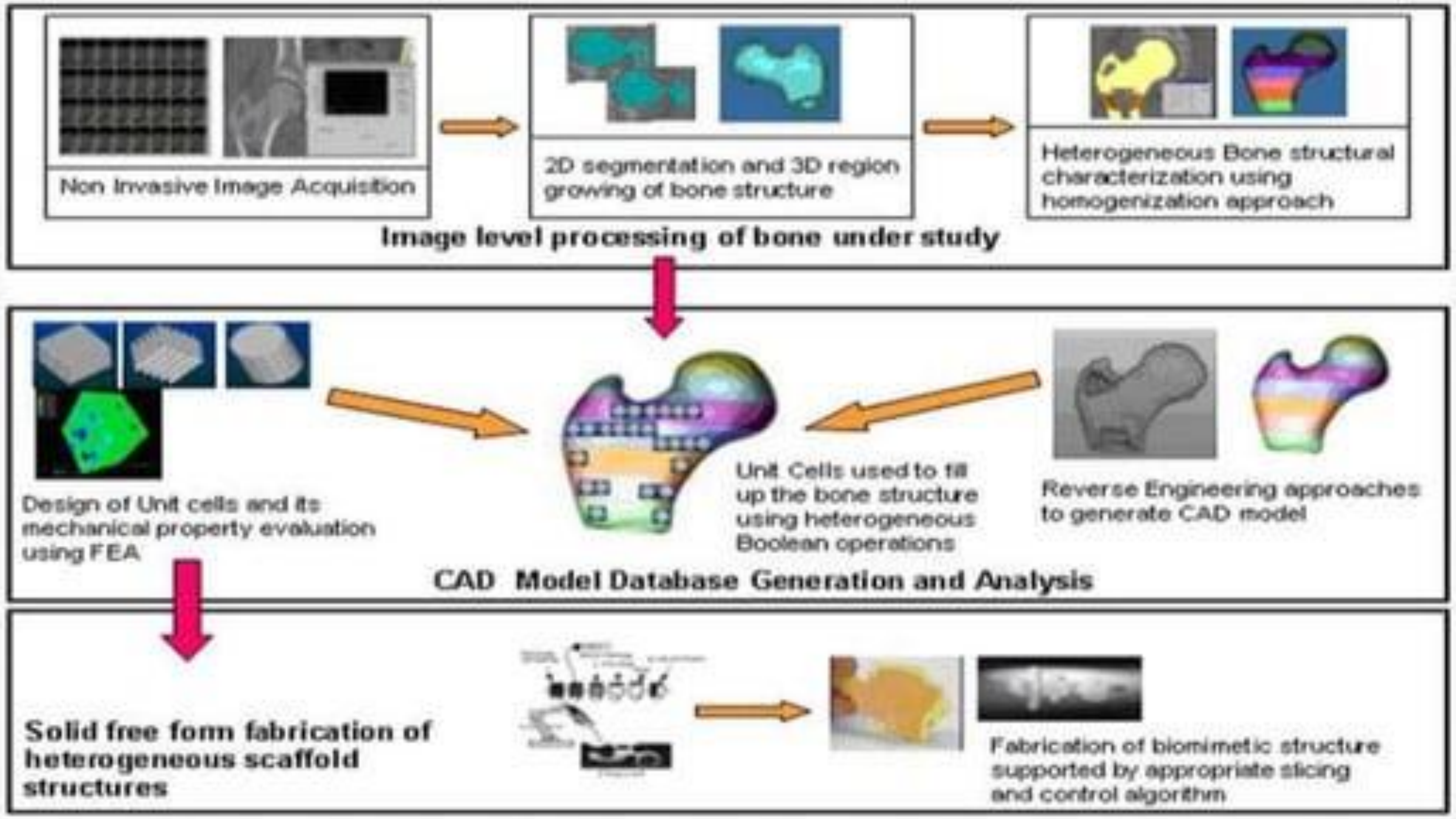
Bio-CAD modeling in CATE

- Reconstruction of data obtained from the noninvasive images of MRI and CT scan in medical reconstructive software MIMICS and Geomagic.
- Characterization of heterogeneity of tissue structure using homogenized techniques
- ABAQUS is used to determine the mechanical properties of the tissues

