Centro de Tecnologia da Informação Renato Archer

Impressão 3D, Biomateriais e a Biofabricação

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Head of the DT3D

Brazilian Science, Technology, Innovation and Communication Ministry - MCTIC

Three Dimensional Technologies Division – CTI/DT3D - Established in 1997

Mission

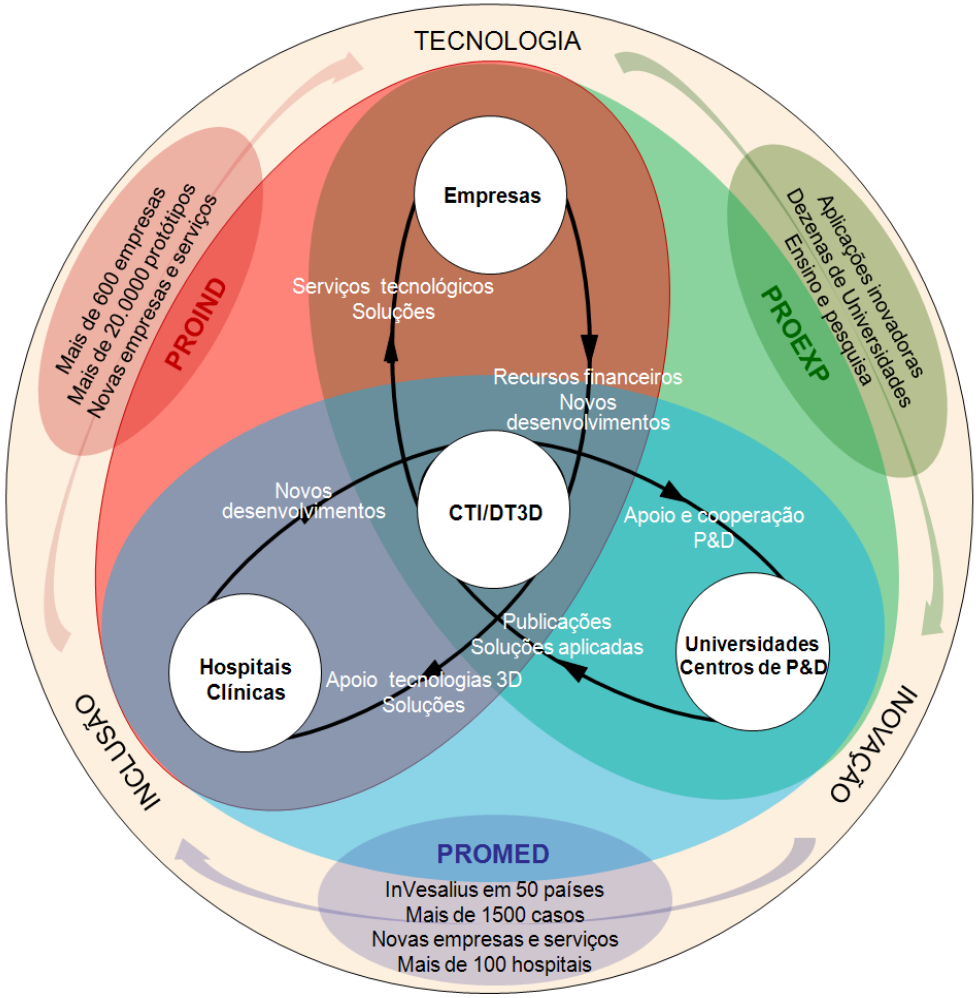
To research, develop, utilize, and diffuse three dimensional technologies (virtual and physical) focusing in innovation and multidisciplinary applications driven by society

Partnership

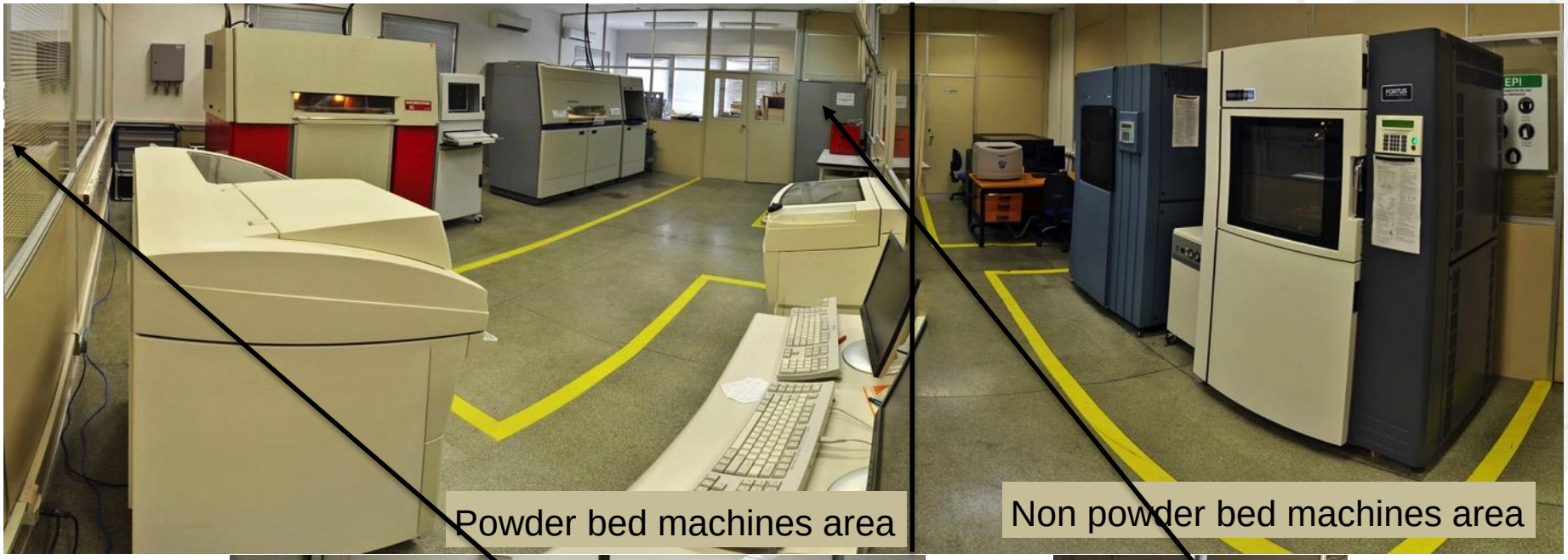
Companies (ProIND)

Hospitals (ProMED)

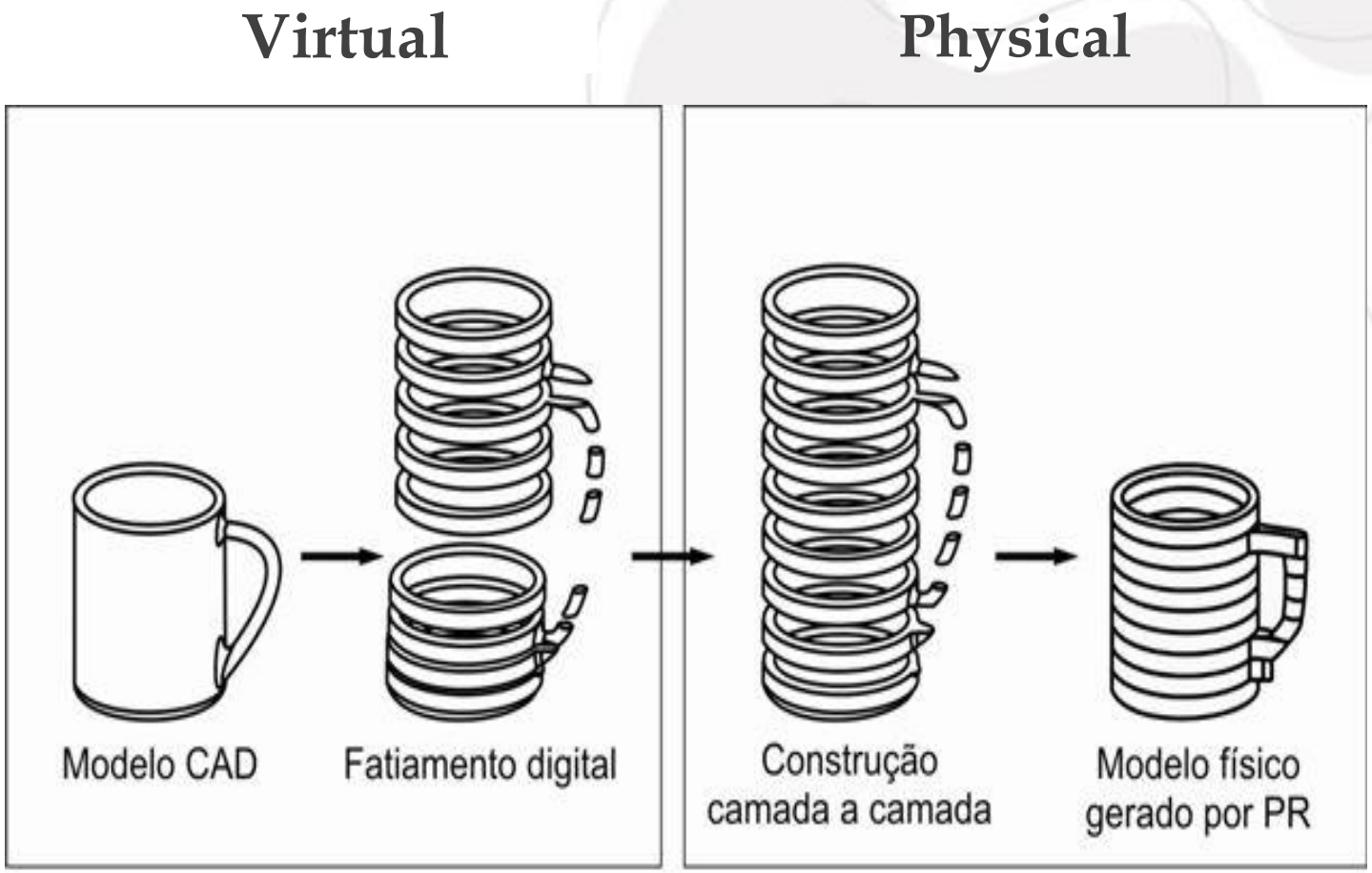
Universities (ProEXP)



CTI Renato Archer - AM infrastructure



3D printing: concepts



Additive Manufacturing

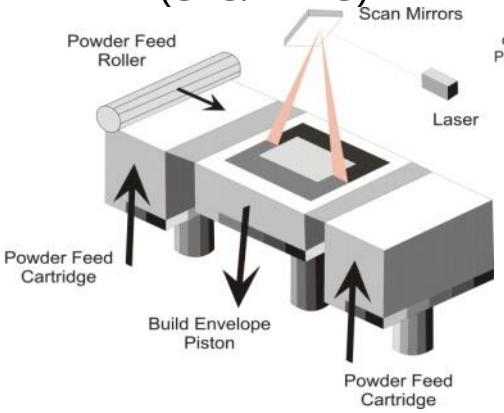
3D Printing / Rapid Prototyping / Freeform Fabrication

First system (SLA) in 1986 – Automotive, aerospace, and consumer products prototyping

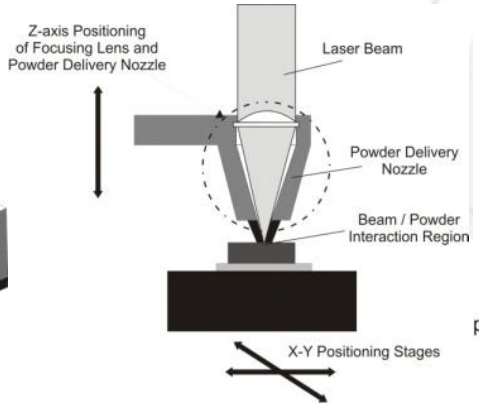
ASTM/ISO Standard – Classes of AM processes

laser

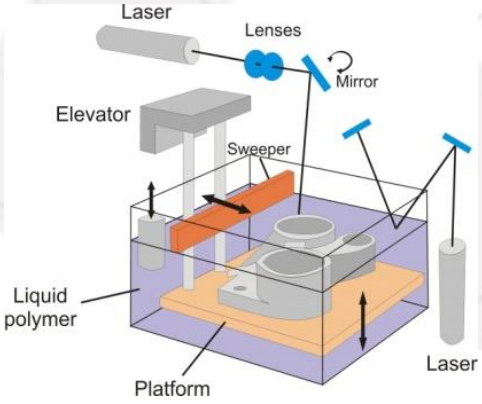
Metallic or polymeric Powder (SLS/DMLS)



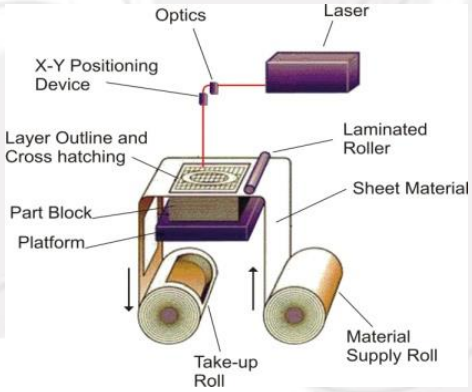
Metallic powder (LENS)



Liquid Resin (SLA)

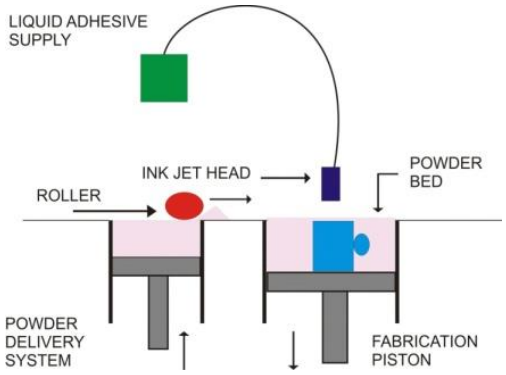


Sheet (LOM)

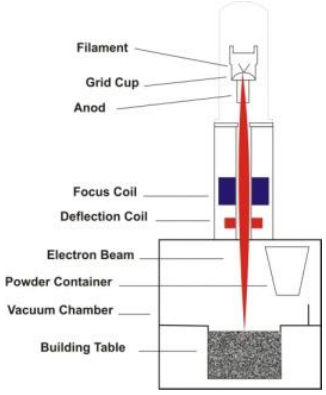


ink-jet head | **electron beam** | **extrusion head** | **UV lamp/ink-jet head**

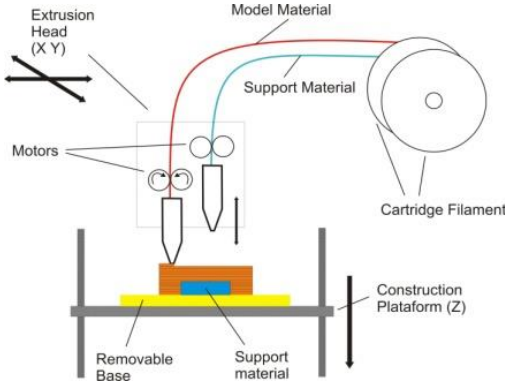
Ceramic Powder (3DP)



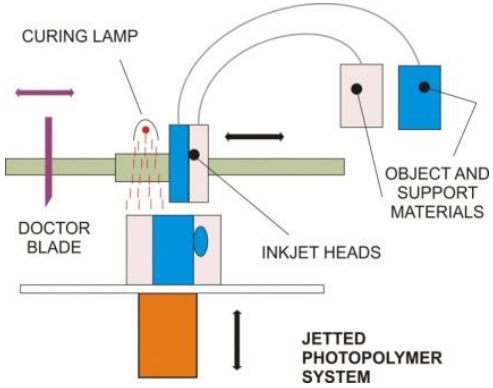
Metallic Powder (EBM)



Polymeric Filaments (FDM)

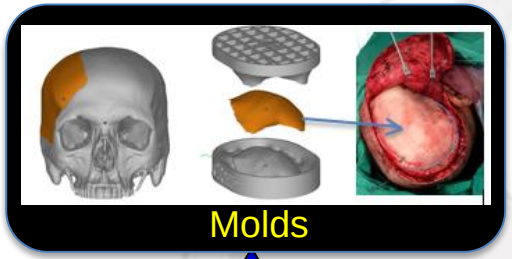


Liquid Resin (Objet)

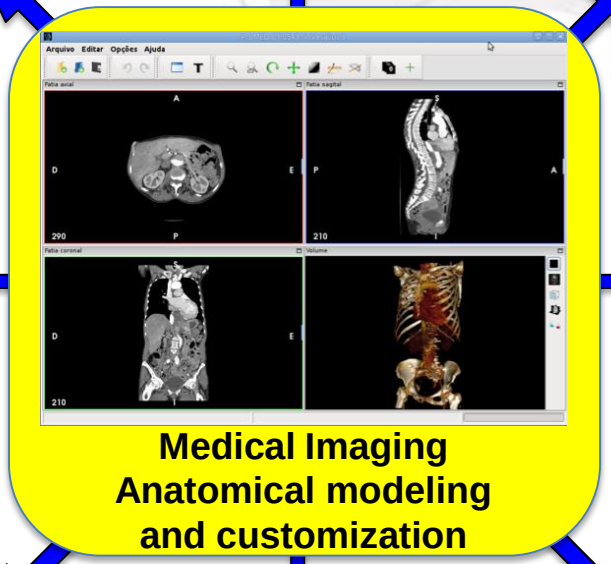


Applications at CTI Renato Archer

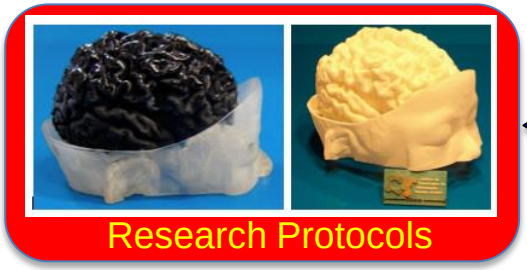

Shaping regular materials

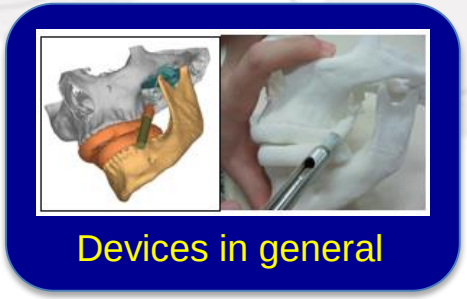

Molds

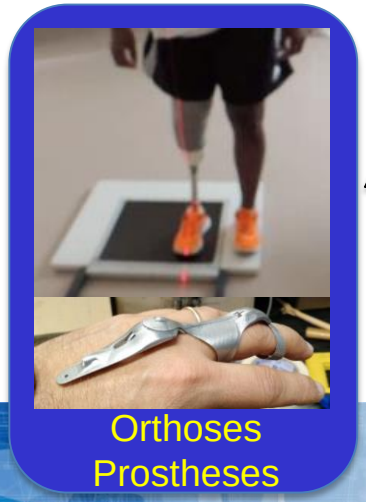
Metal Prostheses



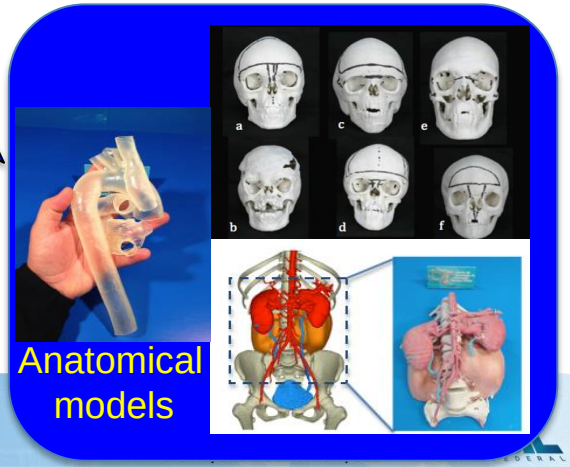
Medical Imaging
Anatomical modeling
and customization


