



Bioimpressão de tecidos e órgãos: o avanço de novas tecnologias visando a Medicina 4.0

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www.biofabricação.com



Centro de
Tecnologia da
Informação
Renato Archer

Tópicos:

- Conceitos da bioimpressão e biofabricação de tecidos;
- Tecnologias envolvidas;
- O papel da tecnologia da informação na bioimpressão de tecidos;
- Projetos desenvolvidos no Brasil e no mundo sobre bioimpressão de tecidos.
- Medicina 4.0 → contribuição significativa da bioimpressão



Núcleo de Tecnologias Tridimensionais (NT3D) 1997

Mission

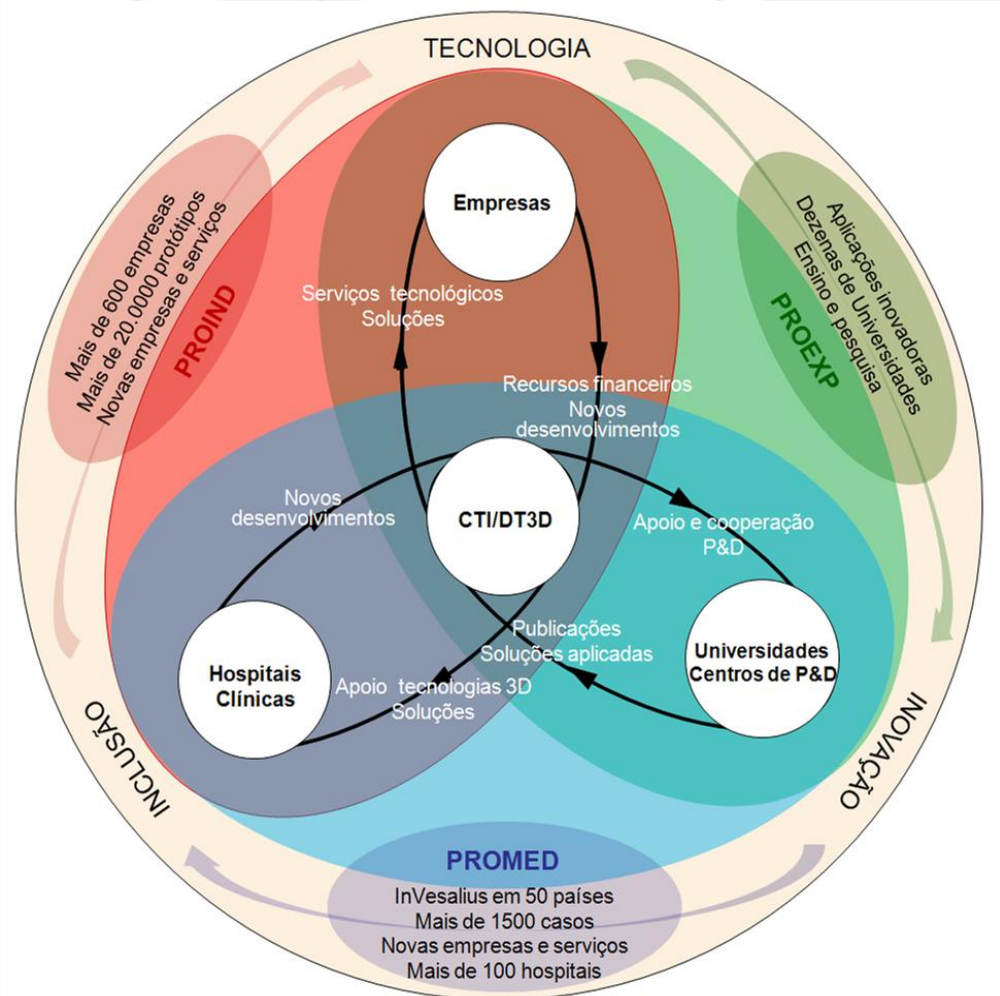
To research, develop, utilize,
and diffuse three dimensional
technologies (virtual and
physical) focusing in
innovation and
multidisciplinary applications
driven by society

Partnership

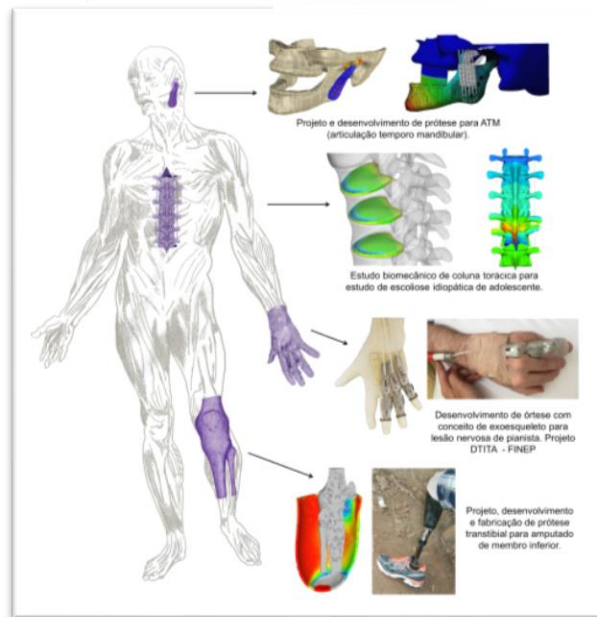
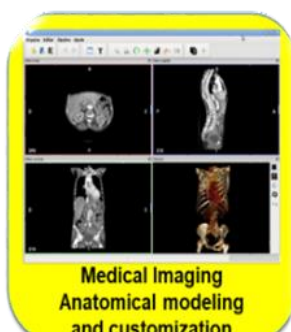
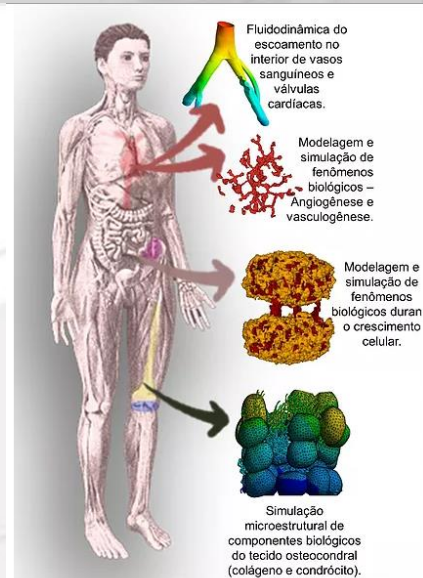
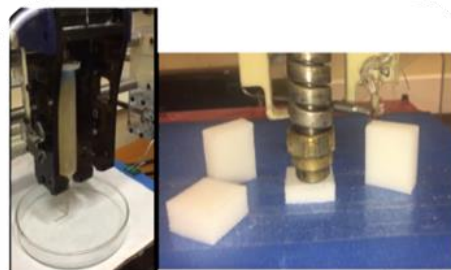
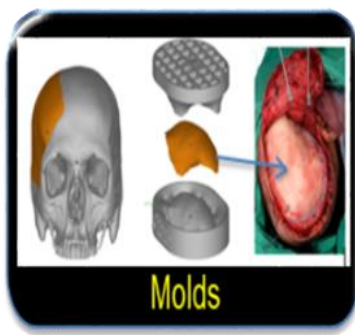
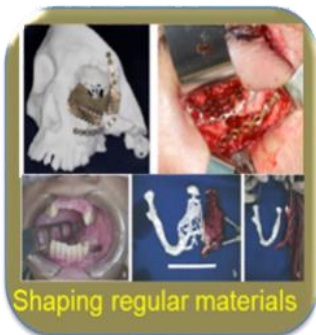
Companies (ProIND)

Hospitals (ProMED)

Universities (ProEXP)



CTI Renato Archer - Aplicações





No Brasil - CTI Renato Archer

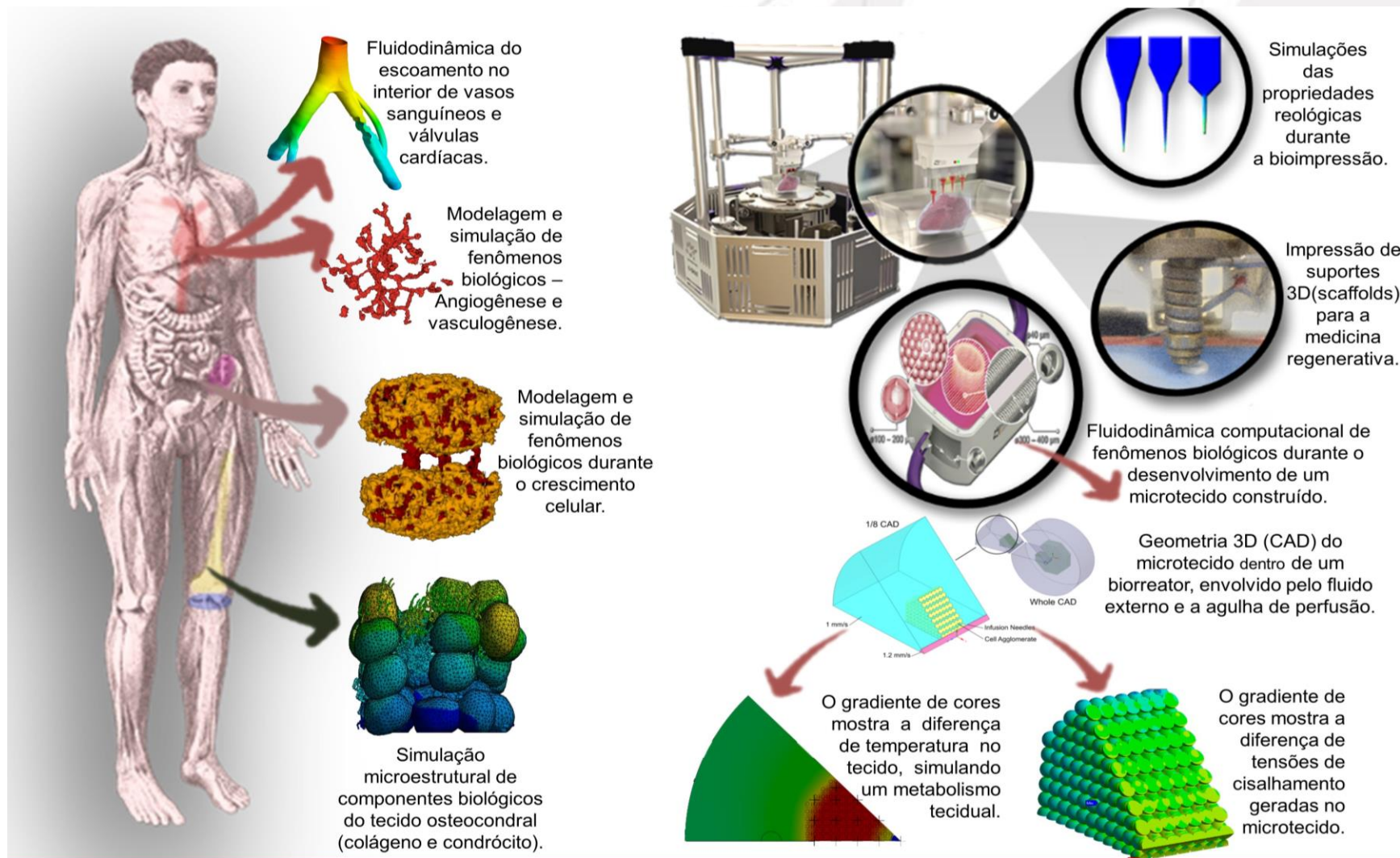
**Software livre para
reconstrução de imagens
provindas de equipamentos
de tomografia
computadorizada ou
ressonância magnética**