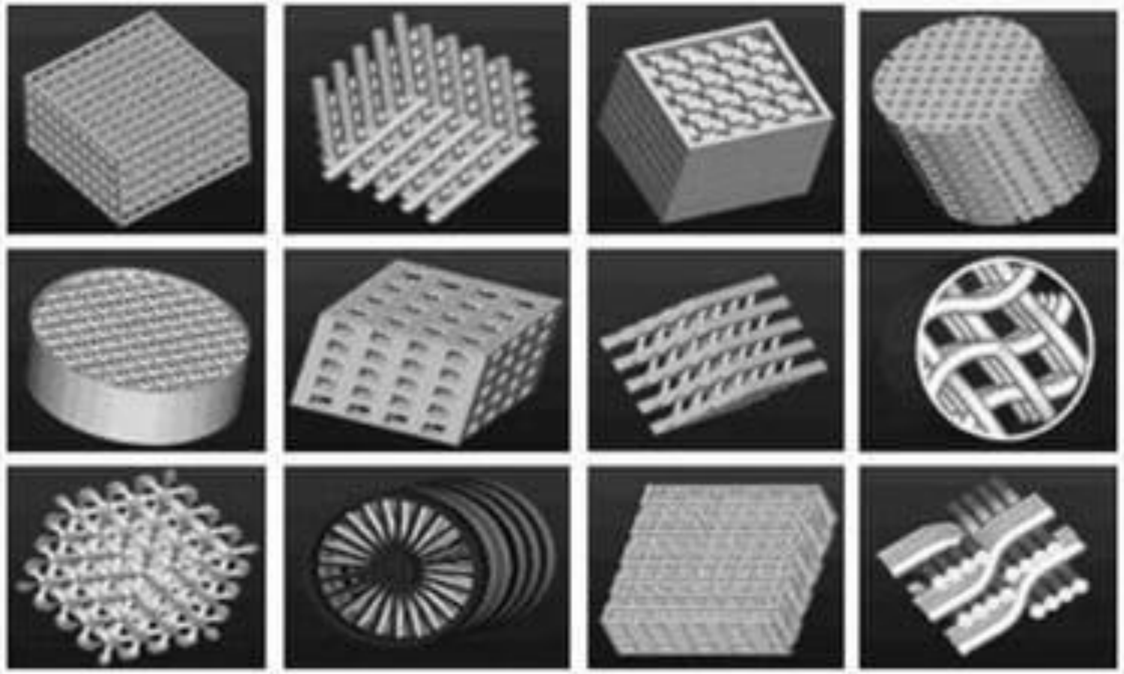
Bio-CAD modeling in CATE

- Using CAD solid modeling based Boolean operations unit cells relating to the internal architecture of candidate's unit cells are integrated with the shape of bone
- CAD model of bone tissues scaffolds is made having the same internal and external properties to that of actual replaced bone.
- Process planning and tool path is generated based on solid freeform fabrications techniques that would be able to design the desired tissue structure by using CAM techniques [1]

Bio-CAD modeling in CATE



Different structures of unit cells



Thanks

References

- [1] Bio-CAD modeling and its applications in computer-aided tissue engineering
- [1] W. Sun*, B. Starly, J. Nam, A. Darling

ORGAN PRINTING

- **SCAFFOLDS** are materials that have been engineered to cause desirable cellular interactions to contribute to the formation of new functional tissues for medical purposes.
- Cells are often 'seeded' into these structures capable of supporting three-dimensional tissue formation. Scaffolds mimic the extracellular matrix of the native tissue, recapitulating the in vivo milieu and allowing cells to influence their own microenvironments.
- They usually serve at least one of the following purposes: allowing cell attachment and migration, delivering and retaining cells and biochemical factors, enabling diffusion of vital cell nutrients and expressed products, and exerting certain mechanical and biological influences to modify the behaviour of the cell phase.

Materials

- Material selection is an essential aspect of producing a scaffold.
- The materials utilized can be natural or synthetic and can be biodegradable or non-biodegradable.
- Additionally, they must be biocompatible, meaning that they don't cause any adverse effects to cells.
- Silicone, for example, is a synthetic, non-biodegradable material commonly used as a drug delivery material,
- while gelatin is a biodegradable, natural material commonly used in cell-culture scaffolds

Total artificial heart developed at ETH Zurich

3D printing techniques

- **Sacrificial writing into functional tissue (SWIFT)**
- **Stereolithographic (SLA) 3D bioprinting**
- **Drop-based bioprinting (Inkjet)**
- **Extrusion bioprinting**
- **Fused deposition modeling**
- **Selective laser sintering**

Printing materials

- Natural Polymers
- Synthetic Polymers - Synthetic polymers are human made through chemical reactions of monomers
- Natural-synthetic hybrid polymers

- Types of printers and processes
- The types of printers used for organ printing include
  - Inkjet printer
  - Multi-nozzle
  - Hybrid printer
  - Electrospinning
  - Drop-on-demand

Applications

- Organ Donation
- Physician and surgical training
- Pharmaceutical research
- Organ-on-a-chip