Research Protocols


Devices in general


Orthoses
Prostheses

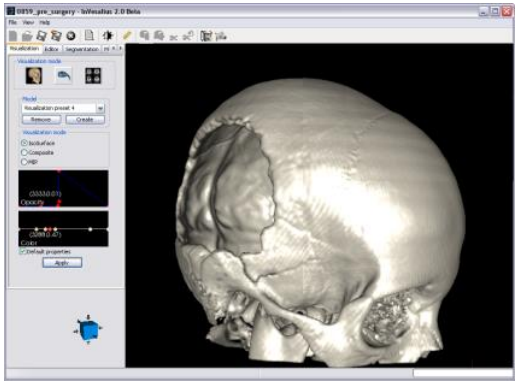

Surgical Guides


Anatomical
models

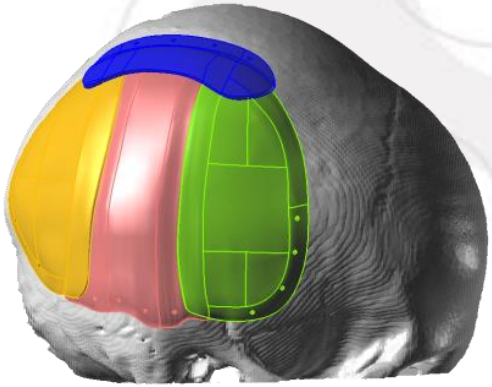
Applications at CTI Renato Archer

Material Final: PMMA

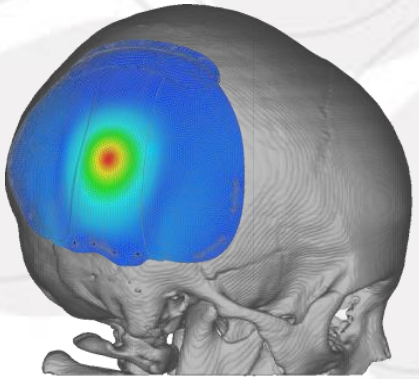
ABS/FDM



Reconstrução 3D



Modelagem de Superfície Complexa em BioCAD



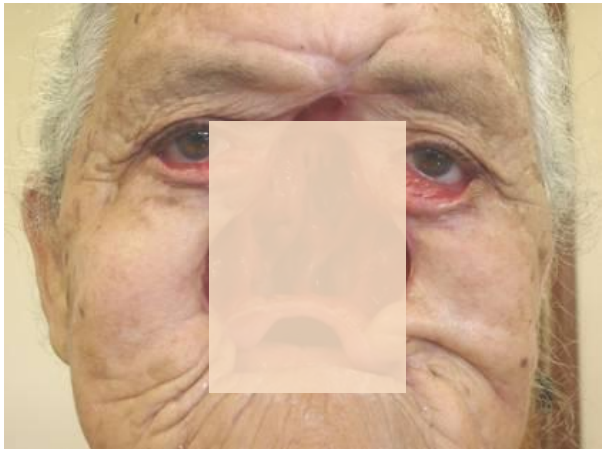
Análise FEM

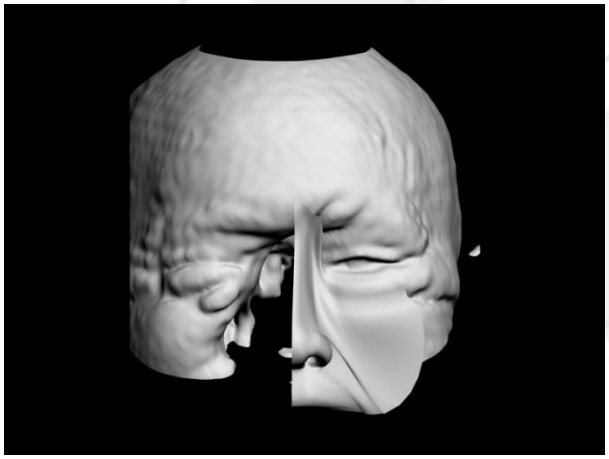
Simulação do Biomodelo

Simulação final com biomaterial (Polimetacrilato de Metila)

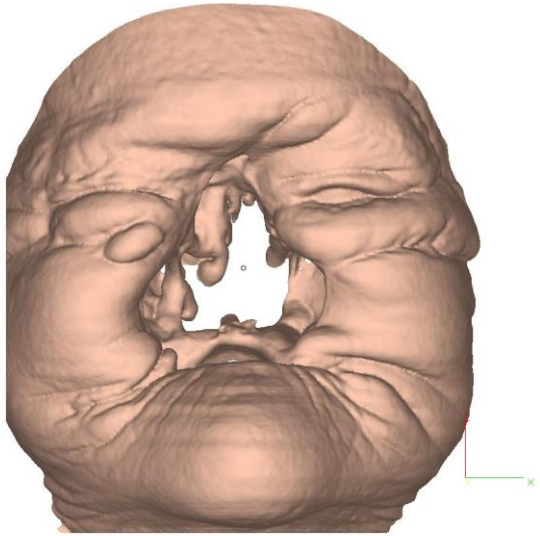
Processo Cirurgico

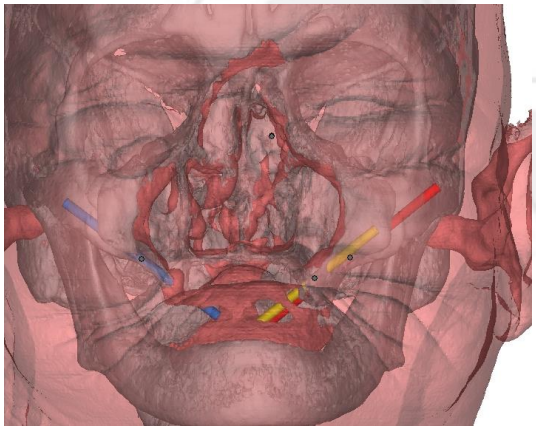
Bucomaxilo Prostheses using BioCAD

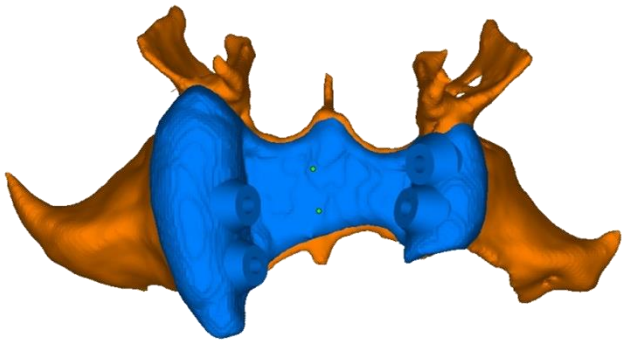




Bucomaxilofacial prostheses







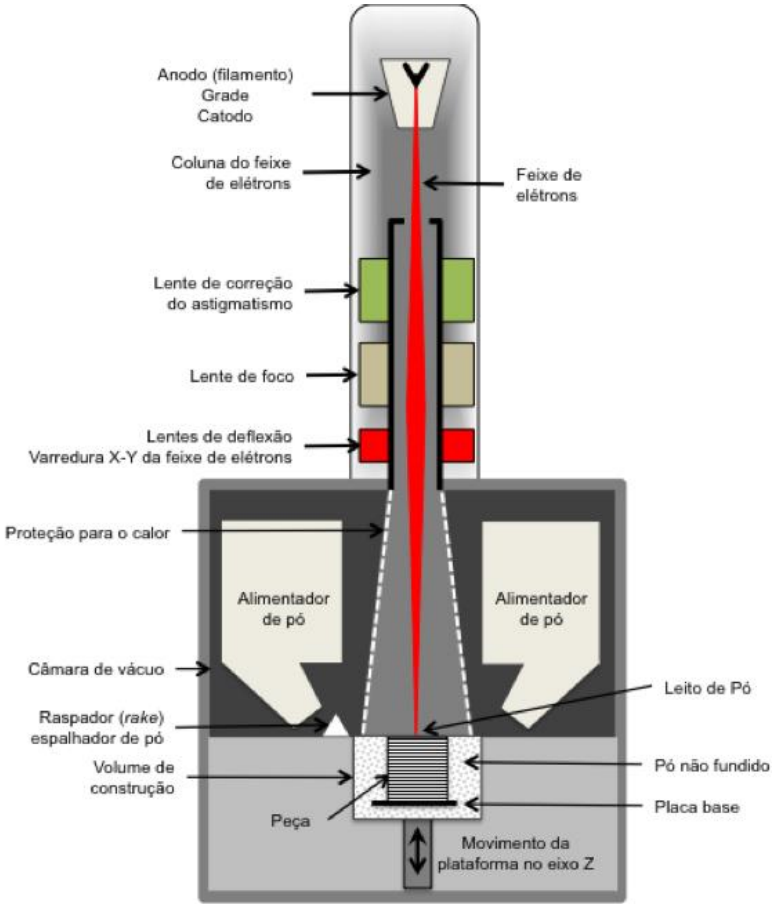
Dispositivo Metálico

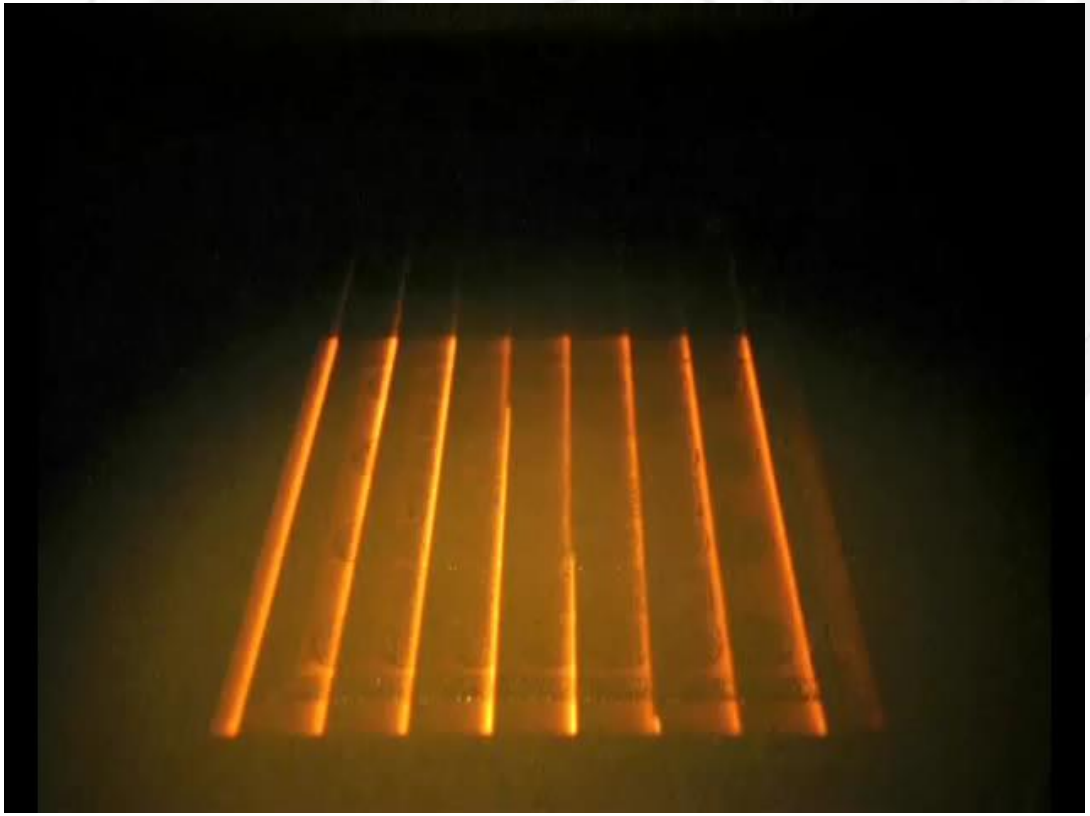
LaserCUSING – Concept Laser

A fiber laser melts down a powder metal bed

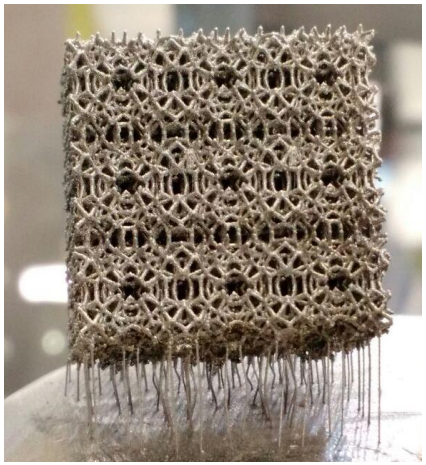
Thanks to Concept Laser and Techno How for the availability of a Mlab at CTI

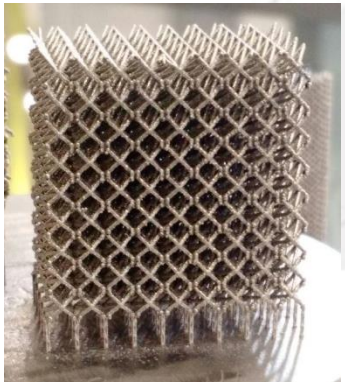
EBM – Electron Beam Melting → Metallic parts





Topological optimization



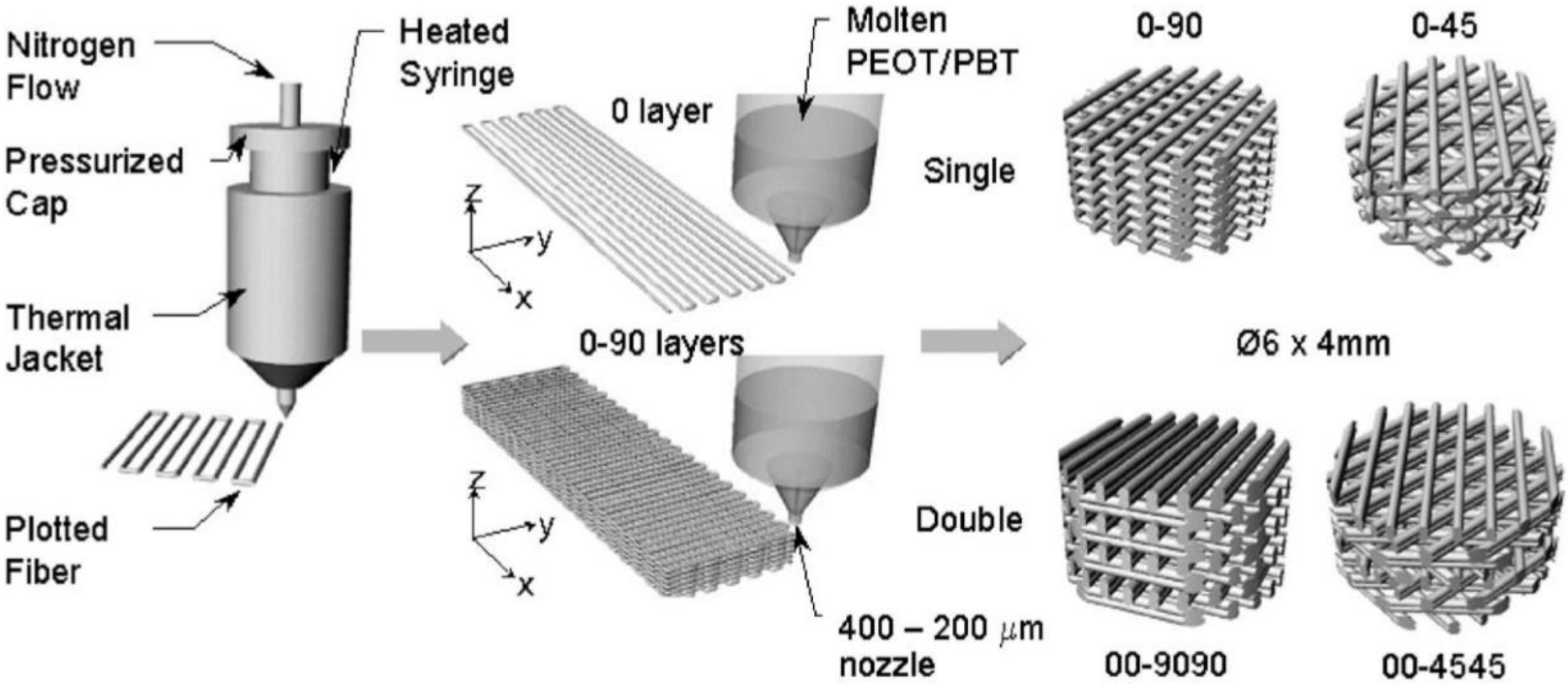


Agradecimentos à ARCAM-EBM

Extrusion head

PCL, PHB, PLA, PLLA, ...

3D fiber-deposited scaffolds for tissue engineering: Influence of pores geometry and architecture on dynamic mechanical properties