<https://www.cti.gov.br/pt-br/invesalius>

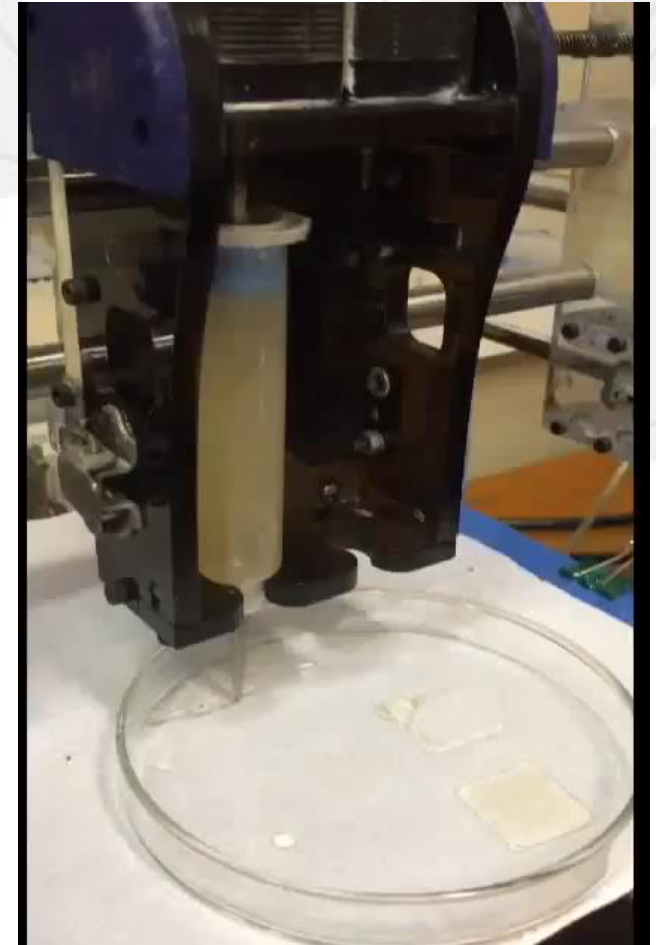
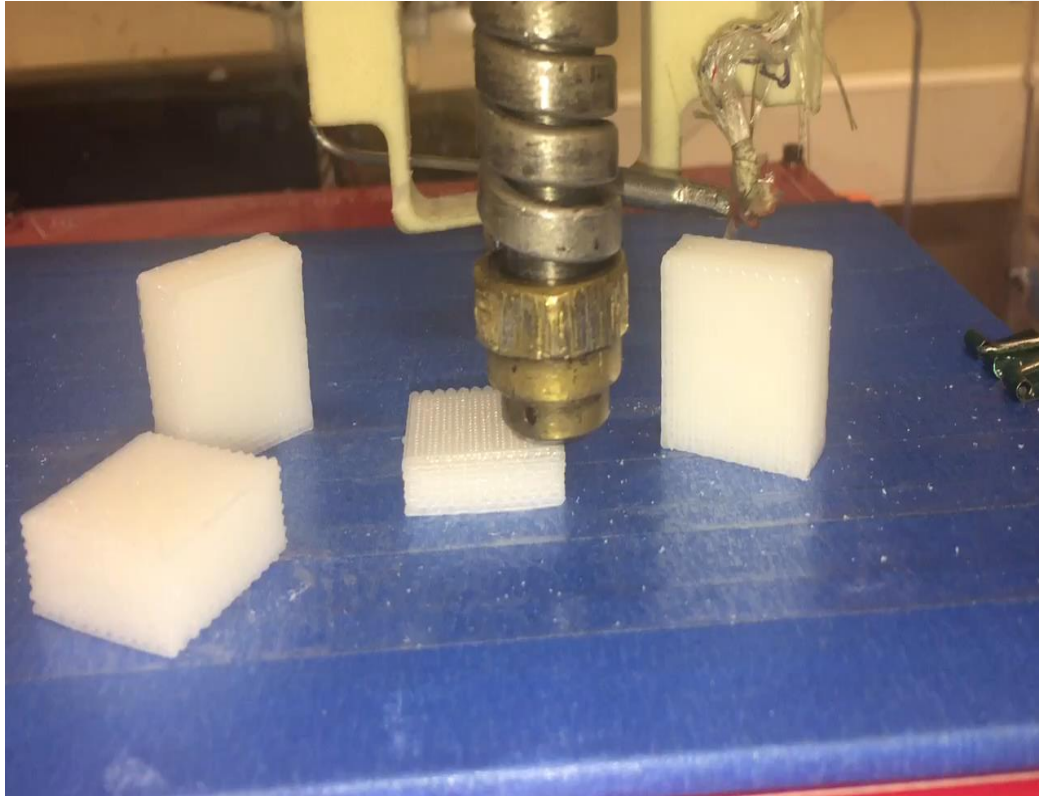