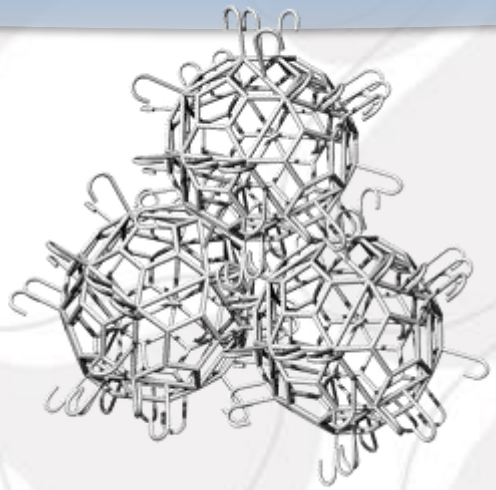
Moroni et al., 2006

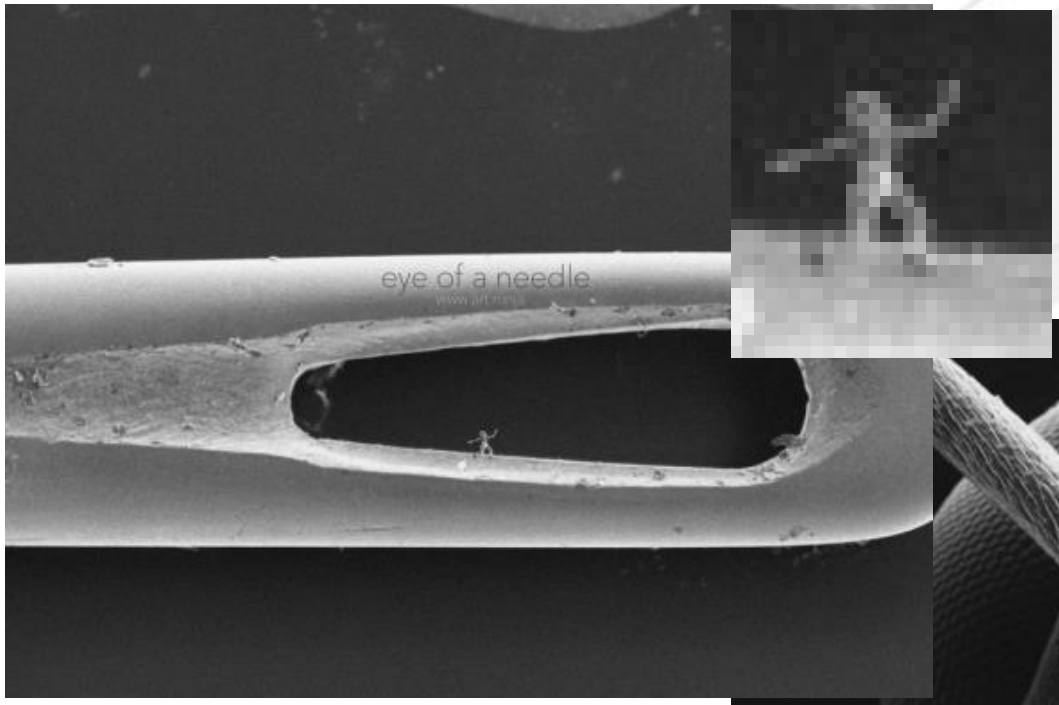
Two-Photon Polymerization

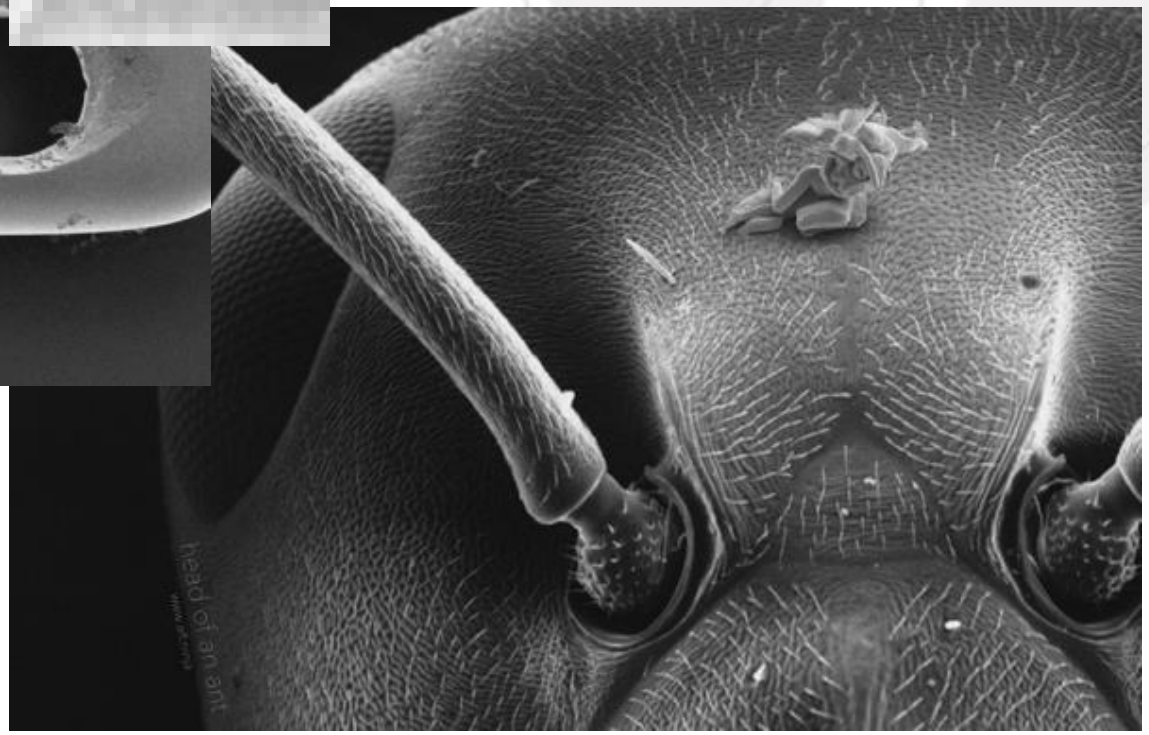
FINEP 8 Mi Grant

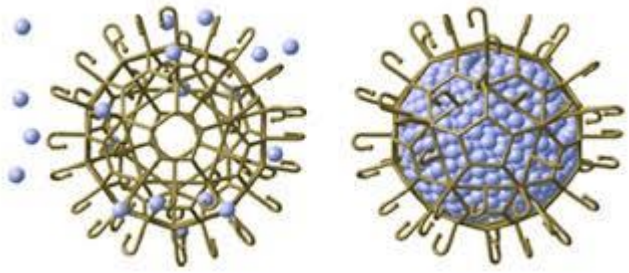
Application Video: 3D µ-Printing

Two Photon Polymerization – 2PP







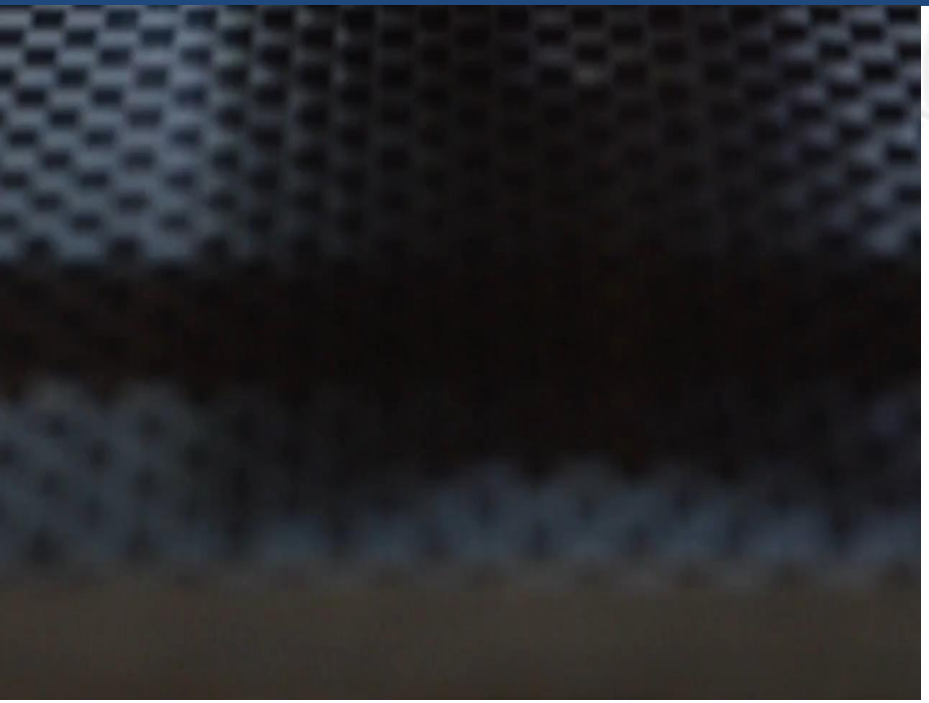


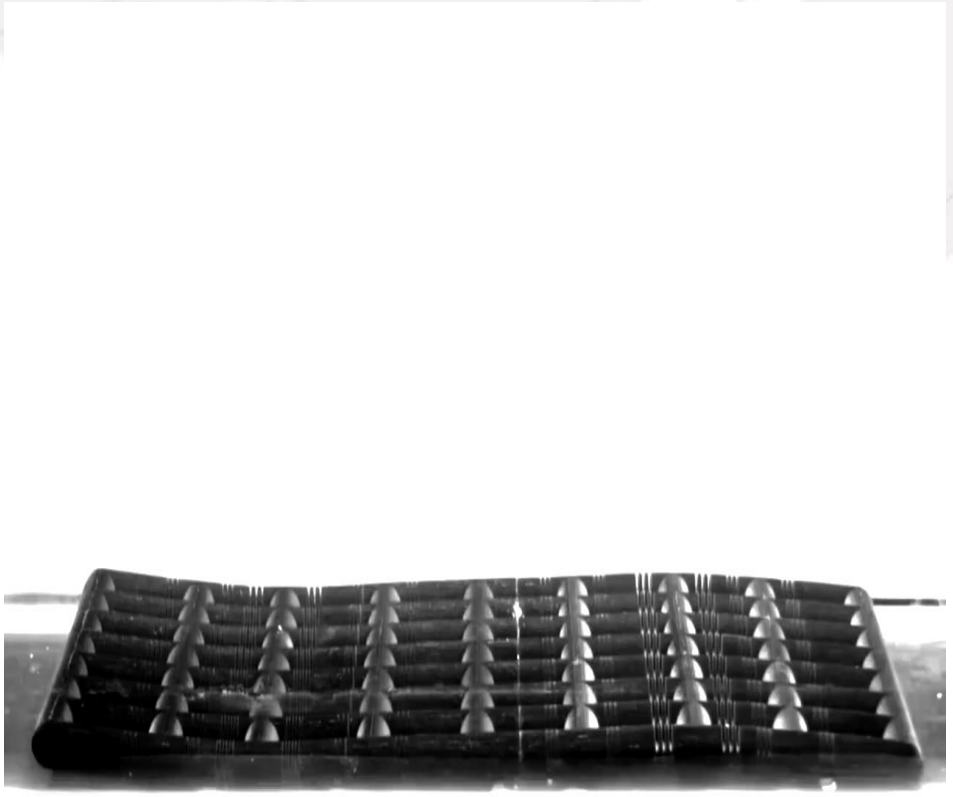
200 um

Source: http://www.3ders.org/articles/20141115-jonty-hurwitz-3d-printed-nano-sculptures-at-the-same-scale-as-a-human-sperm.html

4D Printing: Programmable materials

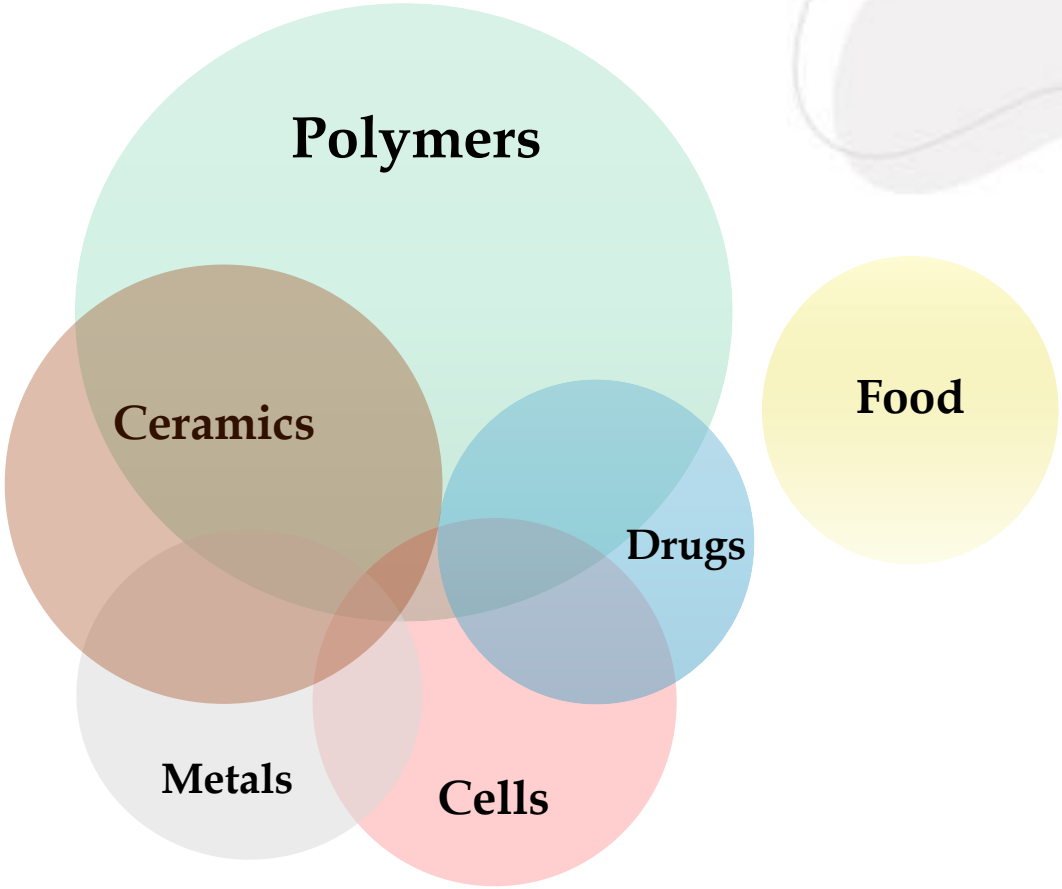
"Programmable Materials consist of material compositions that are designed to become highly dynamic in form and function, yet they are as cost-effective as traditional materials, easily fabricated and capable of flat-pack shipping and self-assembly"





Source: http://www.selfassemblylab.net/ProgrammableMaterials.php

Materials for AM - Processes X Materials

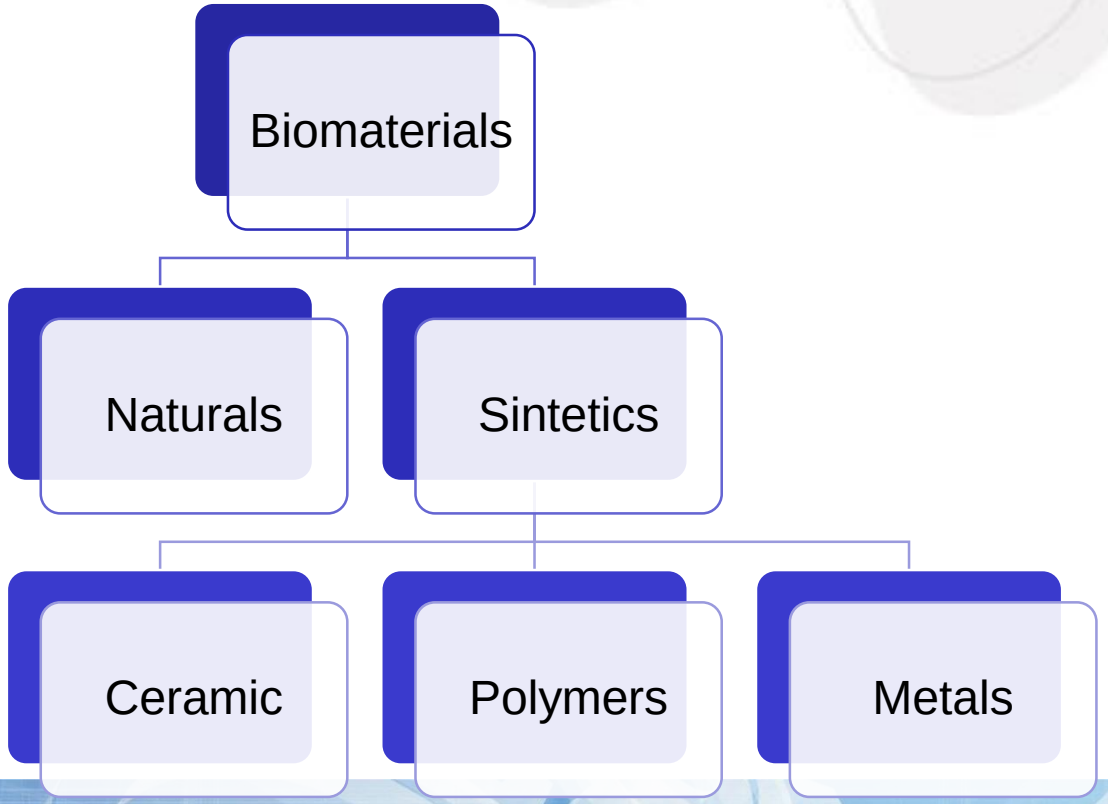


Composite
Functional graded materials
Incorporation of nanomaterials

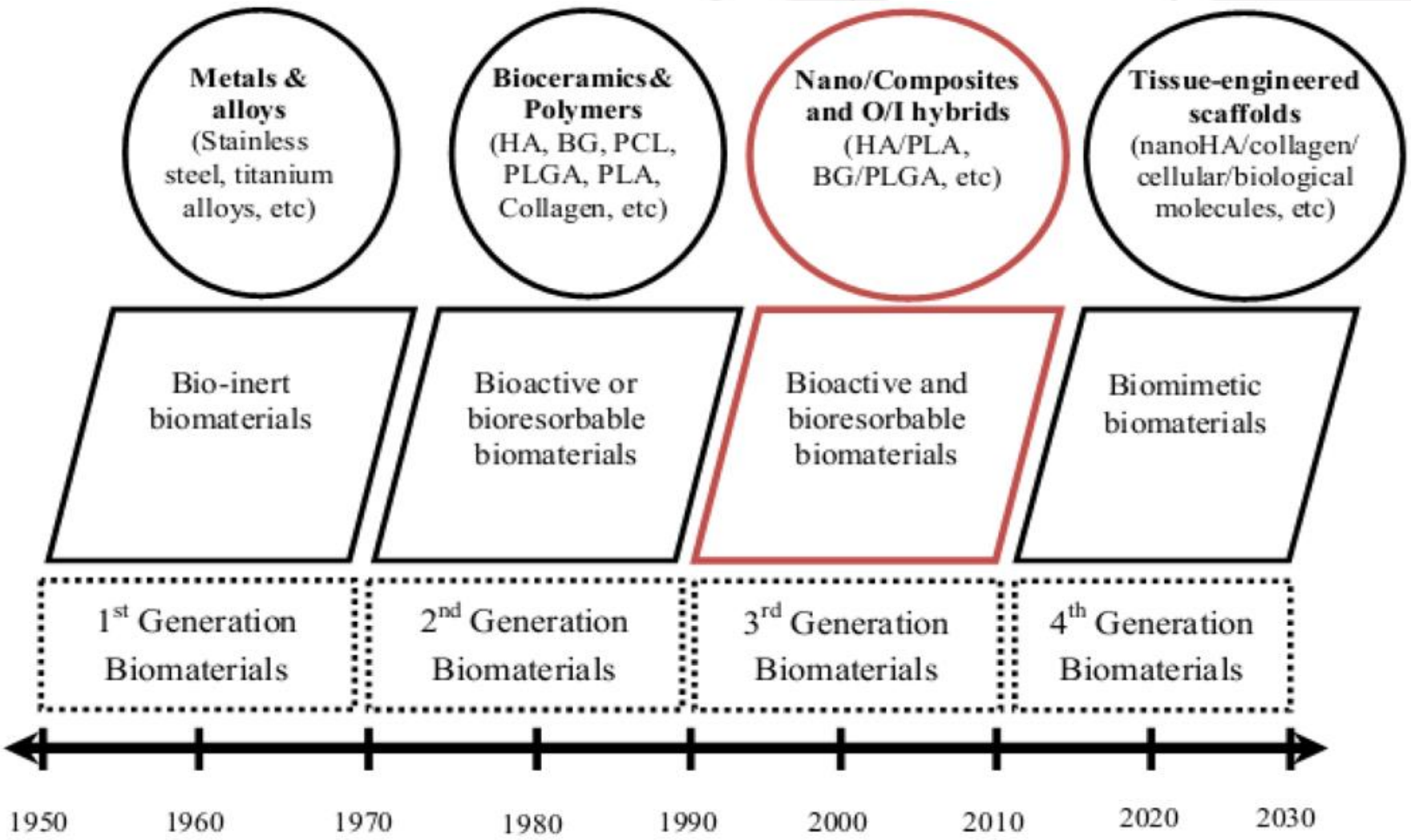
Biomaterials
(synthetic and biological)
A very restricted class of materials for AM can be implanted in to the human body

Biomaterials for Biological Tissue Replacements

Biomaterials are those materials — be it natural or synthetic, alive or lifeless, and usually made of multiple components — that interact with biological systems.