CTI Renato Archer - Aplicações

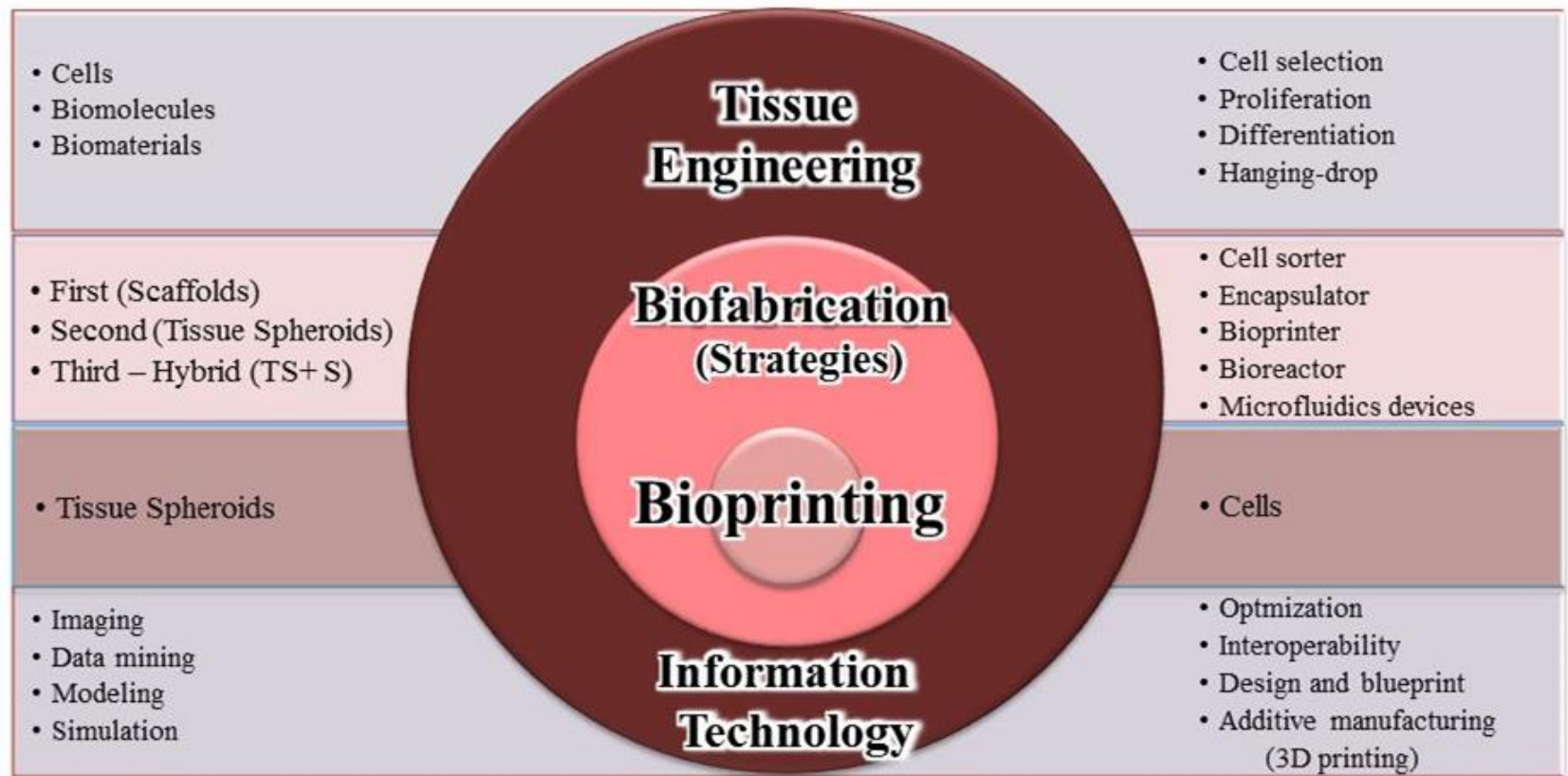




Impressão 3D na Engenharia de Tecidos

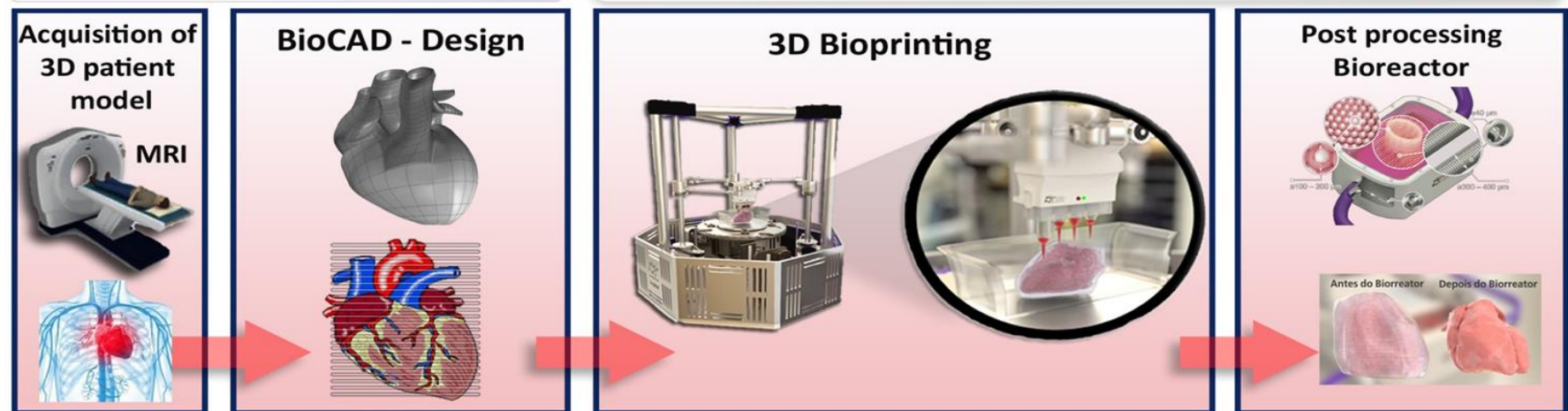
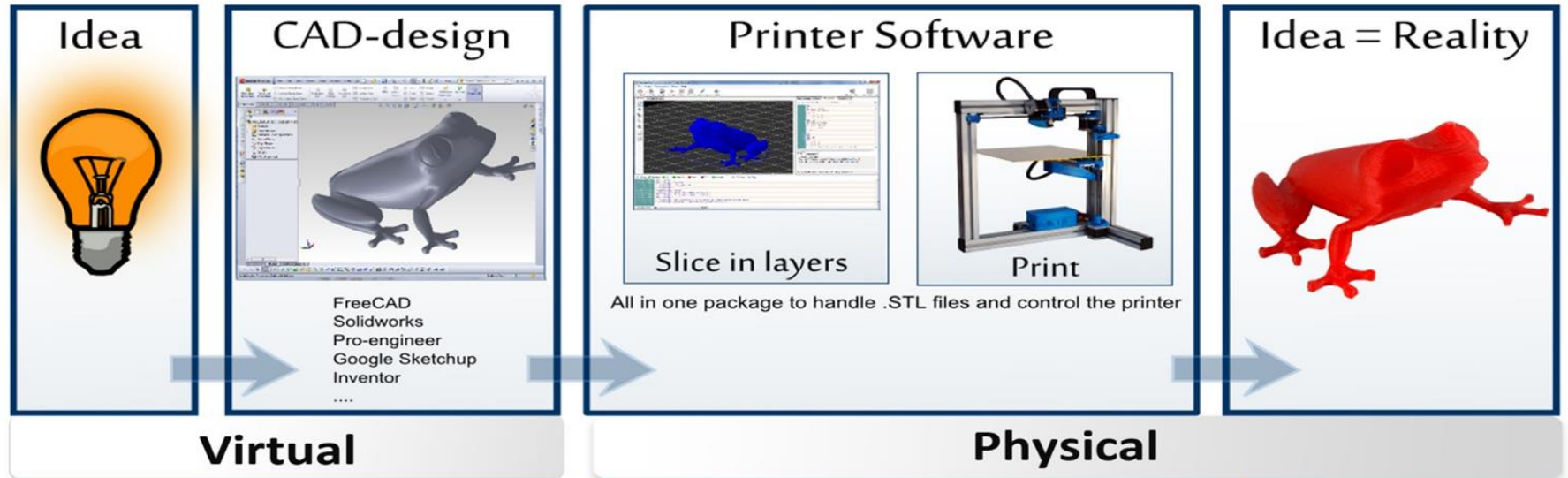


Engenharia Tecidual, Biofabricação, Bioimpressão e Tecnologia da Informação



Dernowsek *et al.*, 2017

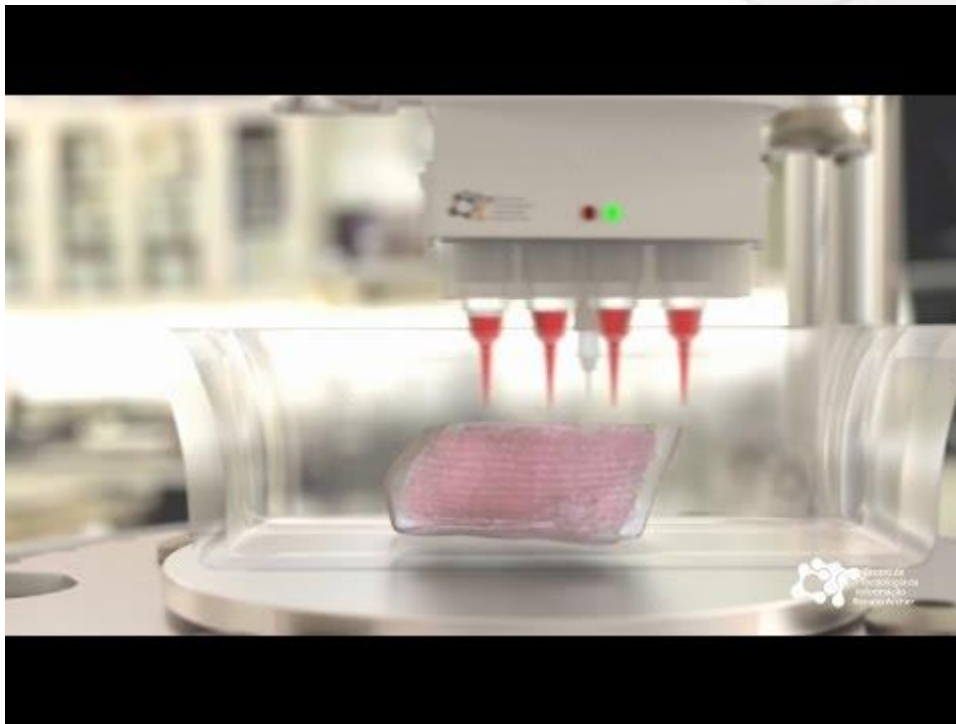
Tecnologias 3D, Tecnologia da Informação e Biofabricação