Evolution of Biomaterials → Tissue engineered scaffolds



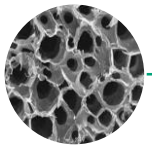
(Murugan and Ramakrishna, 2005)

Scaffolds - Requirements

Biological

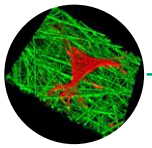
Mechanicals, Physicals and Chemicals

Adequate porosity

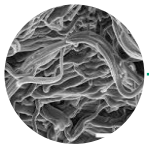


Biocompatibility

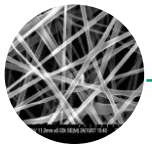
Ability to conduct signals

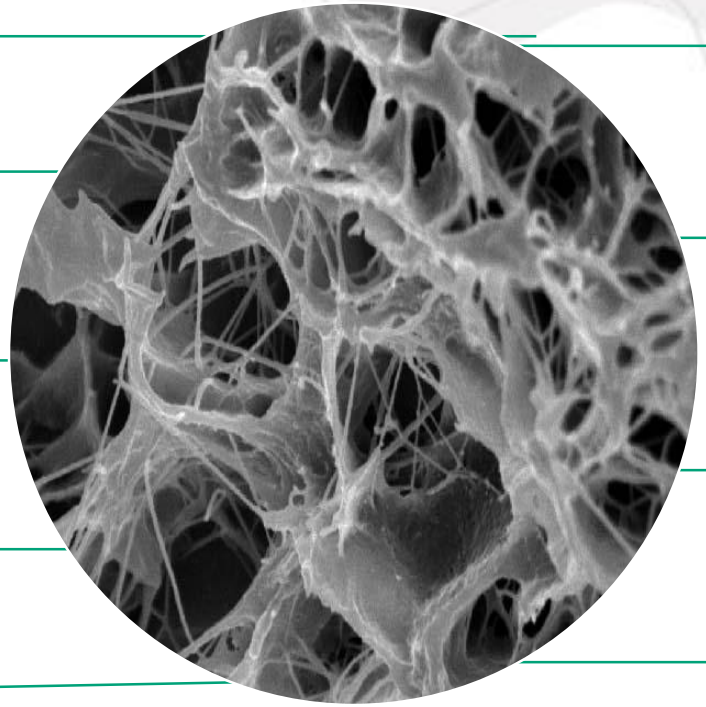


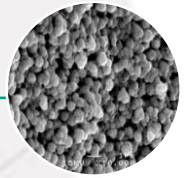
Biodegradability



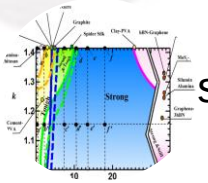
Controlled degradation





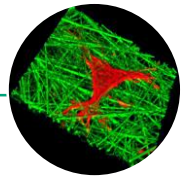


Suitable surface finishing



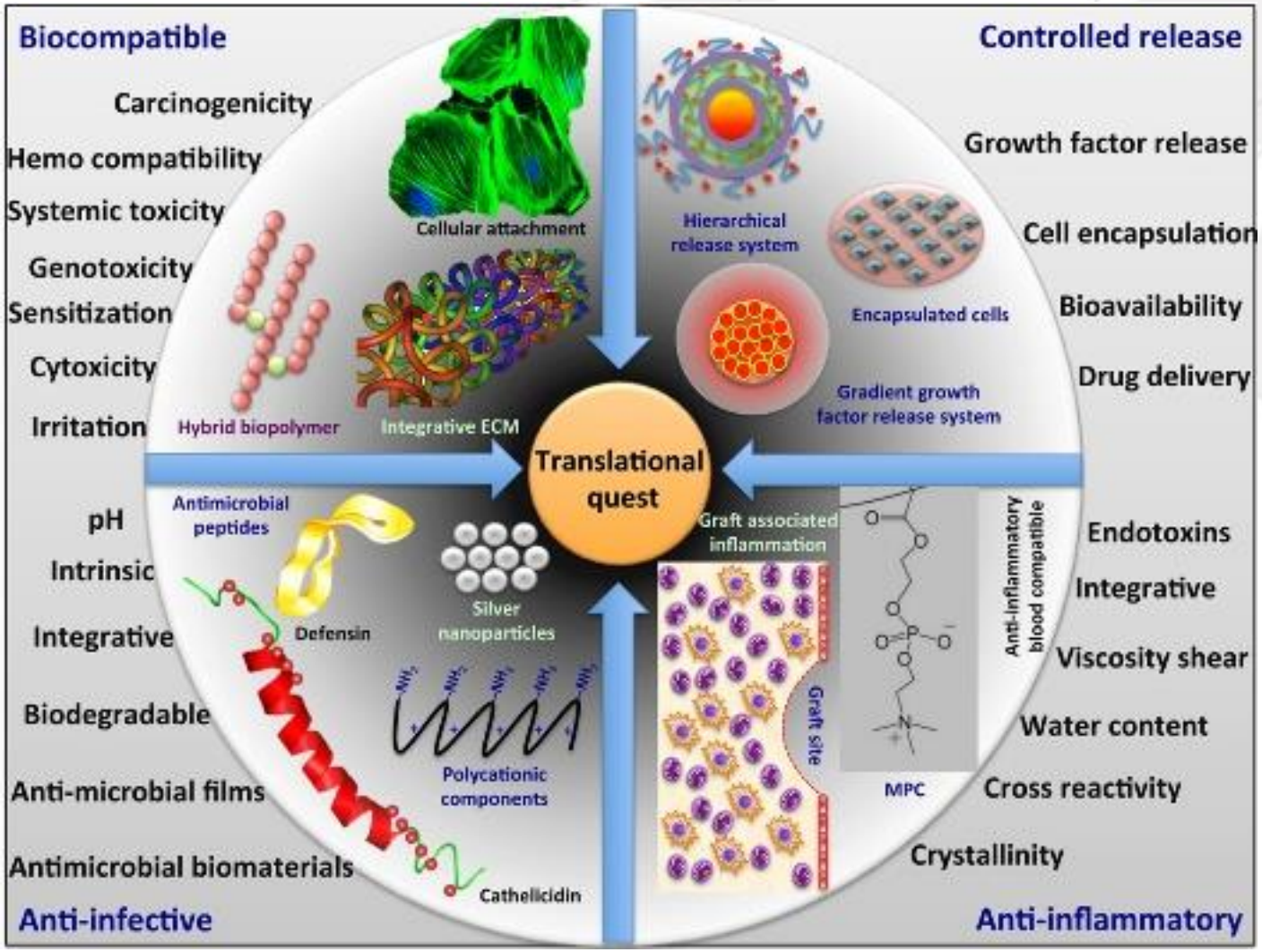
Stiffness and strength enough to resist to stresses at the host environment

Sterilization facility



Controlled swelling property

Different functional aspects of the Biomaterials



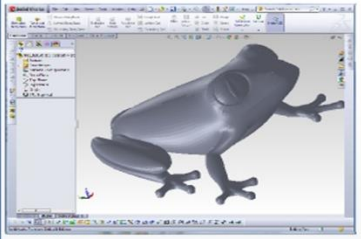
Nature

3D Technologies for Biofabrication

3D Technologies and Information Technology

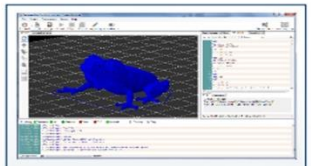
Idea

CAD-design

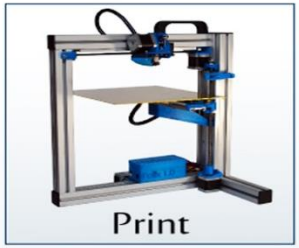


FreeCAD
Solidworks
Pro-engineer
Google Sketchup
Inventor
....

Printer Software



Slice in layers



Print

All in one package to handle .STL files and control the printer

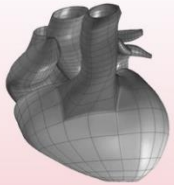
Idea = Reality

Virtual | **Physical**

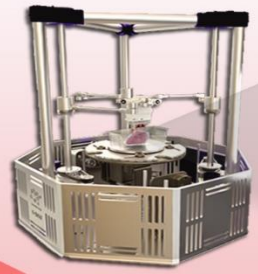
Acquisition of 3D patient model

MRI

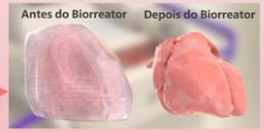
BioCAD - Design



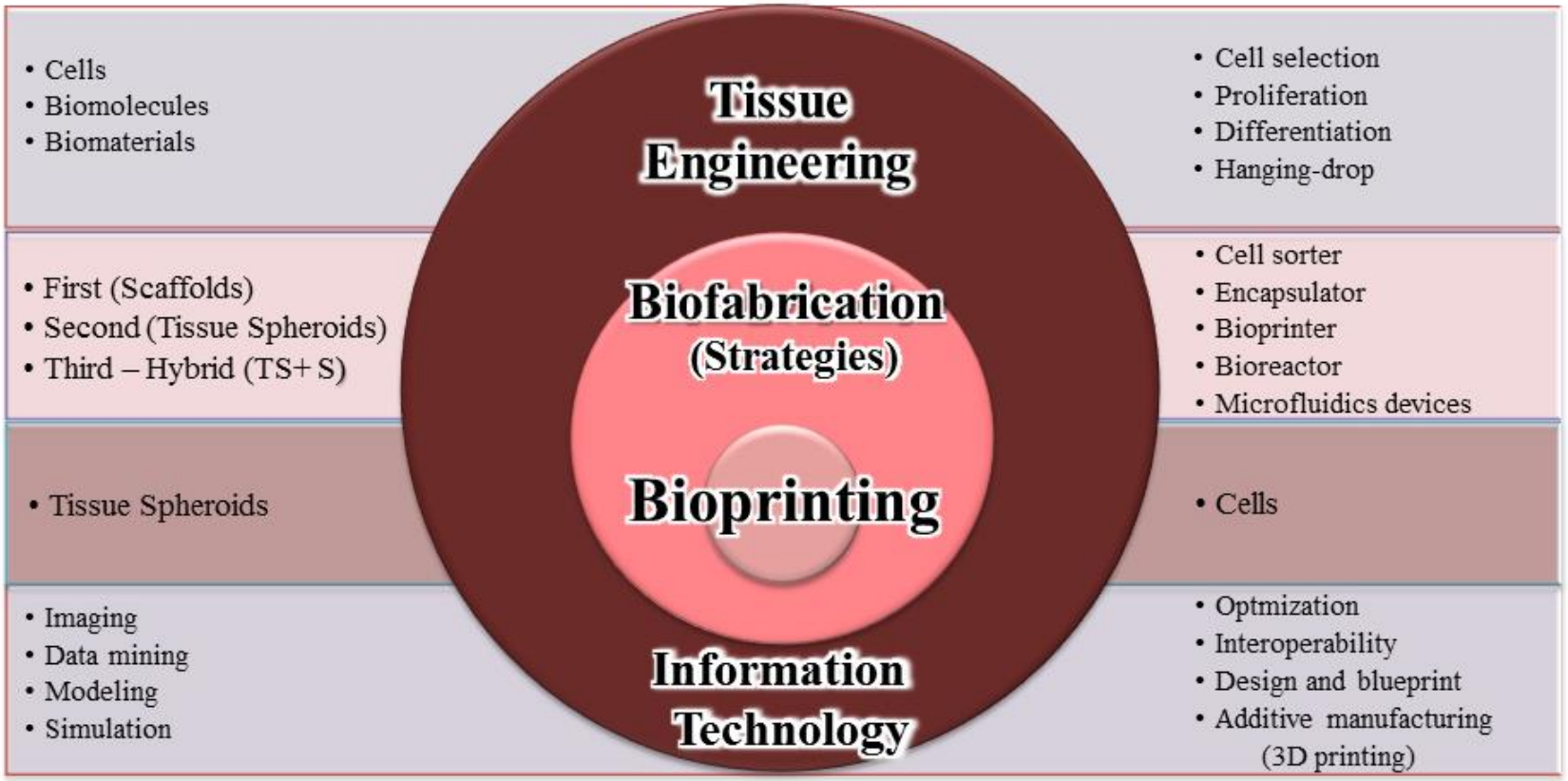
3D Bioprinting



Post processing Bioreactor



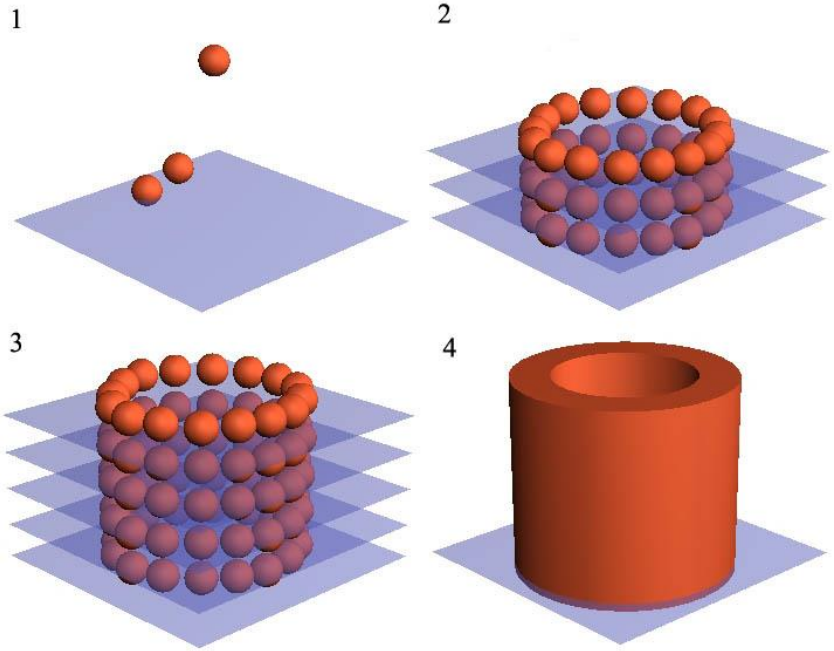
Tissue engineering, Biofabrication, Bioprinting and Information Technology



Dernowsek *et al.*, 2017

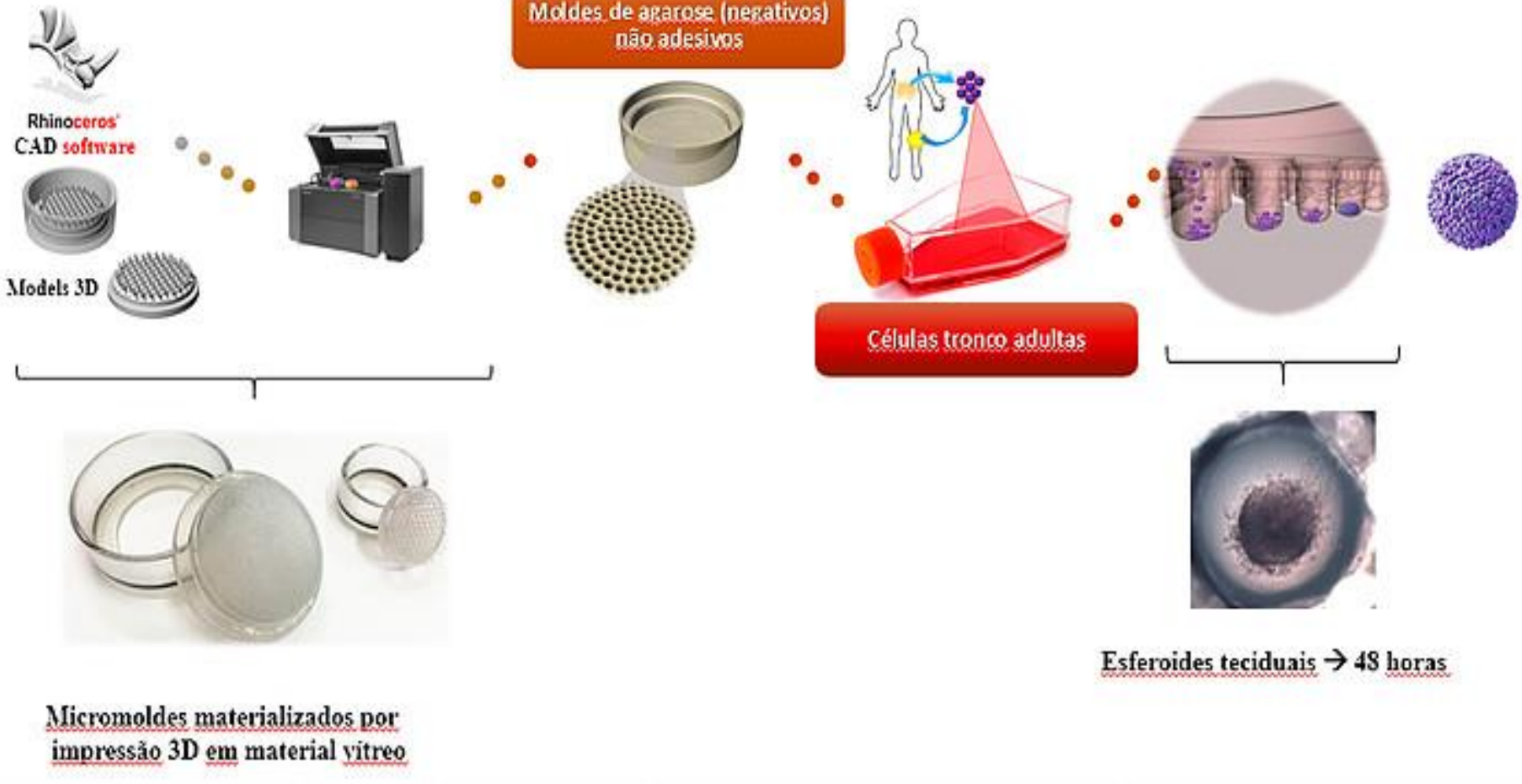
Bioprinting

Bioprinting is a computer-aided robotic layer by layer additive biofabrication of functional living human organ constructs



The bio-ink:
cell aggregates
The cartridge:
TS container
The bio-paper:
gel
The printer:
bio-printer

Non-adhesive micromolds to form tissues spheroids

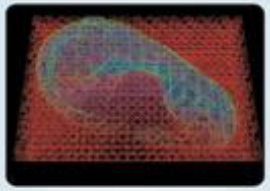
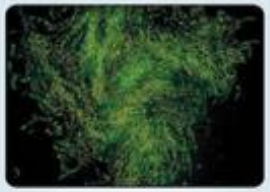
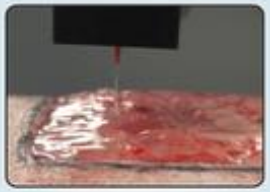
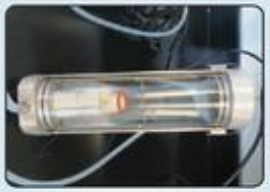
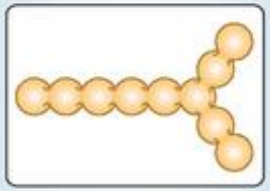
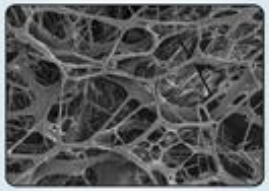
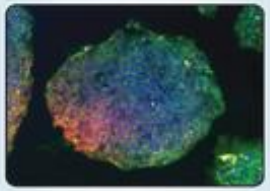
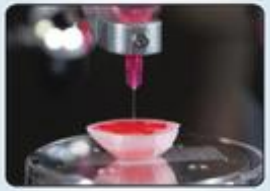
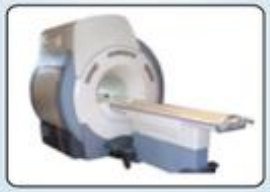
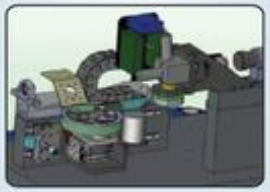


Bioprinting process workflow

Pre-Processing
(CAD, Blueprints), Pre-conditioning

Processing
3D Tissue Printing

Post-processing
Bioreactor → Tissue maturation

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Imaging	Design approach	Material selection	Cell selection	Bioprinting	Application
 X-ray	 Biomimicry	 Synthetic polymers	 Differentiated cells	 Inkjet	 Maturation
 CT	 Self-assembly	 Natural polymers	 Plurpotent stem cells	 Microextrusion	 Implantation
 MRI	 Mini-tissues	 ECM	 Multipotent stem cells	 Laser-assisted	 *In vitro* testing

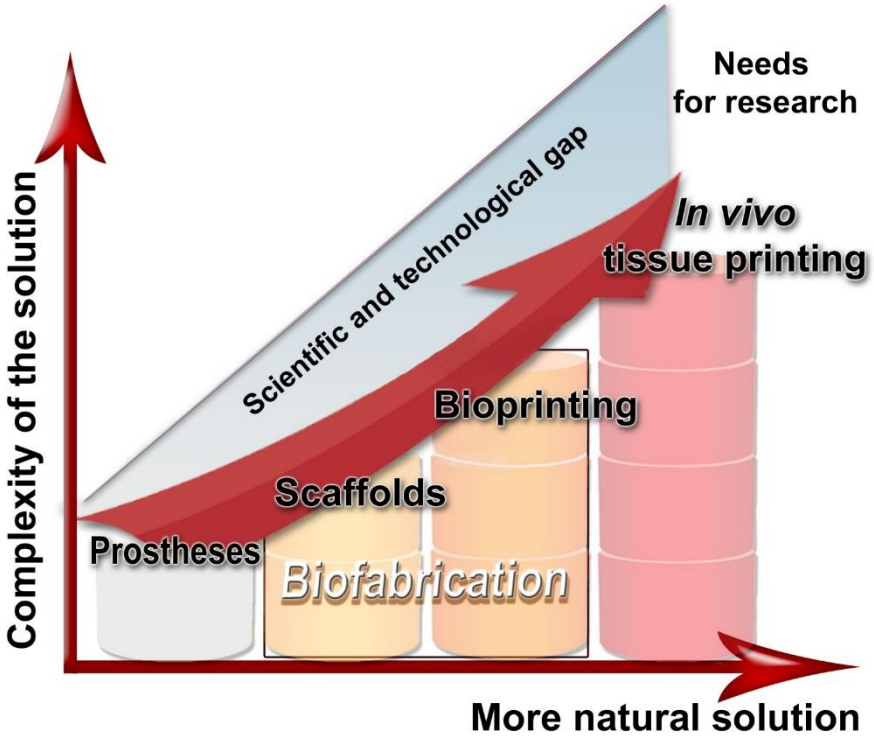
Murphy & Atala, 2014

Pre-Processing
Spheroid formation process →Hanging drop

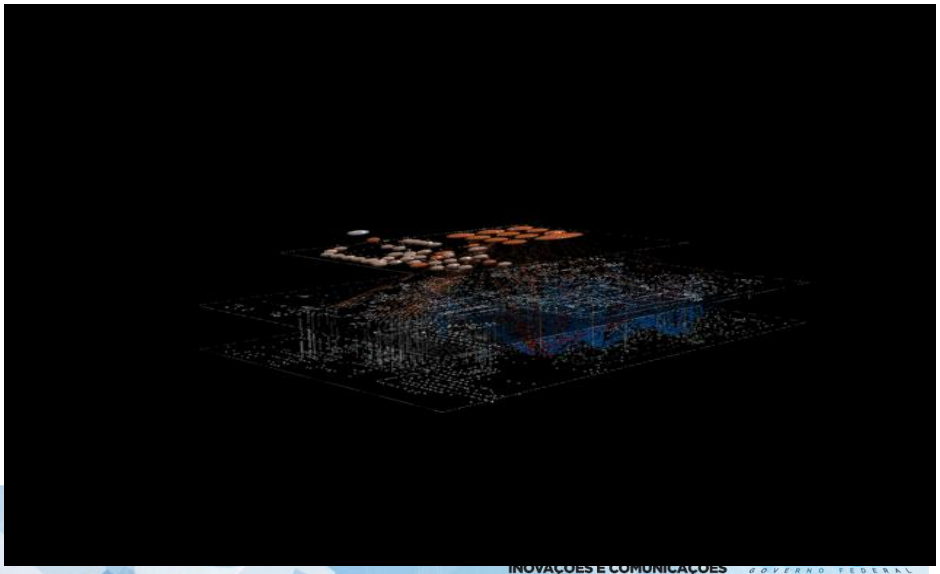
Bioprinting

Bioreactor → Tissue maturation

Biofabrication and the relationship between complexity and nature of the solution



Dernowsek et al. 2017



Organism scale	Tissue scale	Cellular scale	Extracellular scale	Intracellular scale
(Meters - Centimeters)	(Centimeters)	(Milimeters)	(Micrometers)	(Micrometers - Nanometers)
· Finite Element, · Computational Fluid Dynamics · Multi Agent Systems · Spatial Compartiments and Projections	· Multi Agent Systems · Noble model, CPM- GGH · Finite Element,MSNS method · Ising models, Potts model · Spatial Compartiments and Projections	· Agent-based modeling · Lattice Boltzmann · Monte Carlo model · Cellular Automata · CxA multi-scale method	· Partial differential equations · Convective–diffusion models · Noble model, Fenton-Karma model, · Fitzhugh–Nagumo, Hodgkin-Huxley	· Ordinary Differential Equations · Stochastic DIfferential Equations · Quasi-continuum method · Convective–diffusion models
Years	Days - Weeks	Hours - Days	Minutes	Seconds

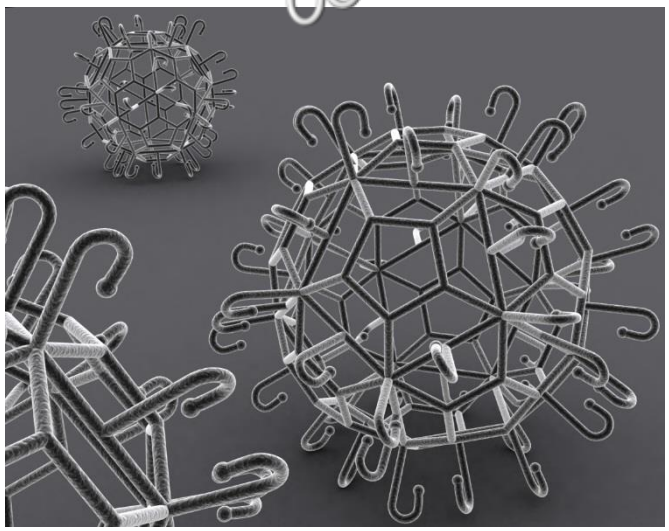
Tissue or Organ	3D Bioprinting	Tissue spheroid	Cell culture	Molecular scale
Fusion, maturation, shear stress, flow rate -inlet and outlet-, waste products, pH	BioCAD, BioCAM, Bioprinter, biopaper, bioink	Stem cells, cell isolation and proliferantion, cell fate specification, organoids	environment pH, temperature, osmotic pressure, culture medium, sterility, cytokines/hormones	Biomolecules, genes, transcription factors, miRNAs, proteins, O2, drugs and other molecules

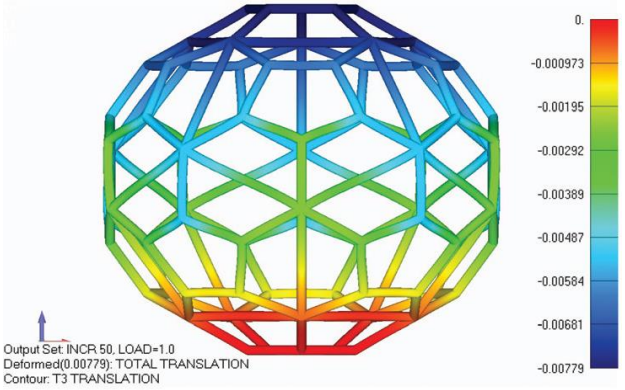
Biofabrication

Dernowsek *et al*., 2016

Lockyballs

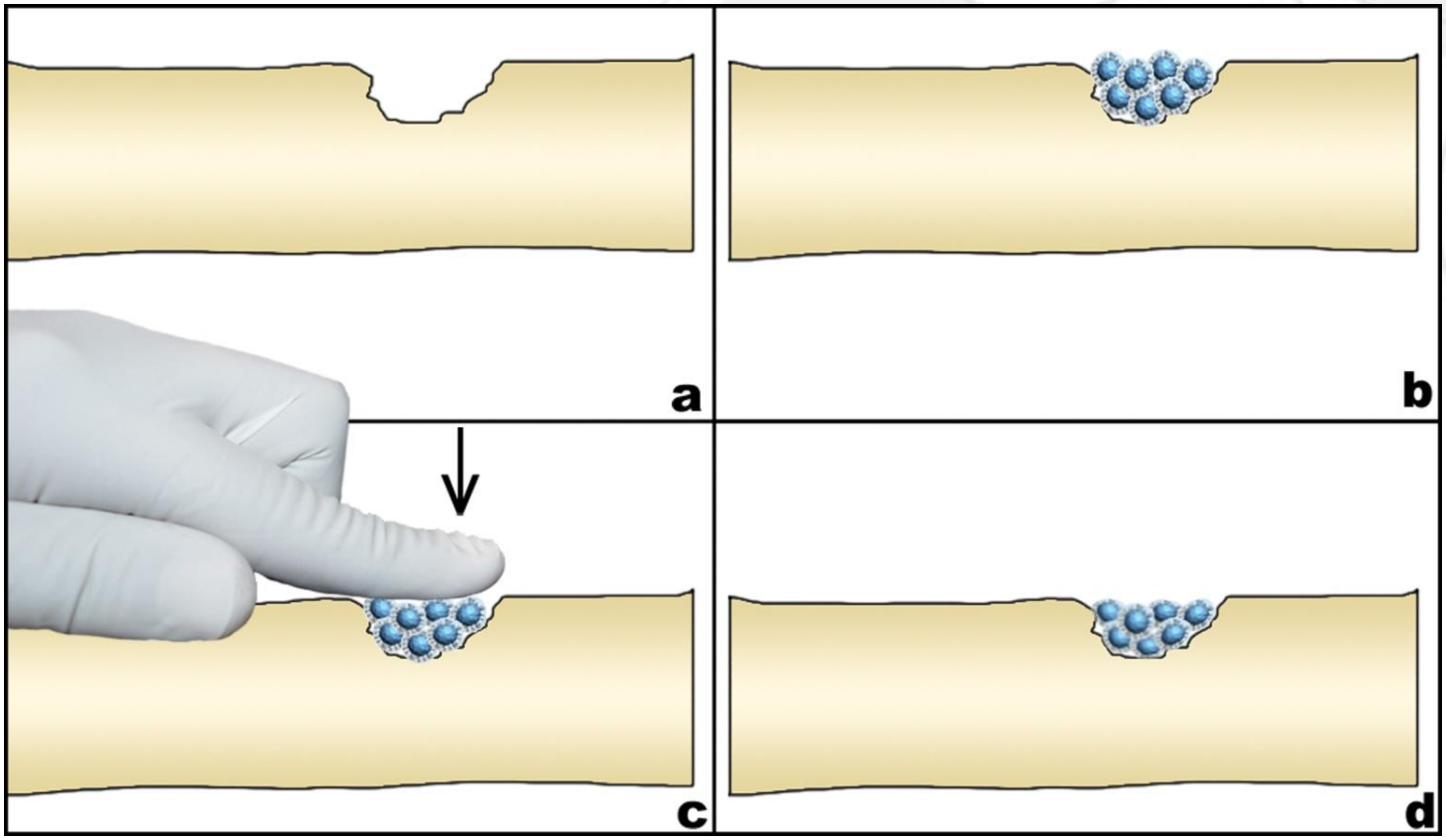
Concept of Lockyballs as a Strategy in TE





Lockyballs

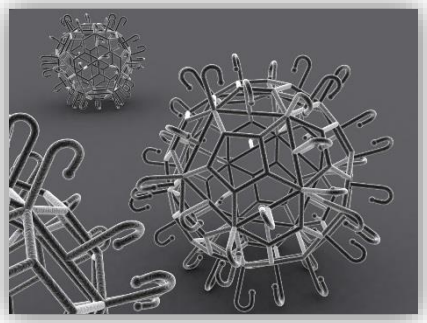
in situ Rapid Tissue Biofabrication using Lockyballs



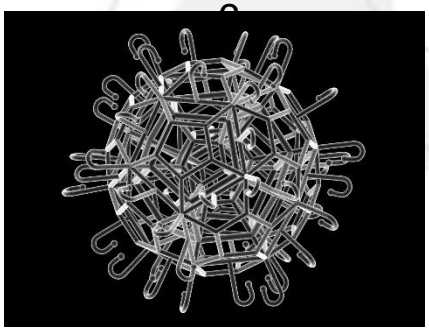
Scheme demonstrating *in vivo* rapid 3D tissue biofabrication using lockable tissue spheroids

Lockyballs - Family of Lockyballs

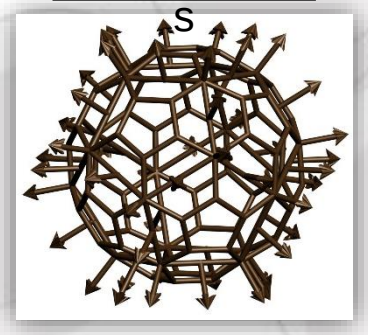
1 Original



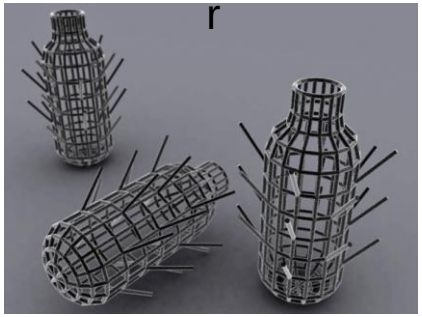
2 Concentric

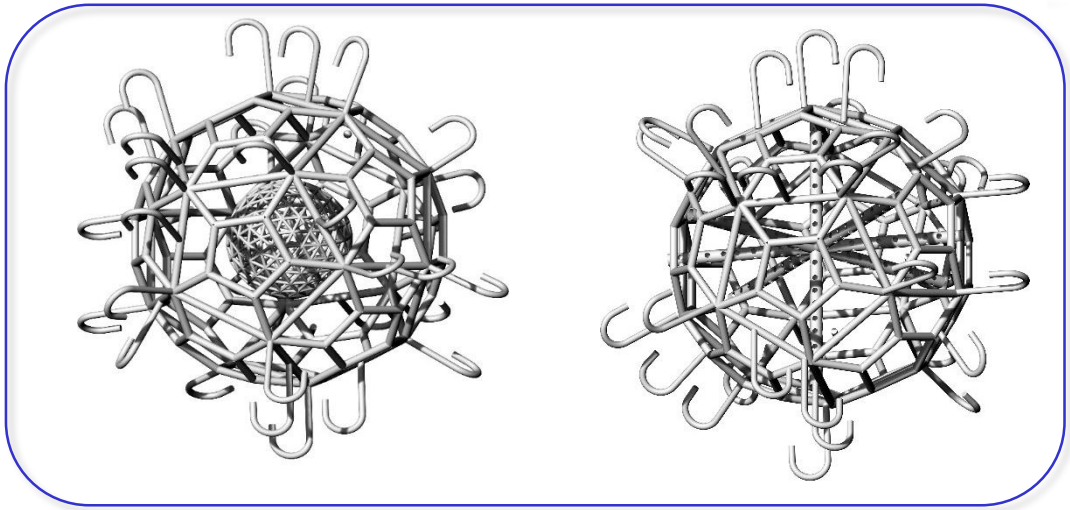


3 Velospheres

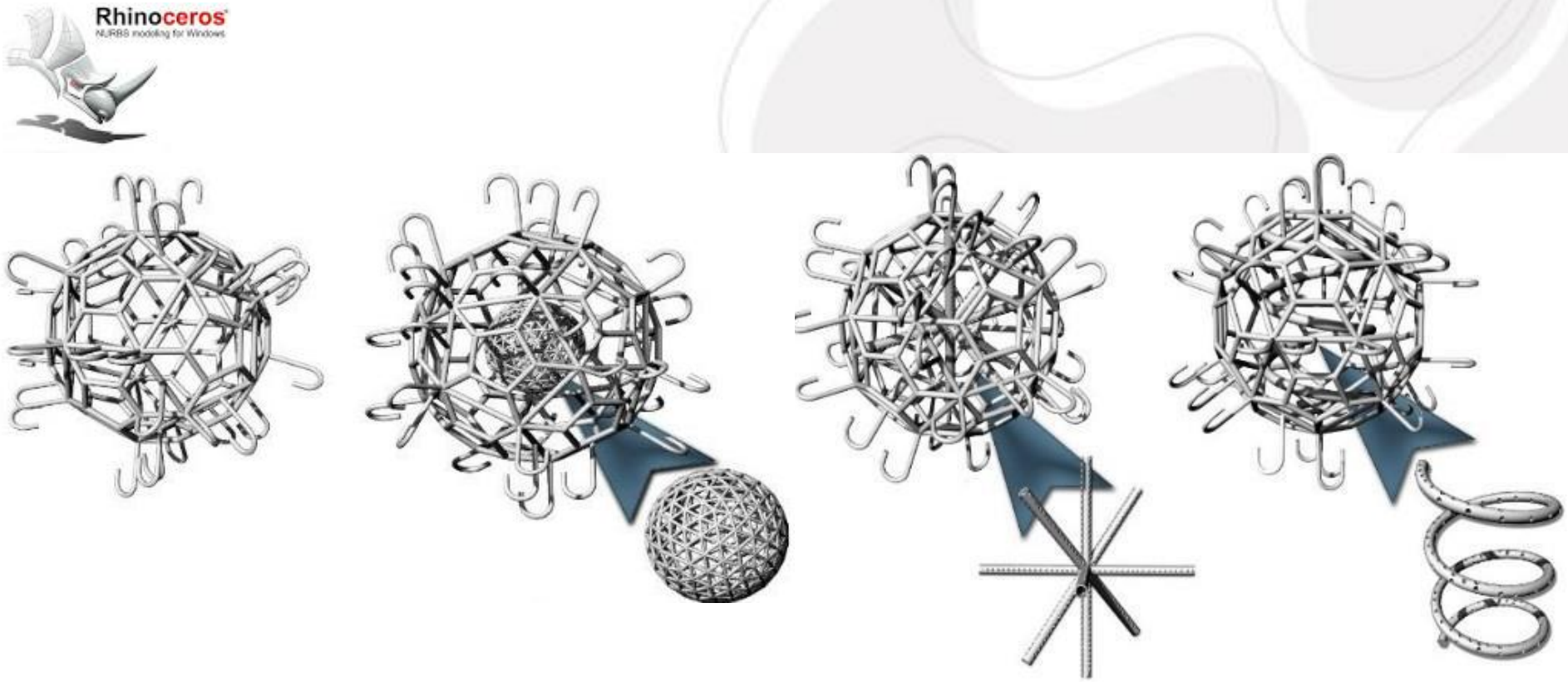


4 Capillinser





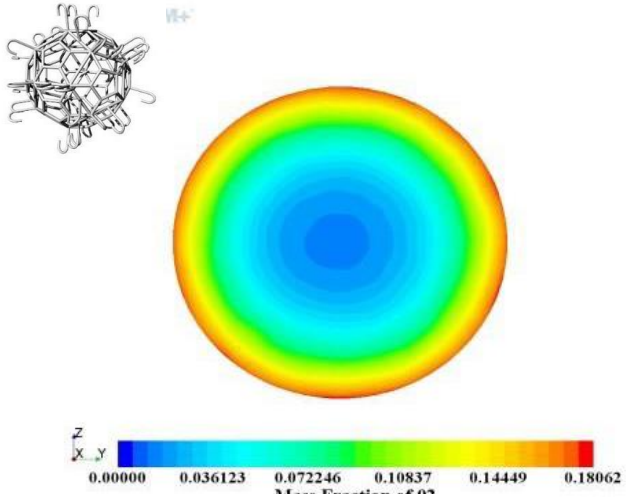
Modeling and Simulation of Diffusion Process in Tissue Spheroids Encaged into Microscaffolds

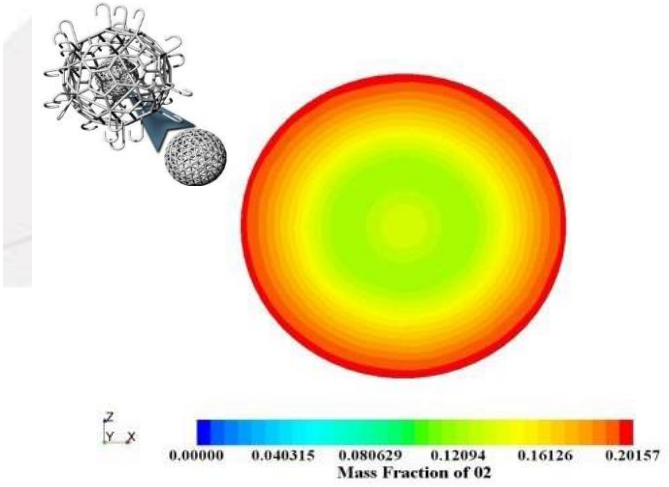


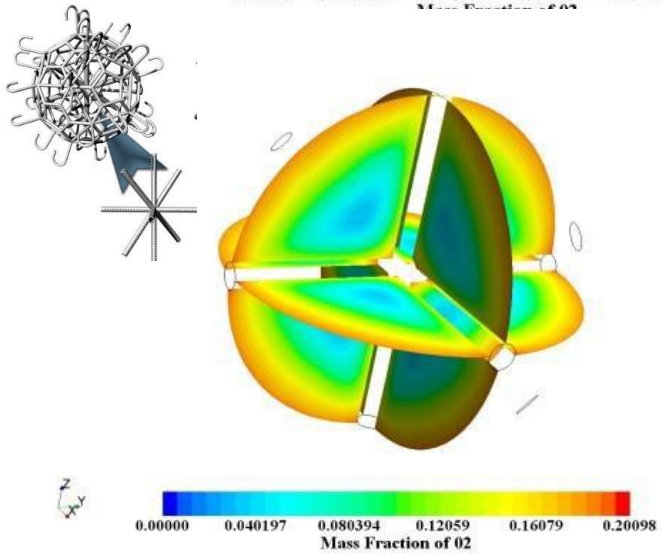
Four geometries were modelled to simulations. (A) Solid microscaffold without internal structure (original lockyball) (Danilevicius et al., 2015). (B, C, D) Solid microscaffolds with internal structures to improve the oxygenation cells