Bioimpressão

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





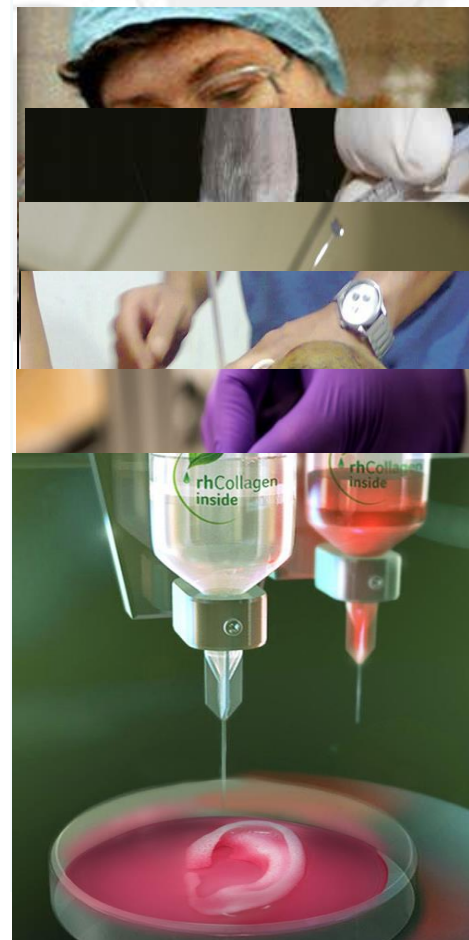
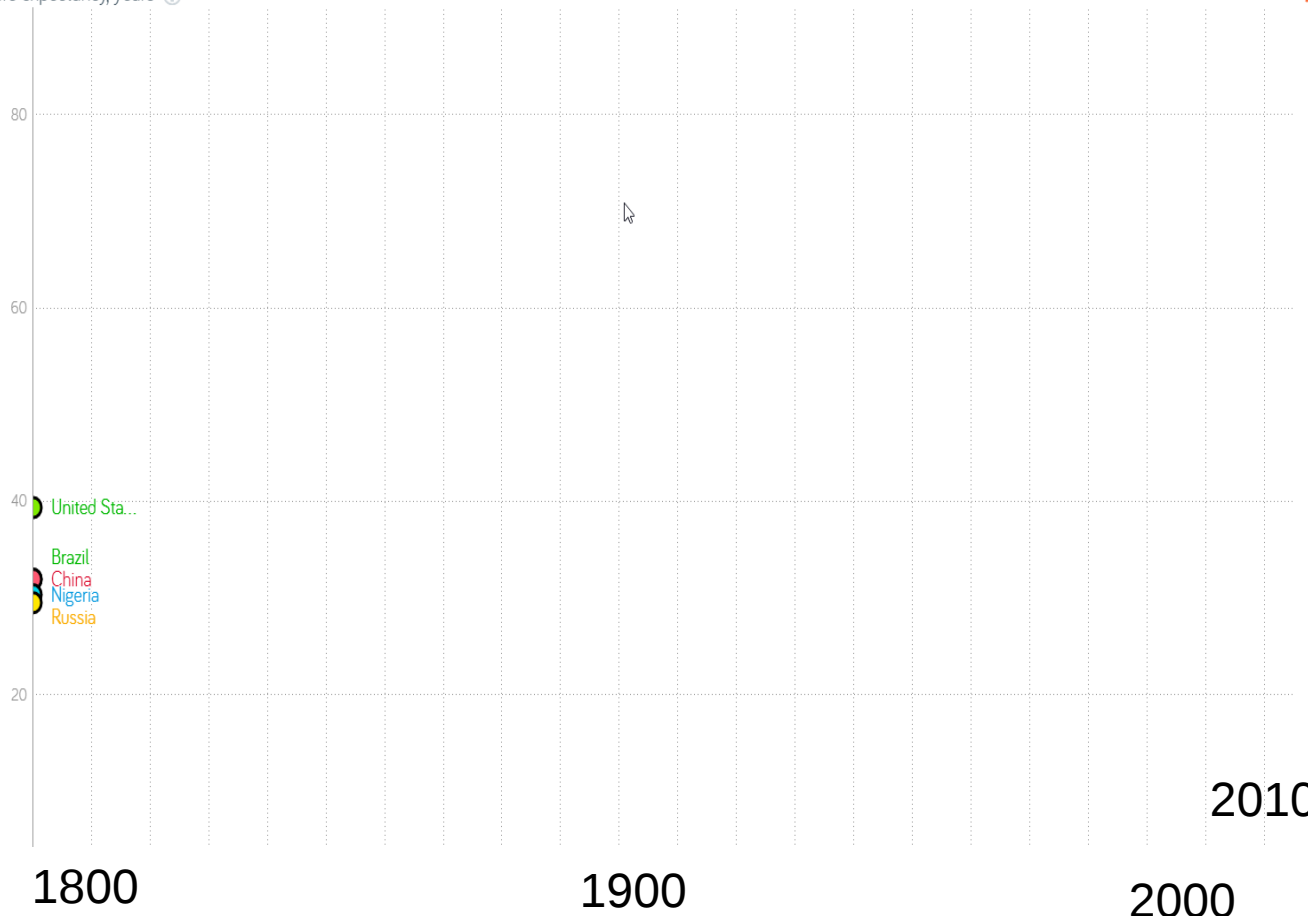
Motivações

GAZMINDER

Uso de animais para teste de drogas e cosméticos

Life expectancy, years ?

▲ DATA DOUBTS



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CONFERENCE & EXPO

BRAZIL

Potencial de Mercado



A IDTechEx prevê que o mercado global de bioimpressão atinja um valor de US \$ 1,9 bilhão até o ano de 2028.



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CONFERENCE & EXPO



Etapas da bioimpressão

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

Processing
3D Tissue Printing

Post-processing
Bioreactor → Tissue maturation

Step 1
Imaging



X-ray

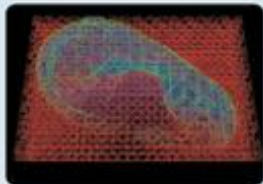


CT

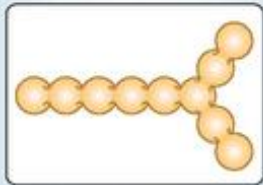


MRI

Step 2
Design approach



Biomimicry



Self-assembly

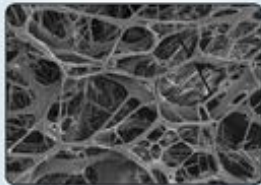


Mini-tissues

Step 3
Material selection



Synthetic polymers

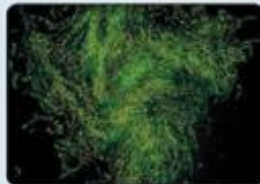


Natural polymers

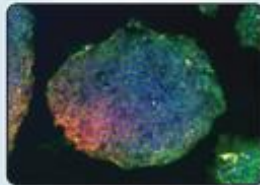


ECM

Step 4
Cell selection



Differentiated cells

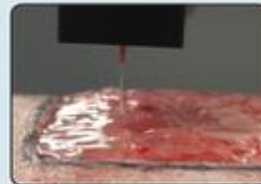


Pluripotent stem cells

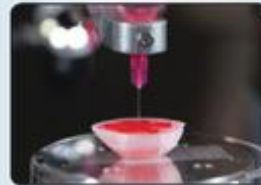


Multipotent stem cells

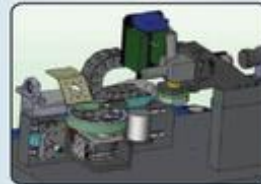
Step 5
Bioprinting



Inkjet

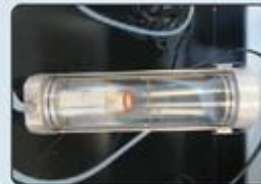


Microextrusion



Laser-assisted

Step 6
Application



Maturation



Implantation



In vitro testing



Etapas da Bioimpressão



Outlook

Today

- Small scale tissues
- Drug Discovery
- Toxicity testing

Tomorrow

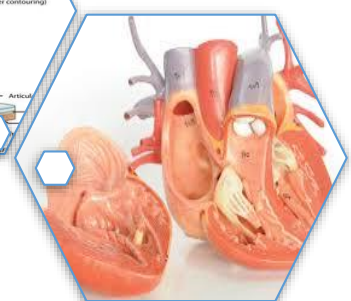
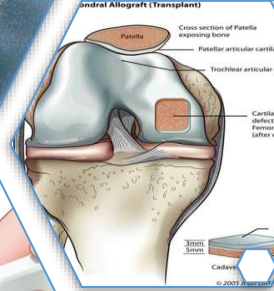
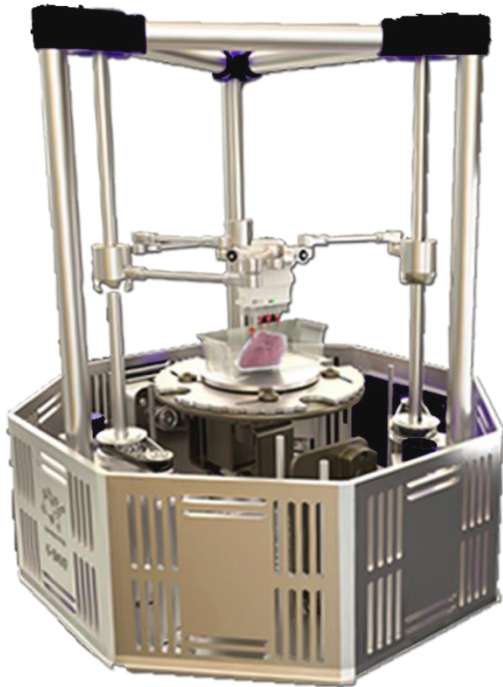
- Microtissues
- Implants

Future

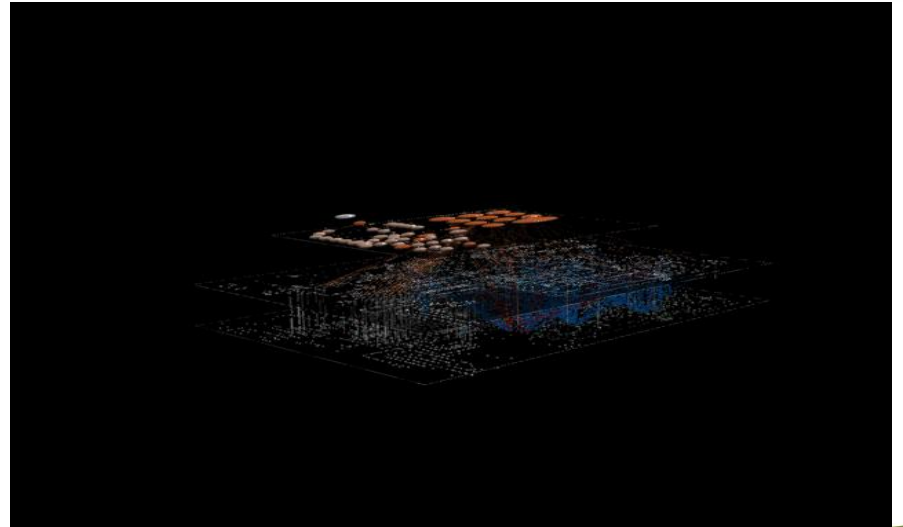
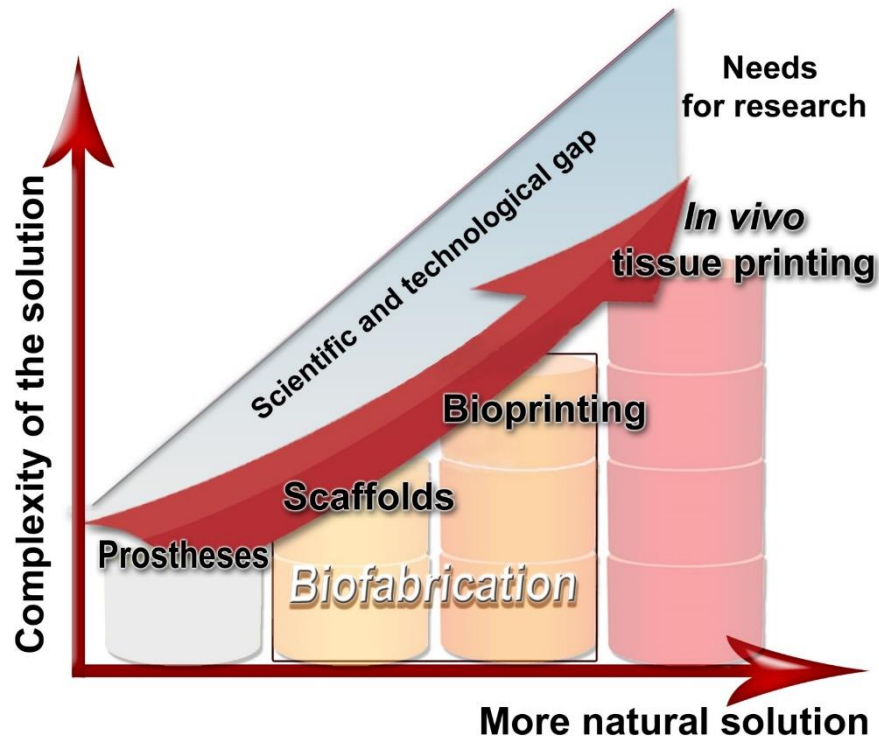
- Lobes
- Pieces of organs