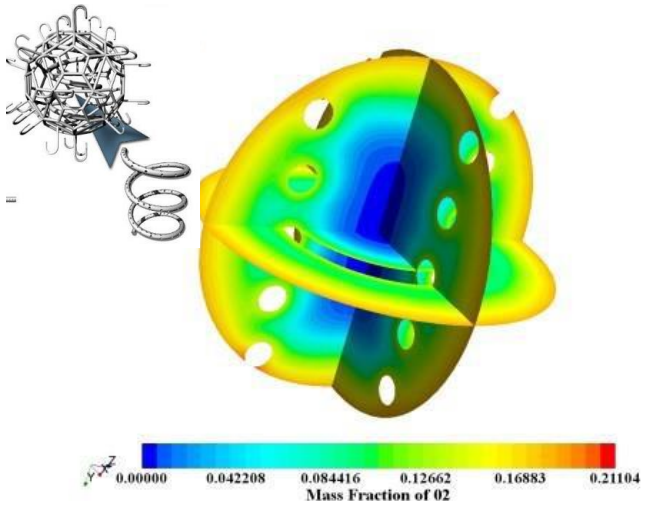
Dernowsek *et al*., 2016

Modeling and Simulation of Diffusion Process in Tissue Spheroids Encaged into Microscaffolds



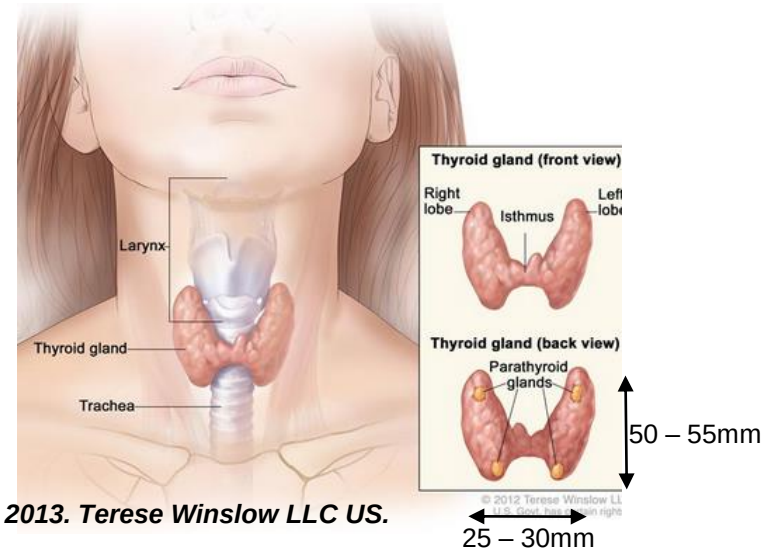






Dernowsek et al., 2016

Near future organ bioprint - Thyroid gland



2013. Terese Winslow LLC US.

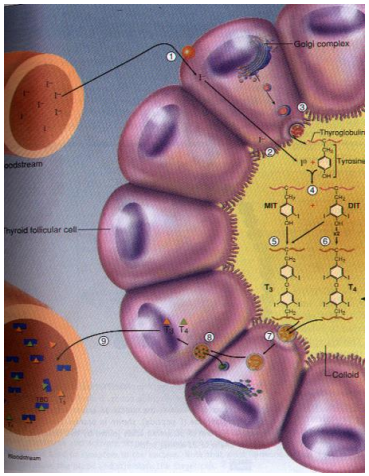
Hystology & Fisiology

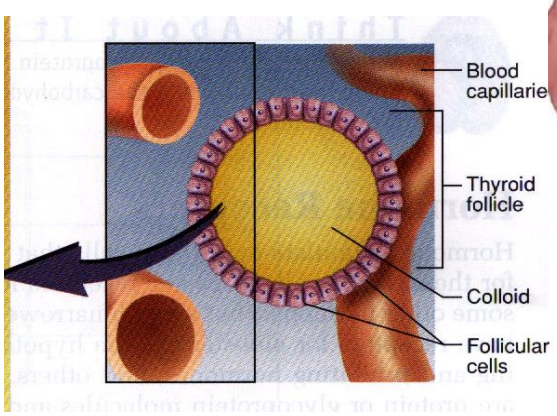
Comprised of aggregates or lobules of **spherical follicles** that are **filled with colloid**

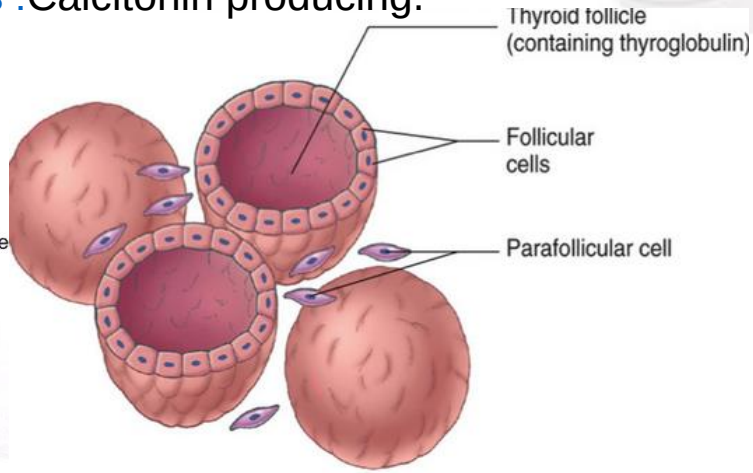
Functional units, hormone synthesis. Single layer of follicular cells. θ=500μm aprox

T3 + T4

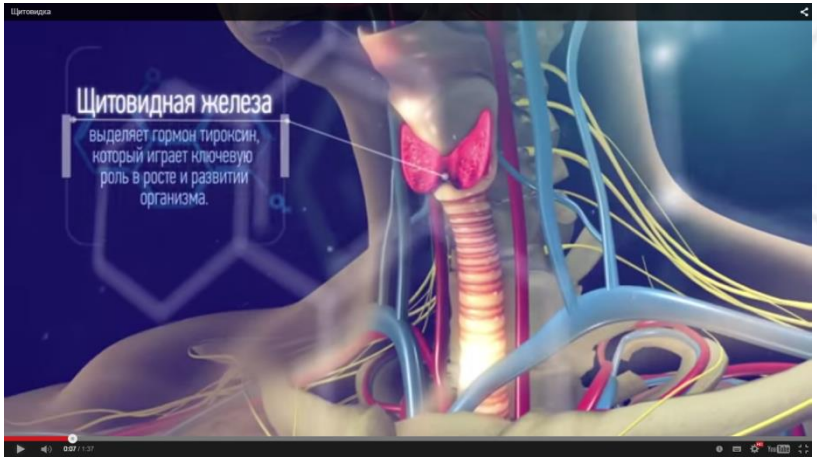
Parafollicular cells :Calcitonin producing.

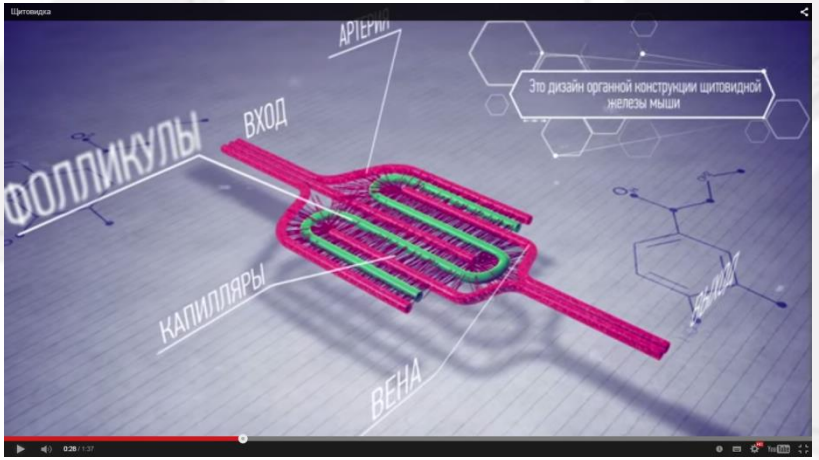


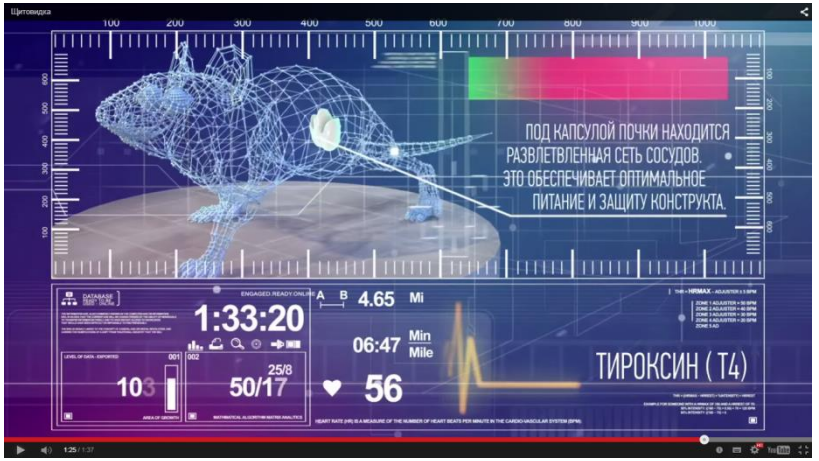




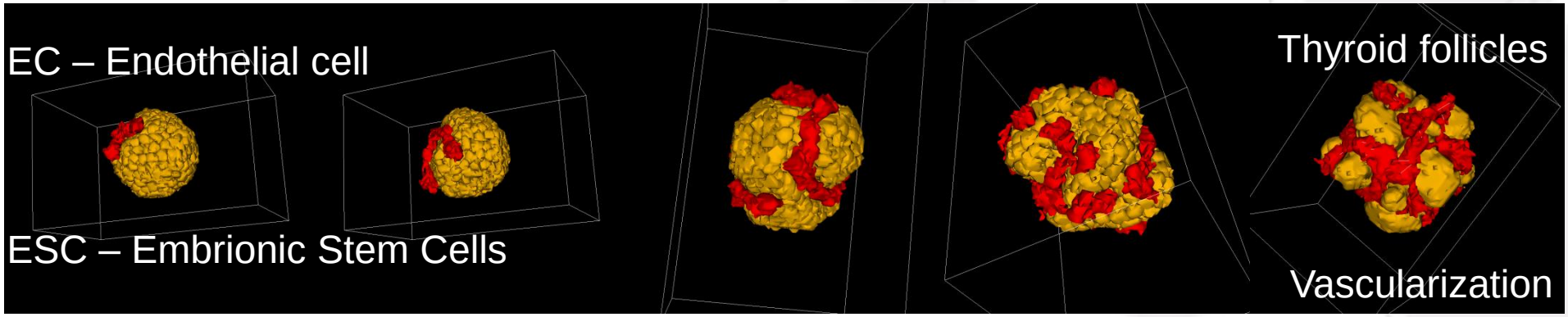
3D Bioprinted Thyroid Gland

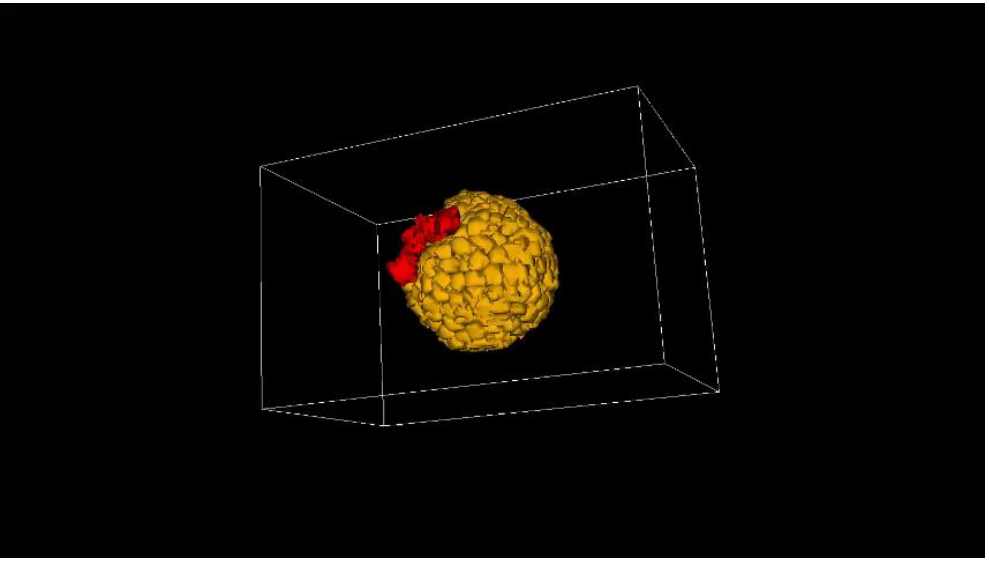






3D multicellular simulation during the self-formation of thyroid follicles



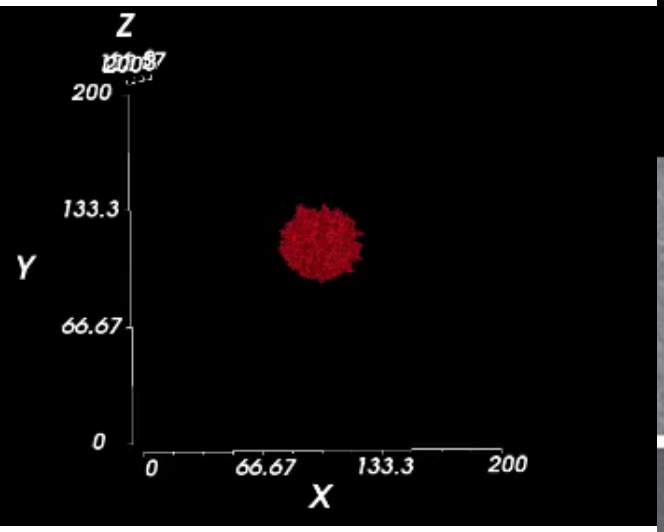


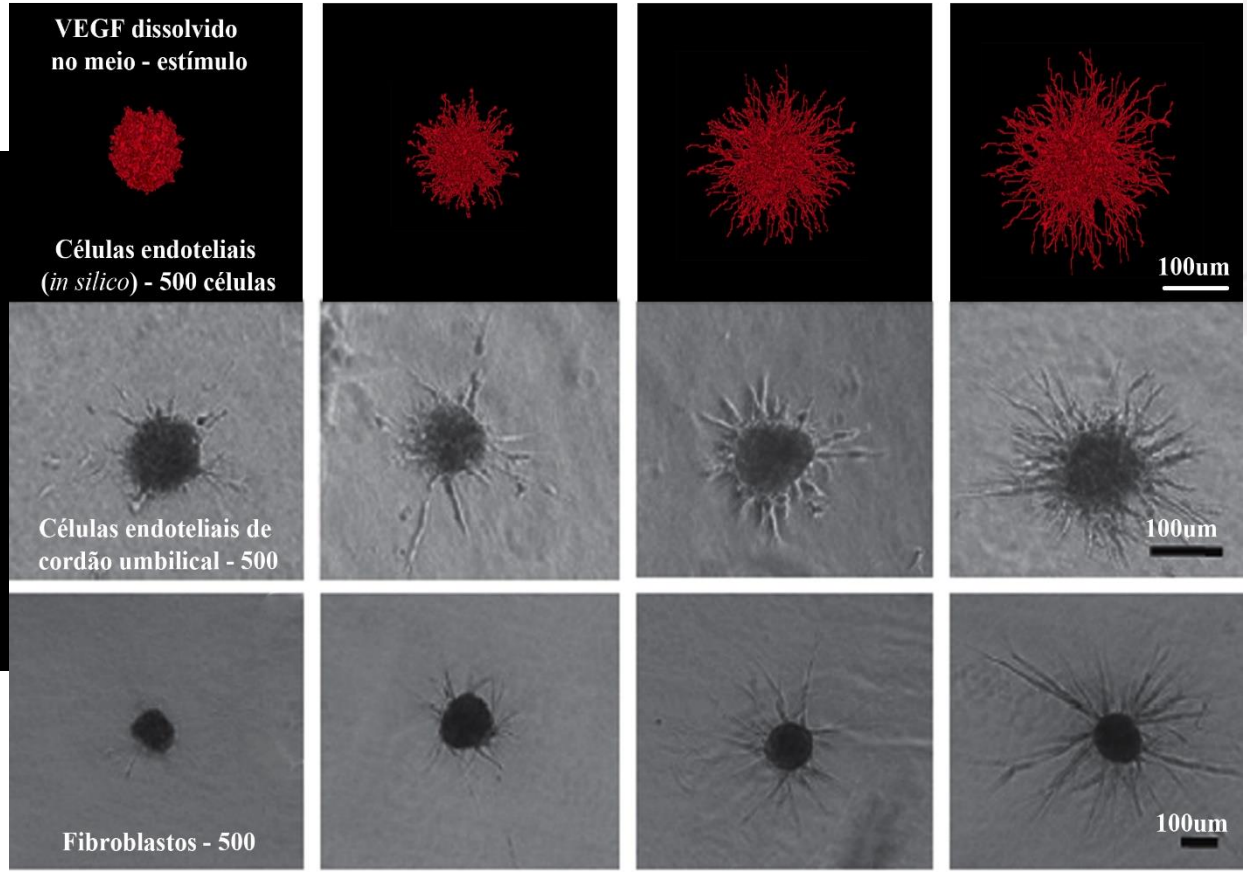
1. Simplified 3D multicell simulation of angiogenesis during the self-formation of thyroid follicles
2. It can be easily extended and adapted to describe other biological phenomena
3. This simulation allowed us to study how the cells interact each other and modulate the growth and morphology of the multicellular spheroids.