Uncertain future

Full organs



Biofabrication and the relationship between complexity and nature of the solution

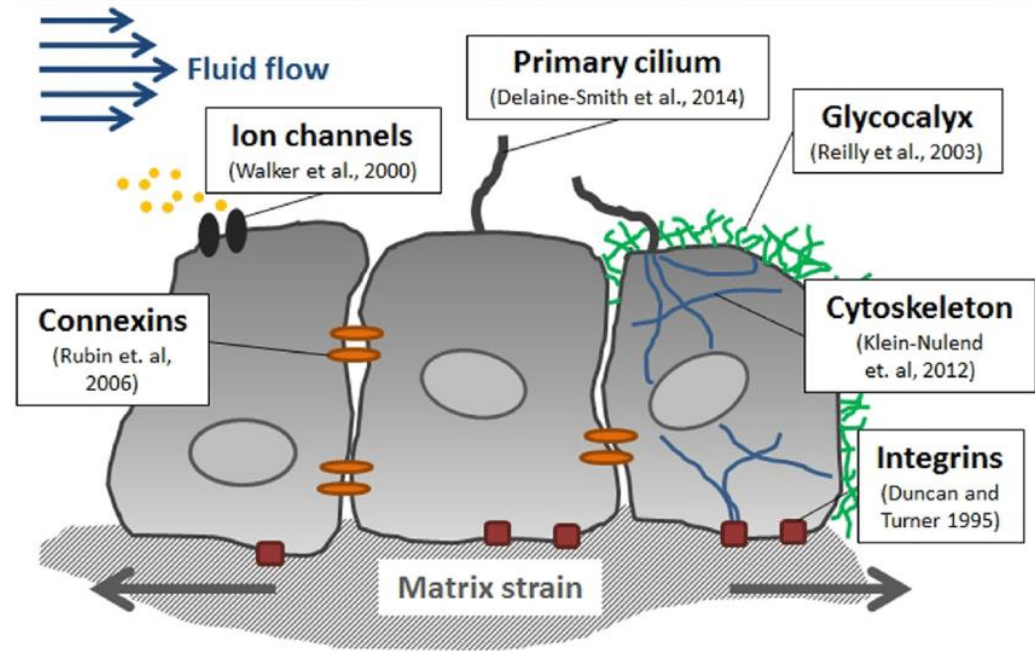
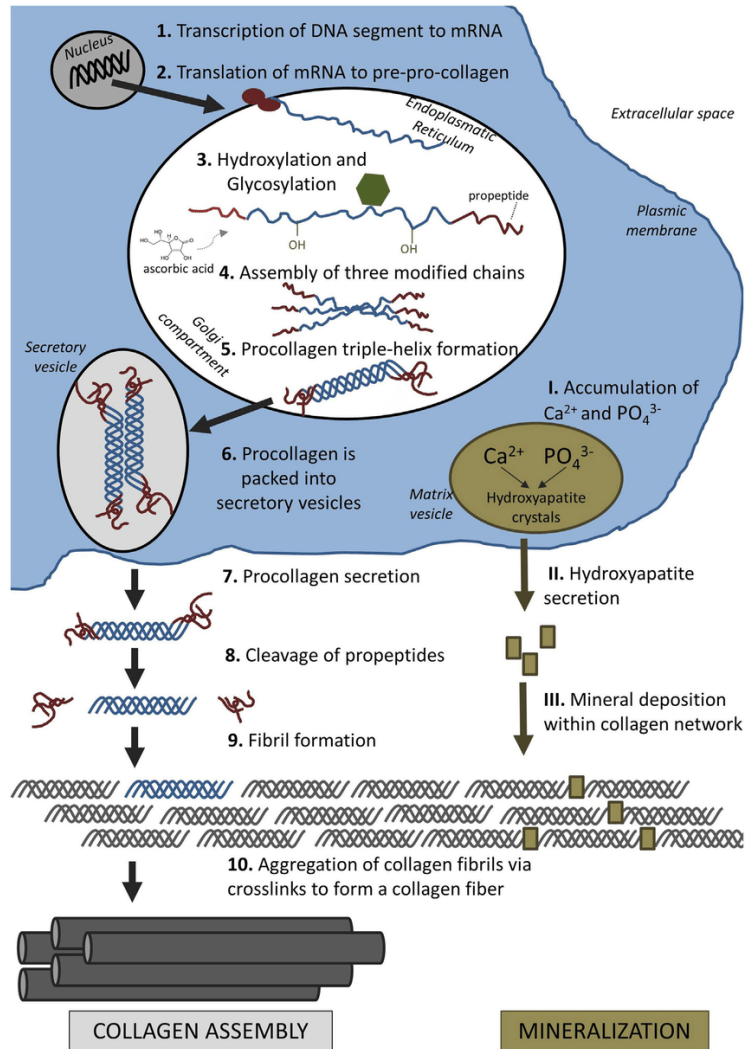


Dernowsek et al. 2017

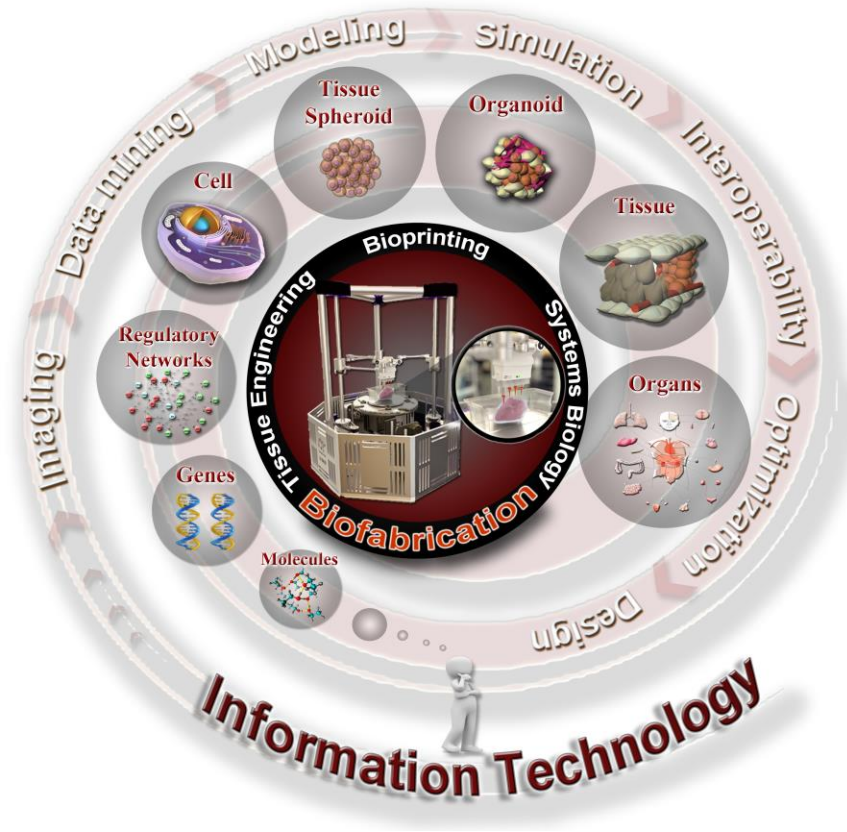
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BRAZIL

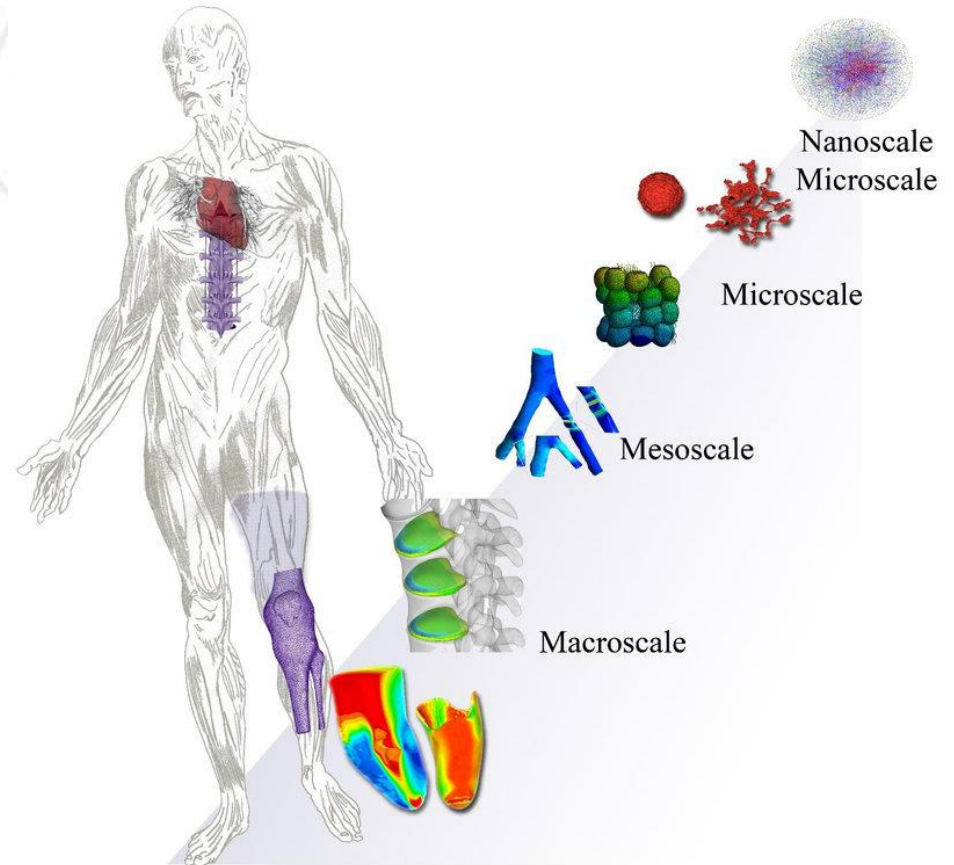
"BioFerramentas"