Dernowsek et al., 2015

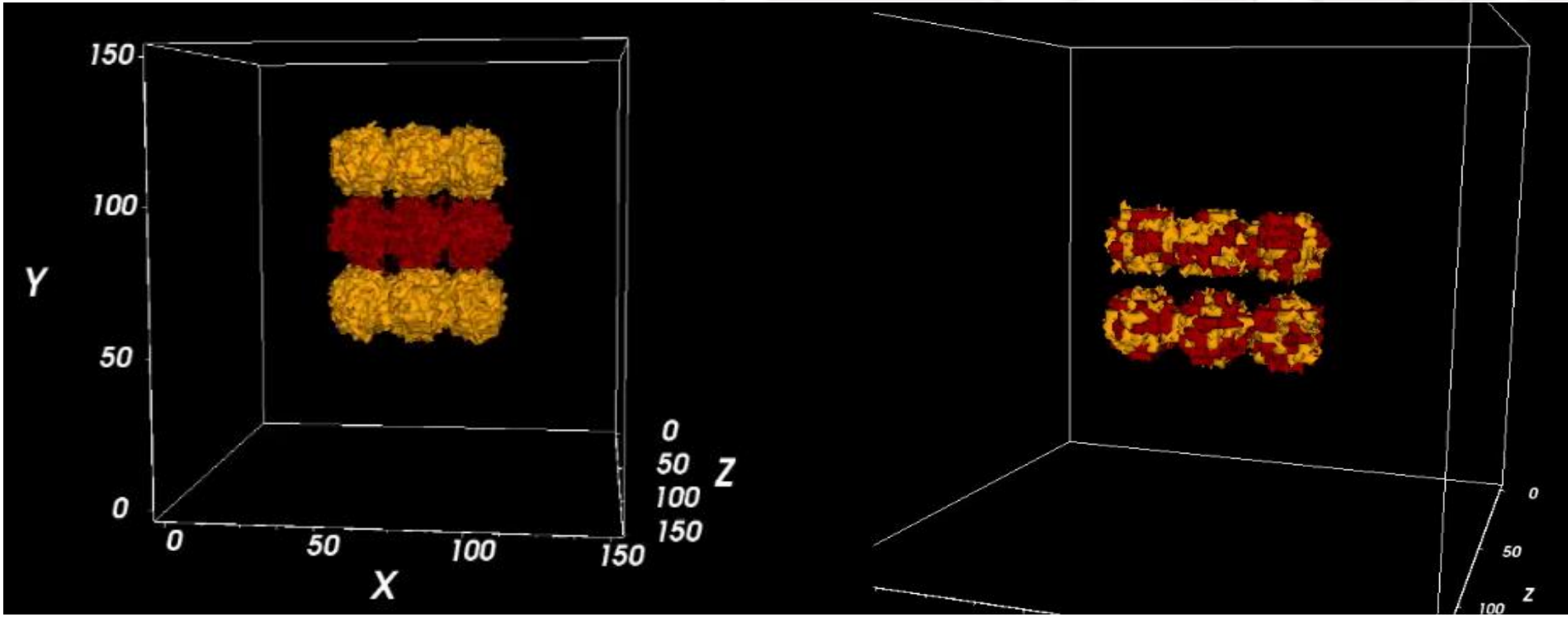
Computational approaches for biofabrication of Tissues →Angiogenesis

Endothelial cell spheroids as a versatile tool to study angiogenesis *in vitro* and in *silico*

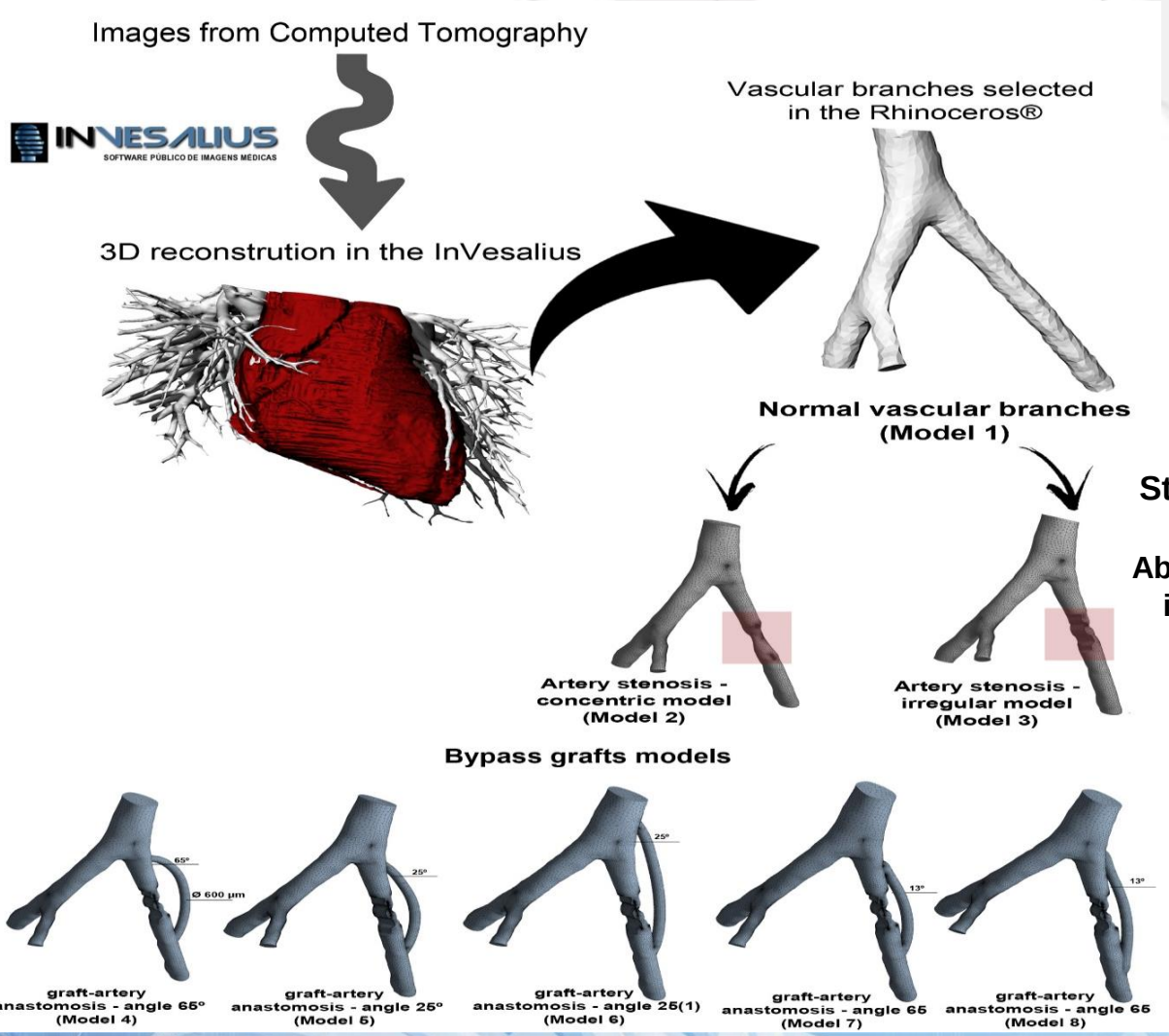




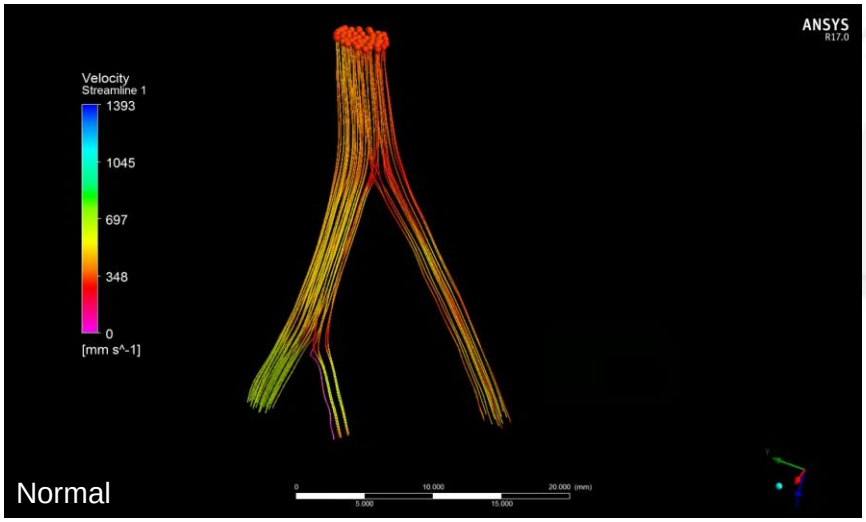
Computational approaches for biofabrication of tissues → Angiogenesis + Proliferating cells

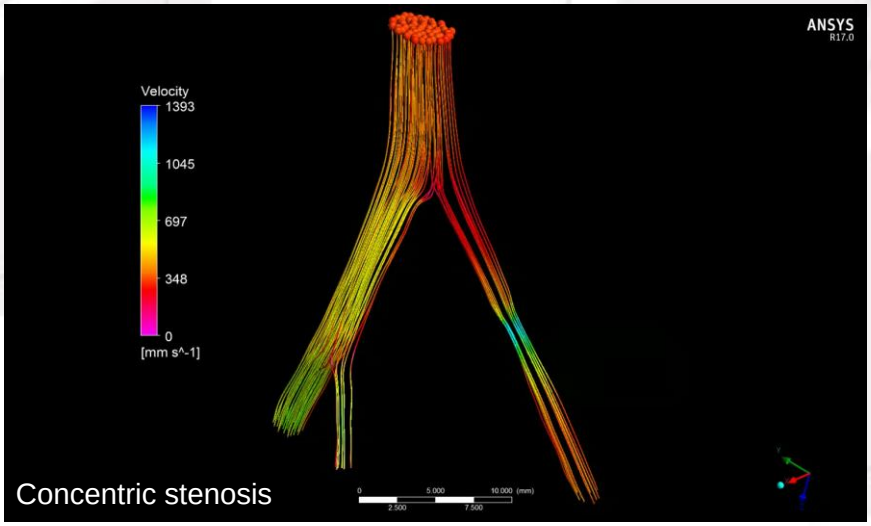


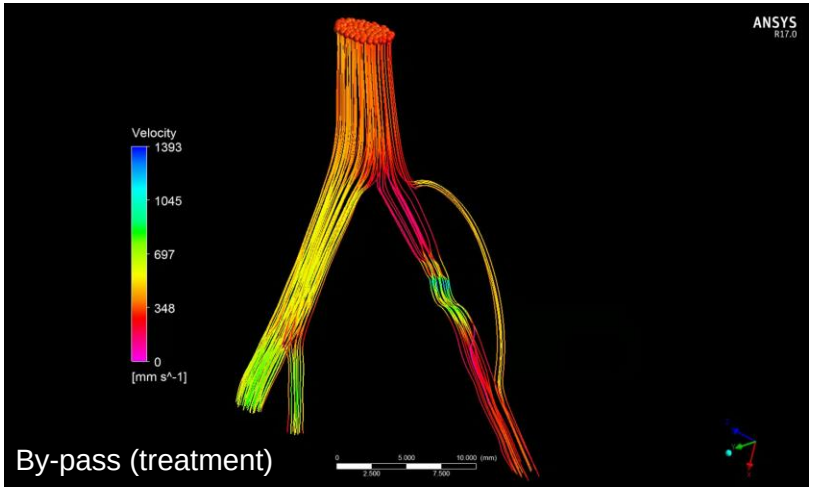
Hemodynamics in artery bypass grafts models based on computational fluid dynamics simulations



Computer simulation – Stenosis and Bypass graft models

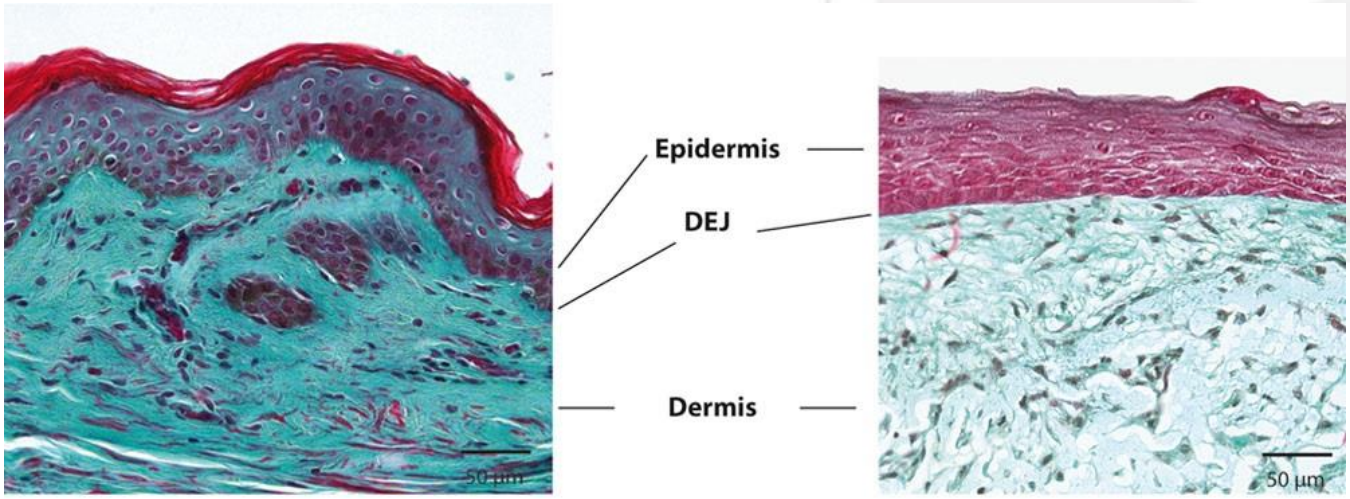






3D printing: Human skin is now being printed in labs

Today



Human skin

3D Bioprinted skin

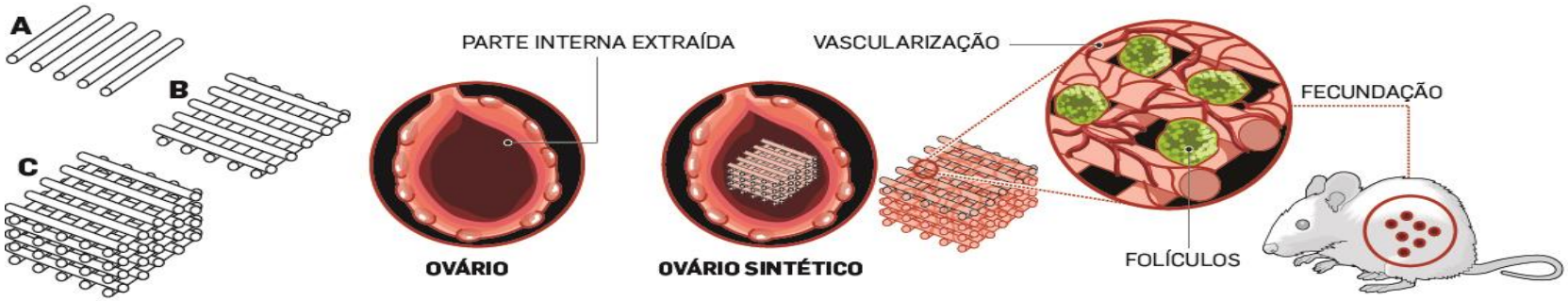
Comparison of optical microscopy images of equivalent slices of normal human skin and printed skin after 26 days of culture. The tissues were stained with Masson's trichrome. DEJ, dermoepidermal junction.

Ovary created using 3D printed scaffolds restores ovarian function

Today

OVÁRIO SINTÉTICO

● **Próteses de hidrogel feitas em impressora 3D substituíram os ovários de camundongos, [illegible] deram gerar filhotes; objetivo era testar se infertilidade causada por tratamentos contra o câncer pode ser revertida em mulheres**



1 A **prótese de hidrogel biológico** foi montada, camada a camada, em uma impressora 3D

2 A parte interna dos ovários dos camundongos foi extraída, tornando o **animal infértil**. A prótese feita em 3D foi implantada na cavidade, formando um **ovário sintético**

3 Em uma semana, o ovário sintético já estava **vascularizado**. A prótese recebe **folículos** - as pequenas bolsas com fluidos que contêm ovócitos (óvulos imaturos)

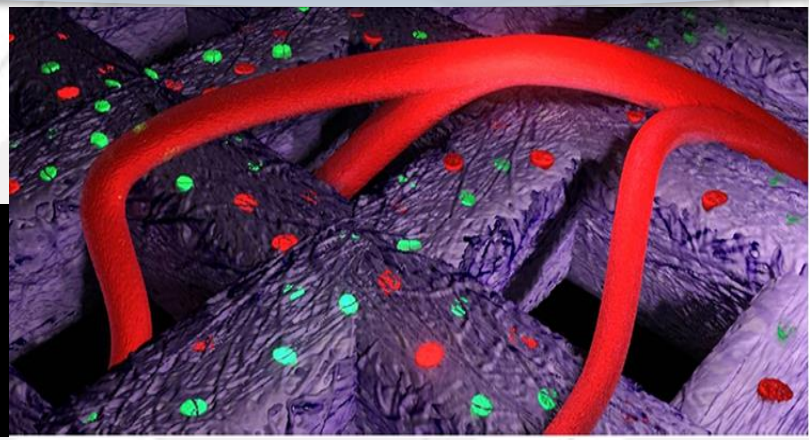
4 O folículo se desenvolveu e **gerou óvulos maduros**. Sete camundogos com ovários sintéticos foram fecundados naturalmente e deram à luz filhotes saudáveis

FONTE: NATURE COMMUNICATIONS

INFOGRÁFICO/ESTADÃO

3D Printed Human Cartilage Cells in Mice

Swedish Researchers successfully Implant 3D Printed Human Cartilage Cells in Mice

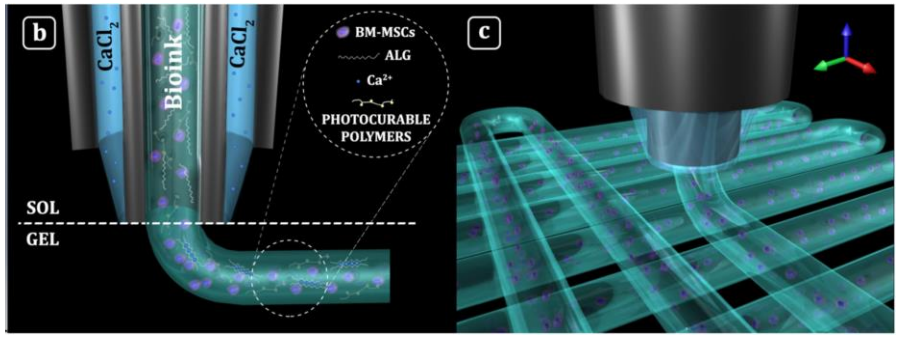


In Vivo Chondrogenesis in 3D Bioprinted Human Cell-laden Hydrogel Constructs

Thomas Möller, MSc*
Matteo Amoroso, MD†
Daniel Hägg, PhD*
Camilla Brantsing, MSc‡
Nicole Rotter, PhD§
Peter Apelgren, MD†
Anders Lindahl, PhD‡
Lars Kölby, PhD†
Paul Gatenholm, PhD*

Background: The three-dimensional (3D) bioprinting technology allows creation of 3D constructs in a layer-by-layer fashion utilizing biologically relevant materials such as biopolymers and cells. The aim of this study is to investigate the use of 3D bioprinting in a clinically relevant setting to evaluate the potential of this technique for in vivo chondrogenesis.