Conhecimento multiescalar



Dernowsek et al., 2017



Dernowsek et al., 2018

Organism scale (Meters - Centimeters)

- Finite Element,
- Computational Fluid Dynamics
- Multi Agent Systems
- Spatial Compartments and Projections

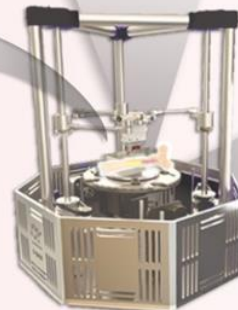
Years



Tissue scale (Centimeters)

- Multi Agent Systems
- Noble model, CPM- GGH
- Finite Element, MSNS method
- Ising models, Potts model
- Spatial Compartments and Projections

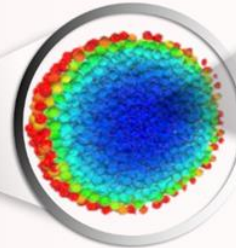
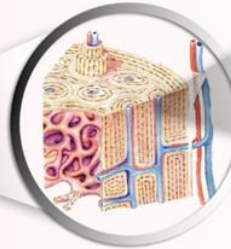
Days - Weeks



Cellular scale (Millimeters)

- Agent-based modeling
- Lattice Boltzmann
- Monte Carlo model
- Cellular Automata
- CxA multi-scale method

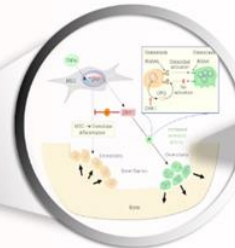
Hours - Days



Extracellular scale (Micrometers)

- Partial differential equations
- Convective-diffusion models
- Noble model, Fenton-Karma model,
- Fitzhugh-Nagumo, Hodgkin-Huxley

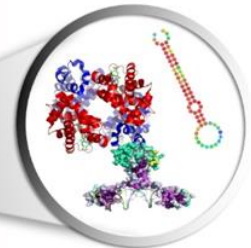
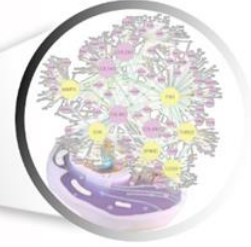
Minutes



Intracellular scale (Micrometers - Nanometers)

- Ordinary Differential Equations
- Stochastic Differential Equations
- Quasi-continuum method
- Convective-diffusion models

Seconds



Tissue or Organ

Fusion, maturation,
shear stress, flow rate
-inlet and outlet-,
waste products, pH

3D Bioprinting

BioCAD, BioCAM,
Bioprinter,
biopaper, bioink

Tissue spheroid

Stem cells, cell isolation
and proliferation,
cell fate specification,
organoids

Cell culture environment

pH, temperature, osmotic
pressure, culture medium,
sterility, cytokines/hormones

Molecular scale

Biomolecules, genes,
transcription factors, miRNAs,
proteins, O₂, drugs
and other molecules

Biofabrication

Dernowsek et al., 2016

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Bioimpressoras



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Bioimpressoras



3D Biotechnologies Solutions

Resolution:

Brasil

- 50 μ m Layer thickness (z)
- 100 μ m (x,y)
- **R\$ 13.000**
- **OPEN-SOURCE PROGRAMS**



3D Biotechnologies Solutions

Resolution:

- 5 μ m Layer thickness (z)
 - 10 μ m (x,y)
 - **R\$ 30.000**
 - Pronterface e Slic3R/Cura
- OPEN-SOURCE PROGRAMS**

Bioimpressoras



BIO X 3D BIOPRINTER
CELLINK

Suécia

Resolution :

- 1 μ m Layer thickness (z)
- 1 μ m (x,y)
- **11,840 - 21,840 USD**



reddot award 2018
winner

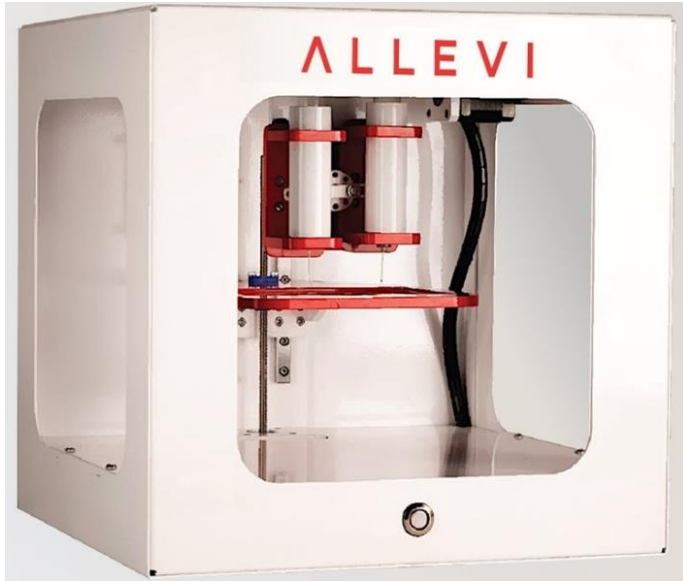
BIO X 3D BIOPRINTER
CELLINK

Suécia

Resolution :

- 50 μ m Layer thickness (z)
- 1 μ m (x,y)
- **40,840 USD**

Bioimpressoras



Allevi 2 Bioprinter

Resolution:

EUA

- 5 μ m Layer Thickness (z)
- 5.5 μ m (x,y) 150
- 150 μ m Print Resolution
- ~ 5,000 USD



Allevi 2 Bioprinter

EUA

Resolution :

- 1 μ m (x, y, z)
- ? μ m Print Resolution



Bioimpressoras



r3bEL MINI BIOPRINTER

SE3D

EUA

Resolution:

- 150 μm Layer thickness (z)



r3bEL X BIOPRINTER

SE3D

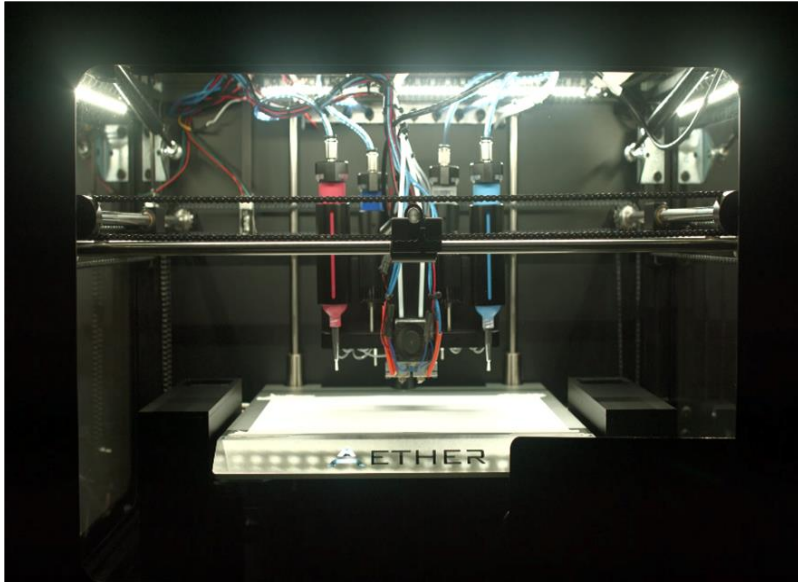
EUA

Resolution:

- 150 μm Layer thickness (z)

OPEN-SOURCE PROGRAMS

Bioimpressoras



Aether Bioprinter
Aether
EUA

Resolution:

- 1 μm (x, y)
- 0.43 nm (z)



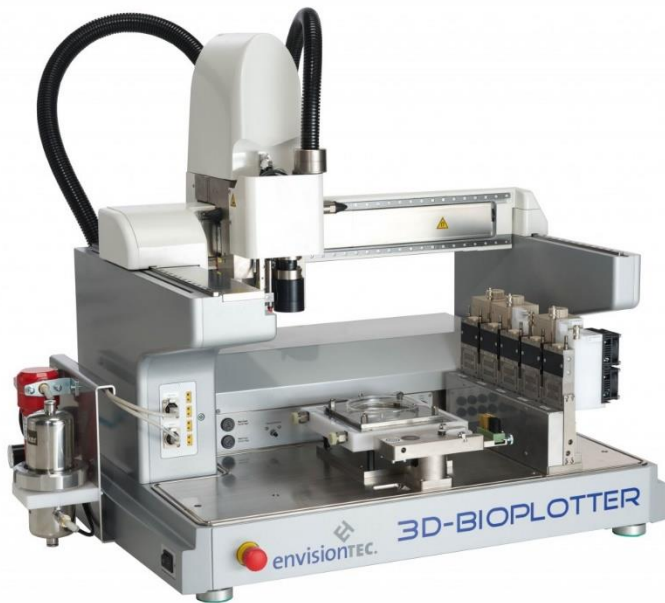
Tissue Scribe Gen. 3
3DCULTURES
EUA

Resolution:

- 0.1mm (x, y)
- 0.04375mm (z)
- 0.1-0.2mm

• **1,099 USD**

Bioimpressoras



3D-Bioplotter

EnvisionTec

Alemanha

Resolution:

- $1\mu\text{m}$ (x,y,z)
- ? μm Print Resolution



BIOASSEMBLYBOT

Alemanha

Resolution:

- $1\mu\text{m}$ (x,y,z)
- ? μm Print Resolution

Bioimpressoras



3DDiscovery™ platform

REGENHU LTD

Suiça

Resolution: $\pm 5\mu\text{m}$

Melt Electrospinning & Bioprinting
technology convergence



INVIVO Standard

ROKIT

Koreia

Resolution:

- Extruder $200\mu\text{m}$ / Dispenser $80\mu\text{m}$



Bioimpressoras

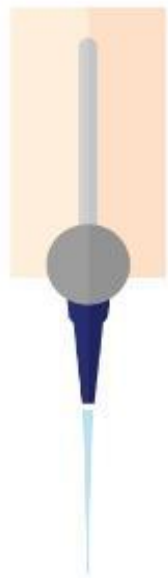


RX1 Bioprinter
Aspect Biosystems Ltd
Canadá

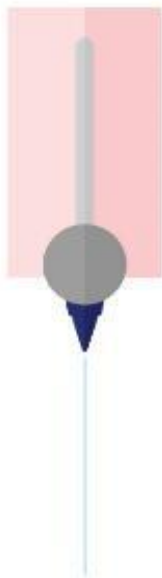
Resolution:

- 0.1mm (x, y)
- 0.04375mm (z)
- 0.1-0.2mm
- **1,099 USD**

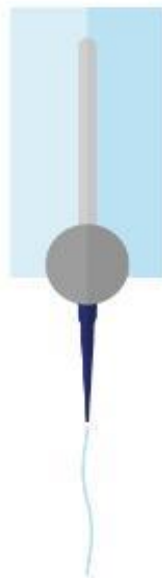
Parâmetros presentes nas Bioimpressororas




EXTRA HEATED
PNEUMATIC HEAD




THERMOPLASTIC
FILAMENT EXTRUDER




COOLED
PNEUMATIC HEAD




INK-JET
PRINT HEAD




SYRINGE PUMP
PRINT HEAD



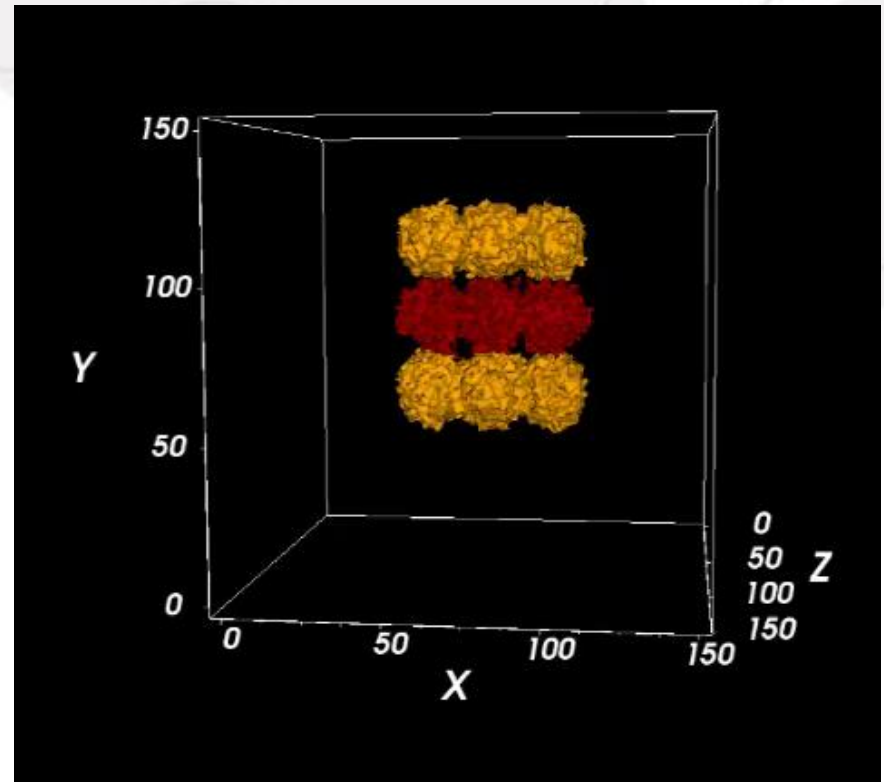
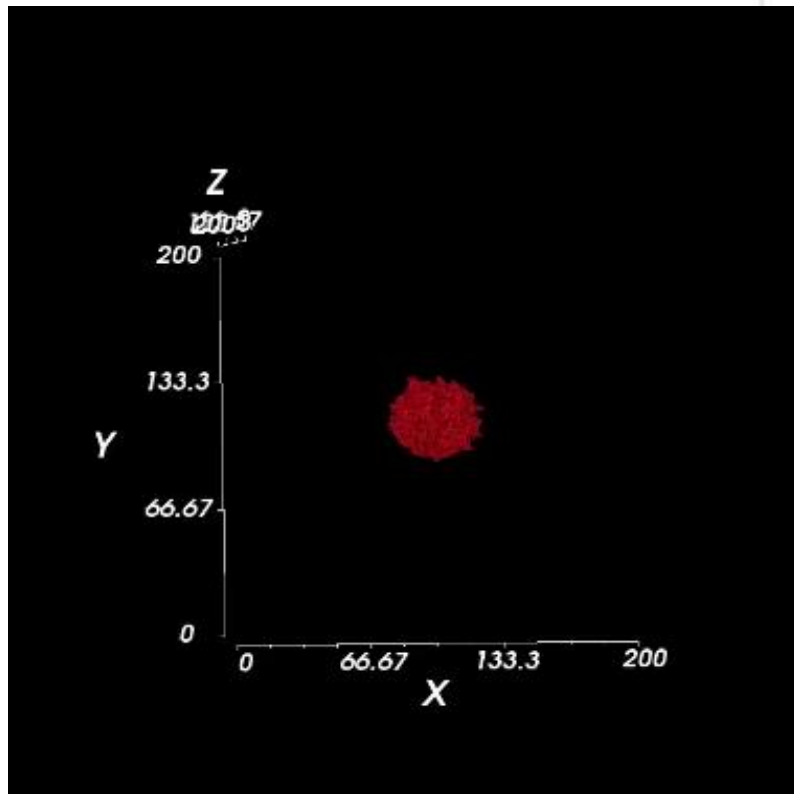

PHOTO CURING
TOOL HEAD
UV light

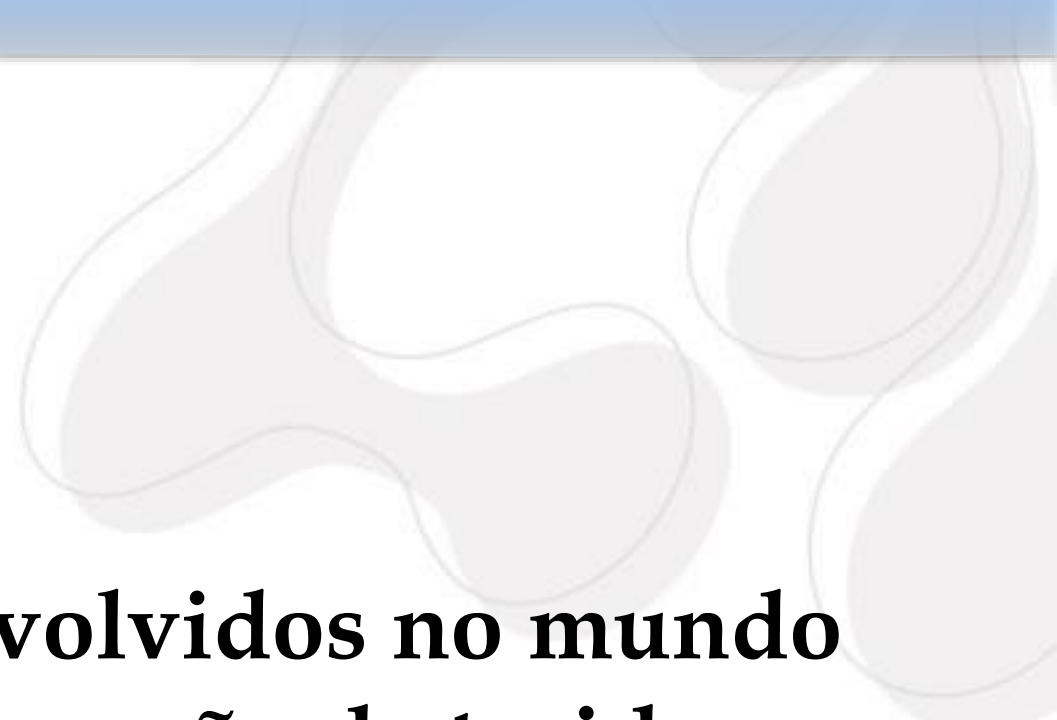



HD CAMERA
TOOL HEAD



Computational approaches for biofabrication of tissues → Angiogenesis + Proliferating cells