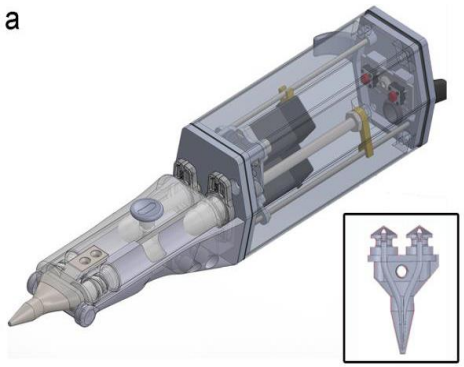
Methods: Thirty-six nude mice (Balb-C, female) received a 5- × 5- × 1-mm piece of bioprinted cell-laden nanofibrillated cellulose/alginate construct in a subcutaneous pocket. Four groups of printed constructs were used: (1) human (male) nasal chondrocytes (hNCs), (2) human (female) bone marrow–derived mesenchymal

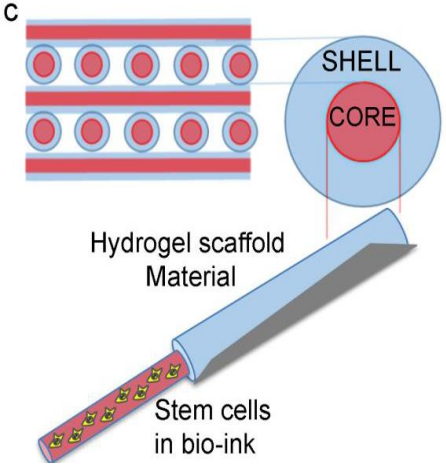


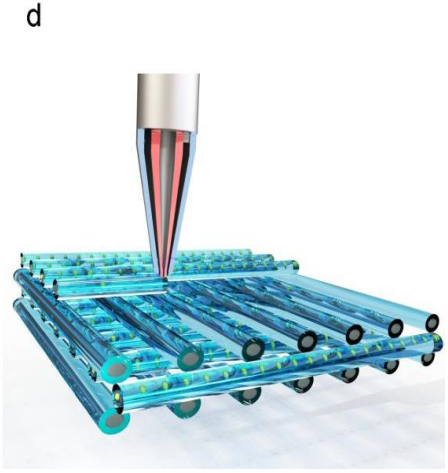
Today

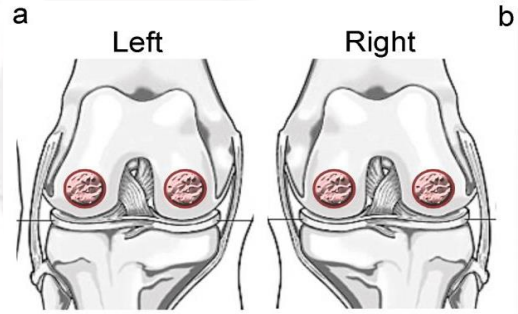
In-situ handheld 3D Bioprinting for cartilage regeneration - May 2017

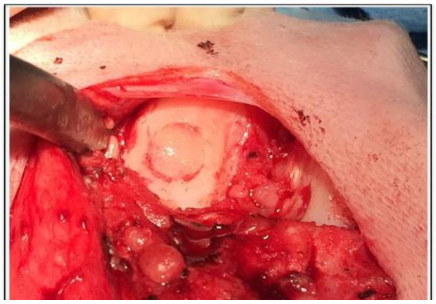
Journal of Tissue Engineering and Regenerative Medicine

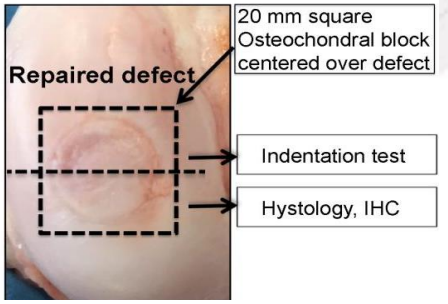








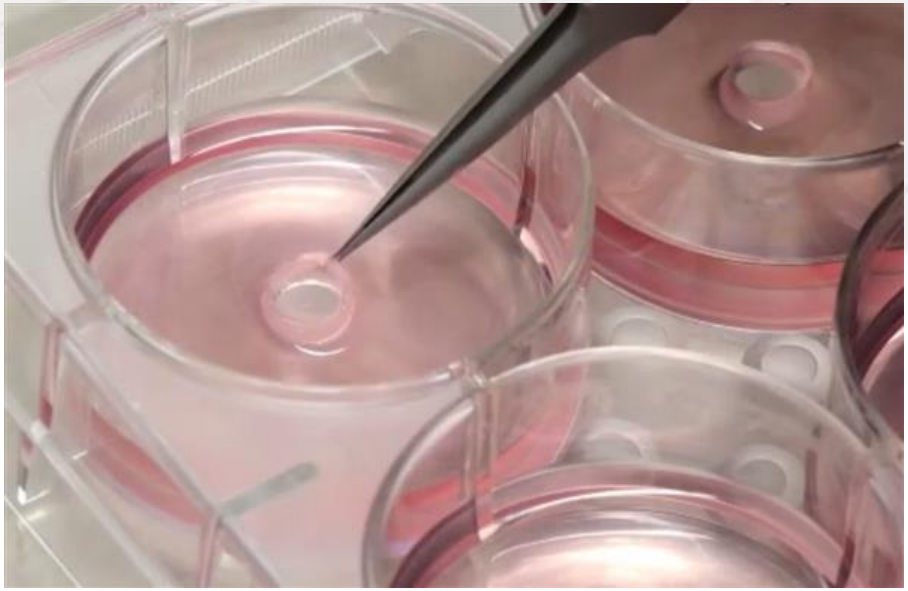




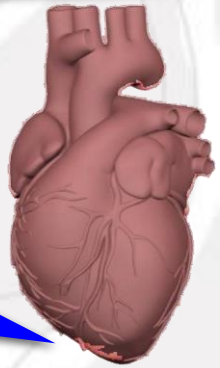
A Scientist Is 3D Printing Blood Vessels for Sick Children

Today

- Scientists are developing flexible materials to 3D print blood vessels
- **Arlington bioengineer awarded $211K NIH grant to develop 3D printed blood vessels for children**

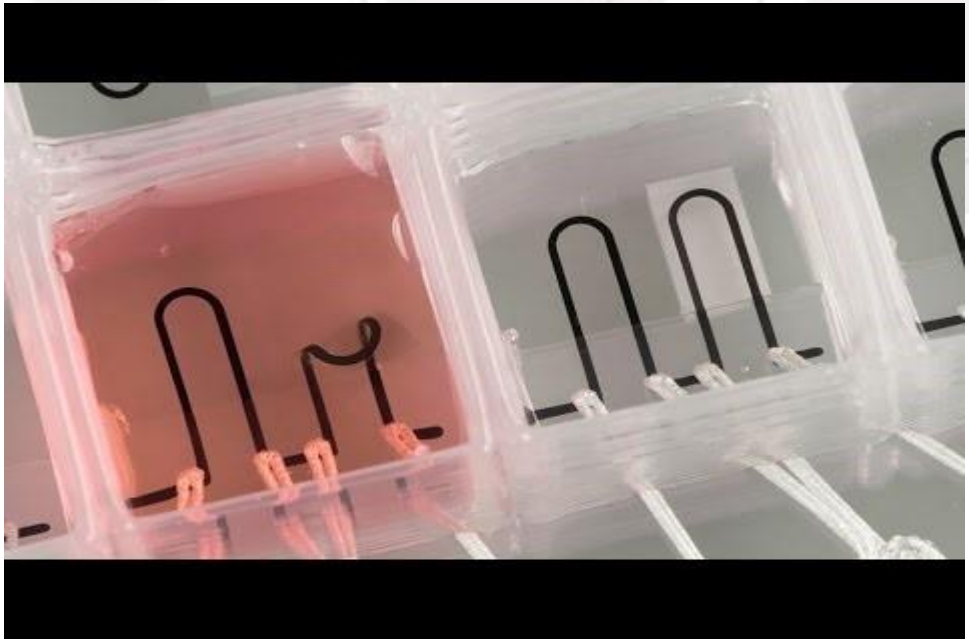


3D-printed heart-on-a-chip with integrated sensors



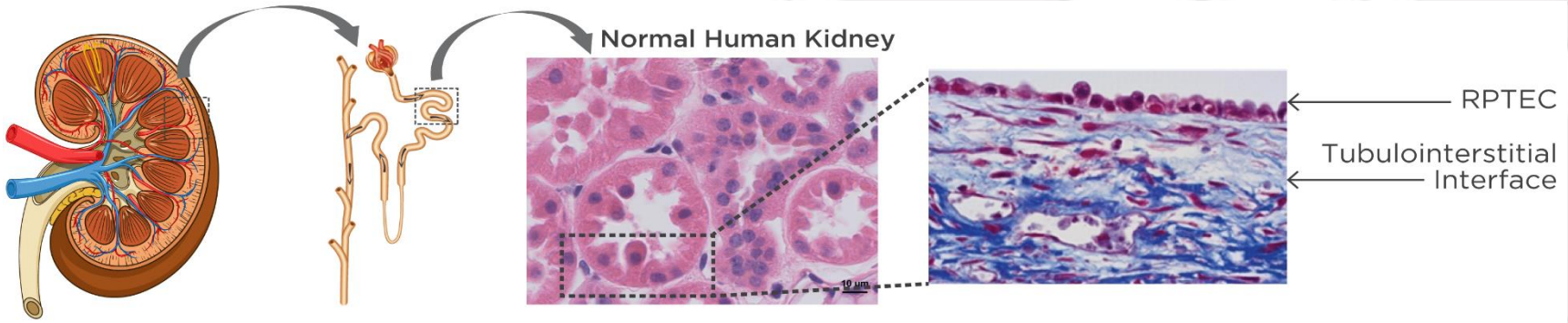
Today

Harvard University researchers have made the first entirely 3D-printed organ-on-a-chip with integrated sensing. Built by a fully automated, digital manufacturing procedure, the 3D-printed heart-on-a-chip can be quickly fabricated and customized, allowing researchers to easily collect reliable data for short-term and long-term studies.

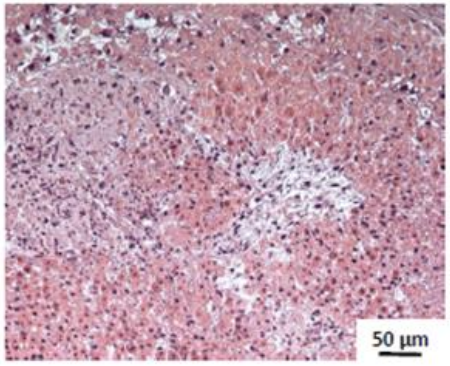


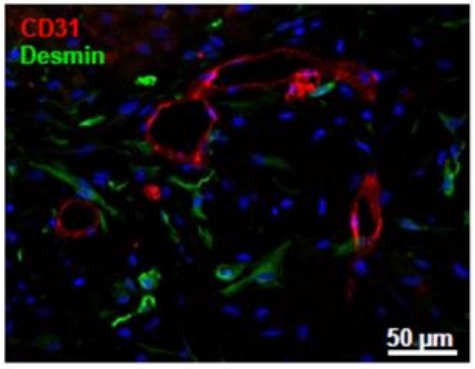
ExVive™ 3D Bioprinted Human Tissue Models

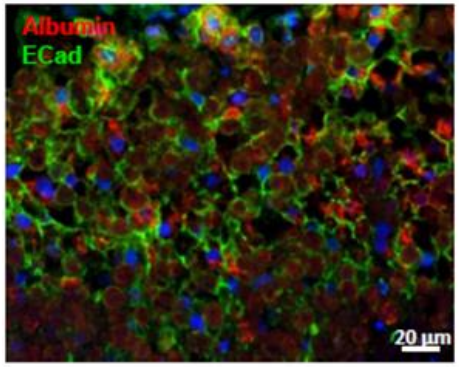
ExVive™ Human Kidney Tissue



ExVive™ Human Liver Tissue Performance







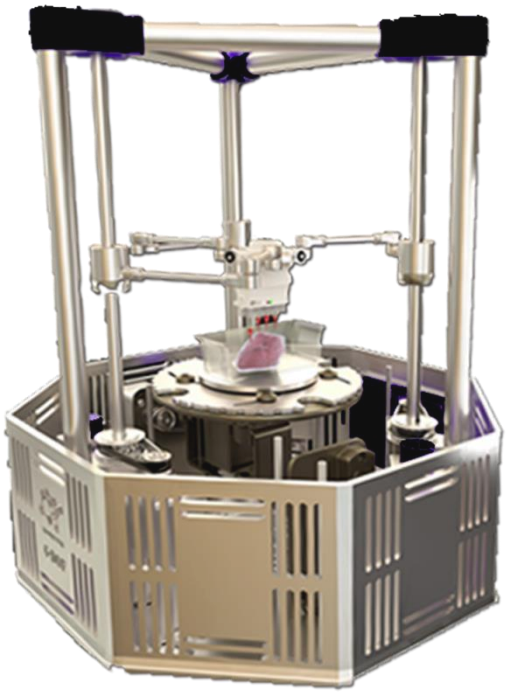
Outlook

Today
- Small scale tissues
- Drug Discovery
- Toxicity testing

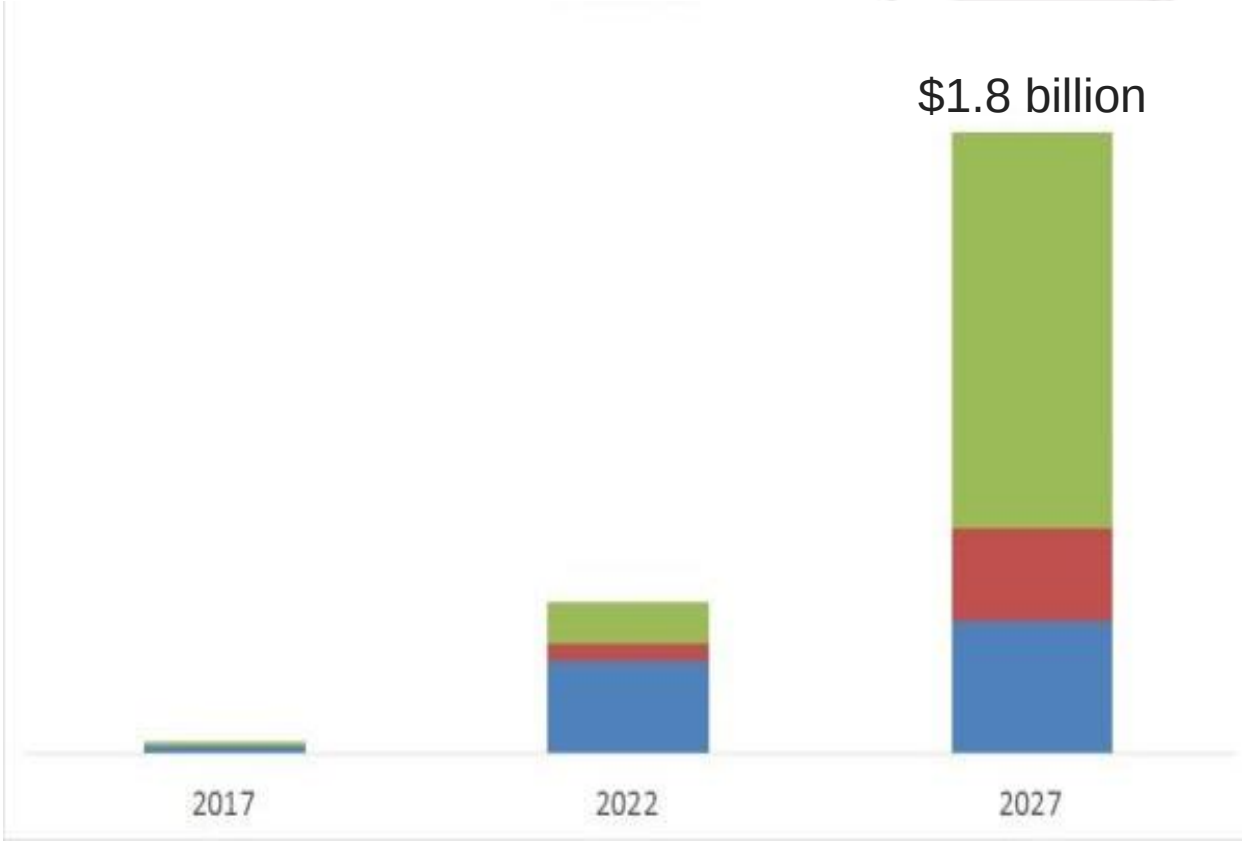
Tomorrow
- Microtissues
- Implants

Future
- Lobes
- Pieces of organs

Uncertain future
- Full organs



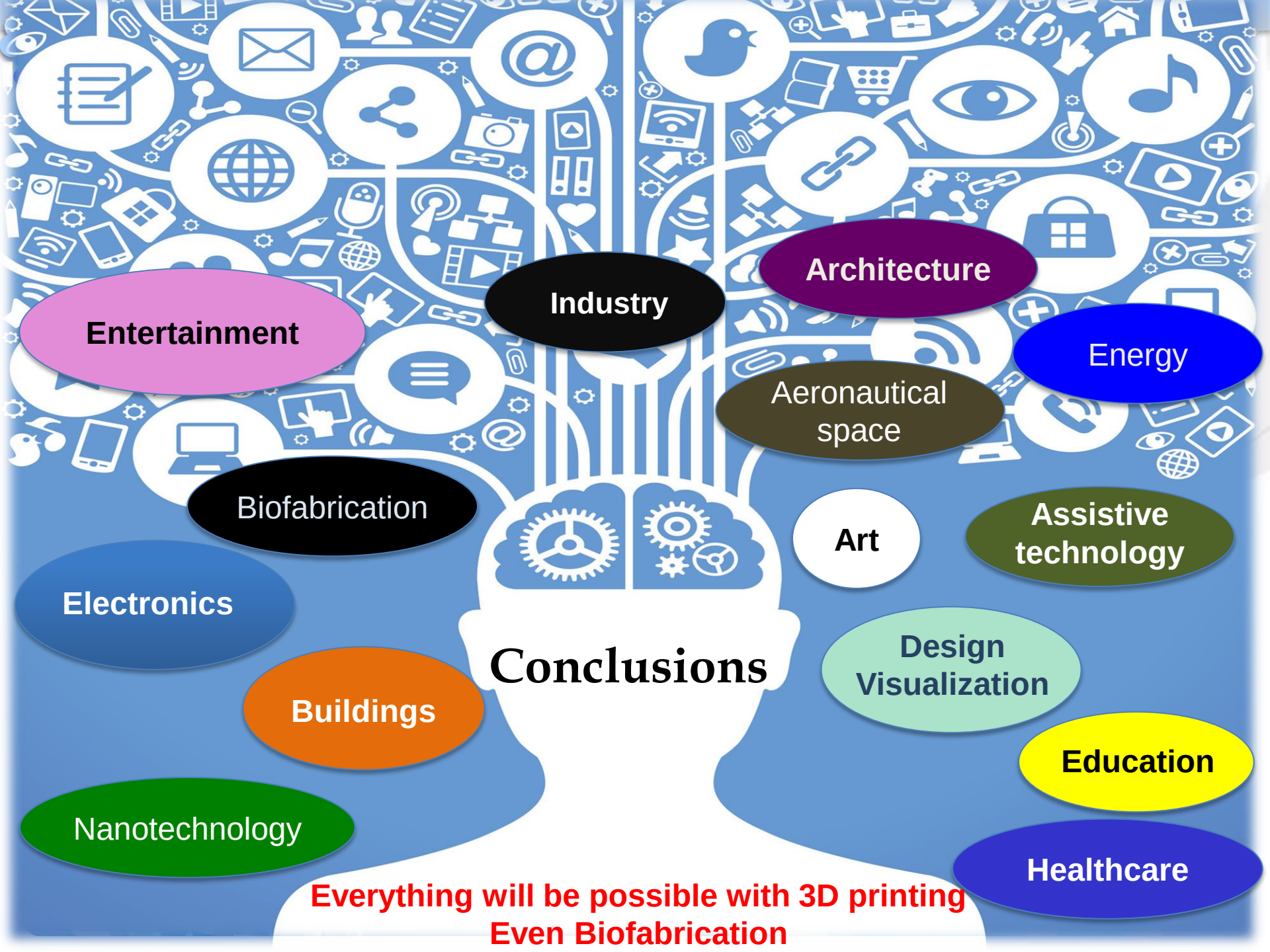
Market projections for 3D Bioprinting.



(Credit: IDTechEx)

Challenges

- ✓ **Integration Engineering x Life Sciences;**
- ✓ **Development of "blueprint" for bioprinting of 3D human tissue and organs;**
- ✓ **Development of new STL file-free function representation based CAD software for digital bioprinting;**
- ✓ **Development of scalable technology for biofabrication millions uniform tissue spheroids (robotic tissue spheroids biofabricators);**
- ✓ **Development of integrated operational system integration of robotic bioprinters (special software);**
- ✓ **Increasing speed and printing resolution of robotic bioprinters;**
- ✓ **Development of new bioreactor for 3D bioprinted tissues;**
- ✓ **Development of *in situ* bioprinting technologies (*in vivo* bioprinting of skin,**
- ✓ **cartilage, bones);**
- ✓ **Development of bioprintable biomaterials;**
- ✓ **Laws and regulations → <u>* Safety + Security</u>**


Entertainment
Industry
Architecture
Energy
Aeronautical space
Biofabrication
Art
Assistive technology
Electronics
Conclusions
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Buildings
Education
Nanotechnology
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Everything will be possible with 3D printing
Even Biofabrication

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Thank you for your kind attention!