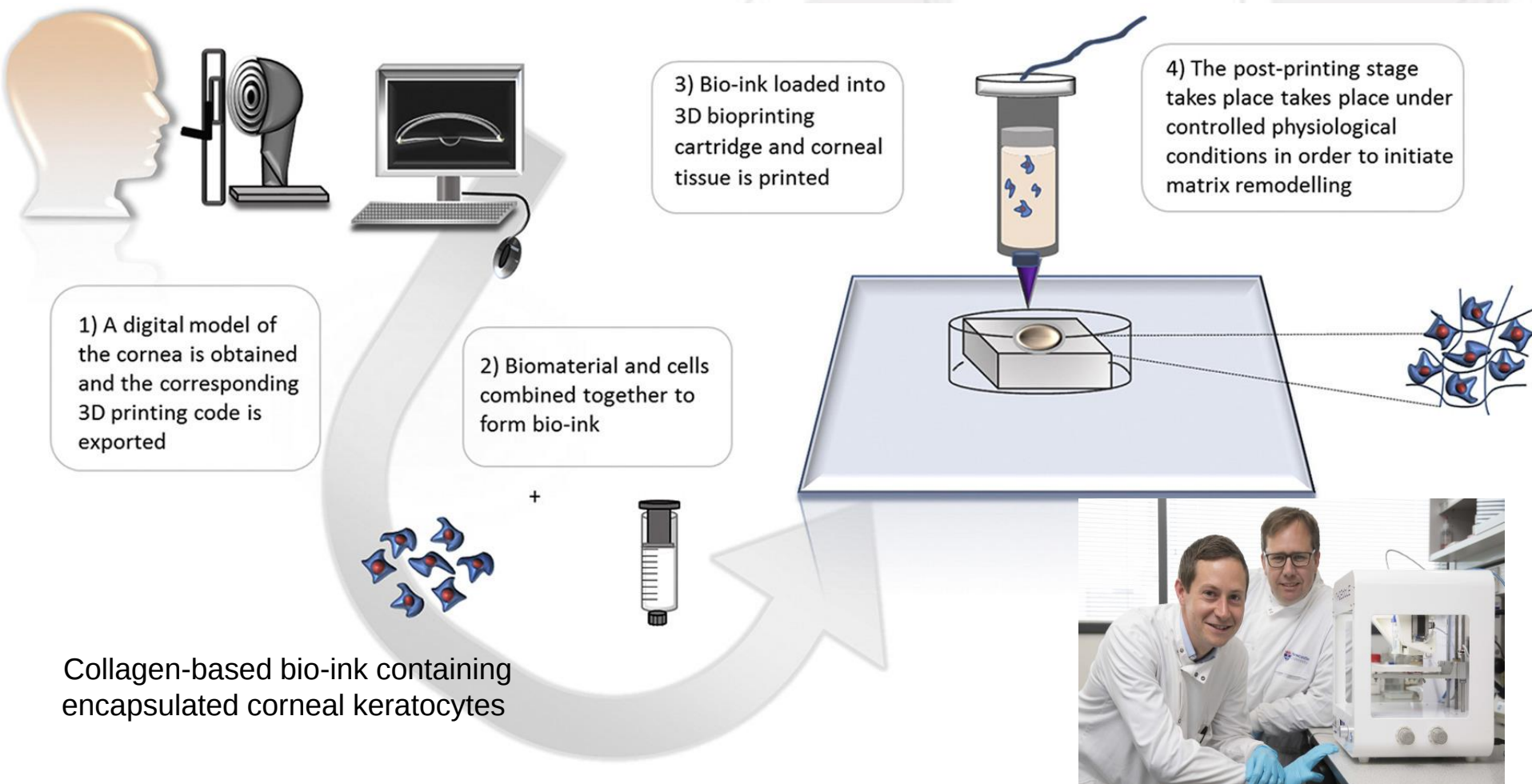




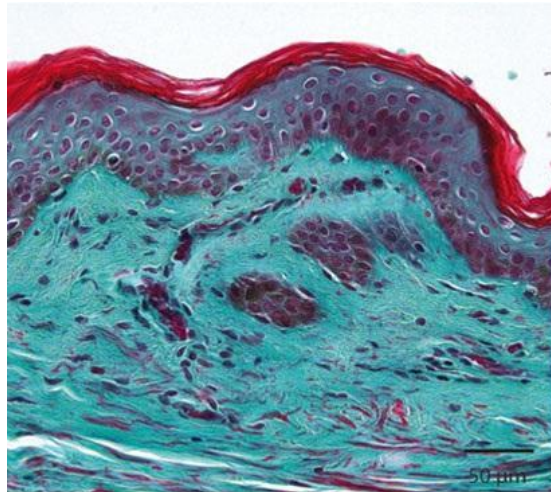
Projetos desenvolvidos no mundo sobre bioimpressão de tecidos

Cientistas BRITÂNICOS imprimem as primeiras córneas humanas

Abigail Isaacson, Stephen Swioklo, Che J. Connon, 2018

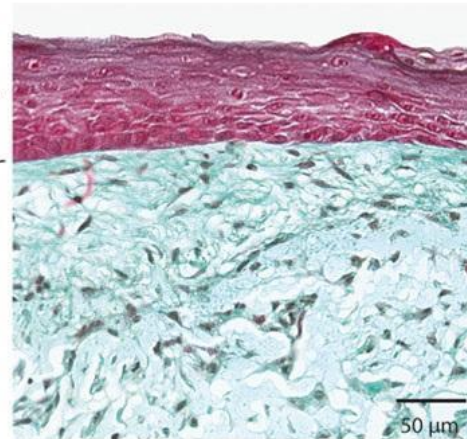


3D printing: Human skin is now being printed in labs



Human skin

Epidermis —
DEJ —
Dermis —



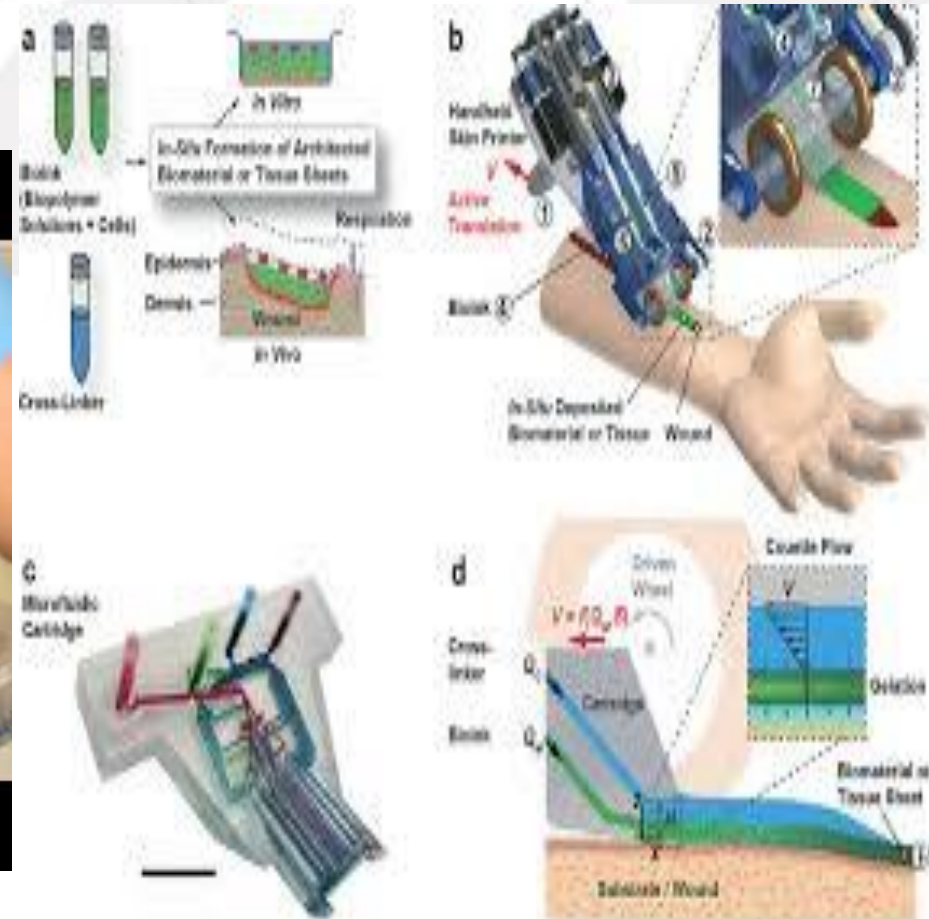
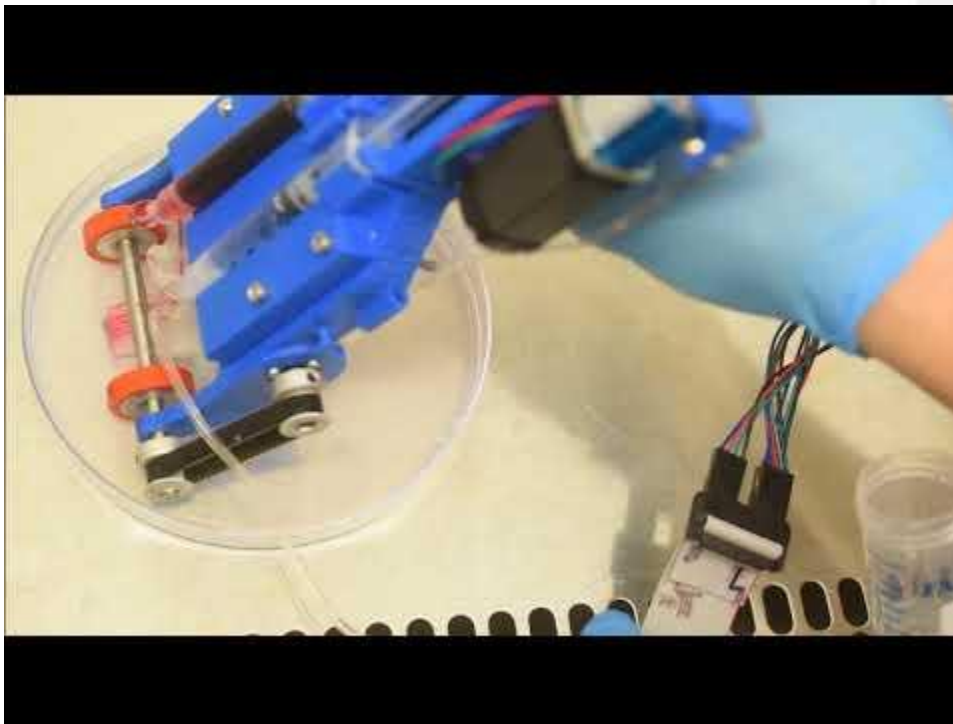
3D Bioprinted skin



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.

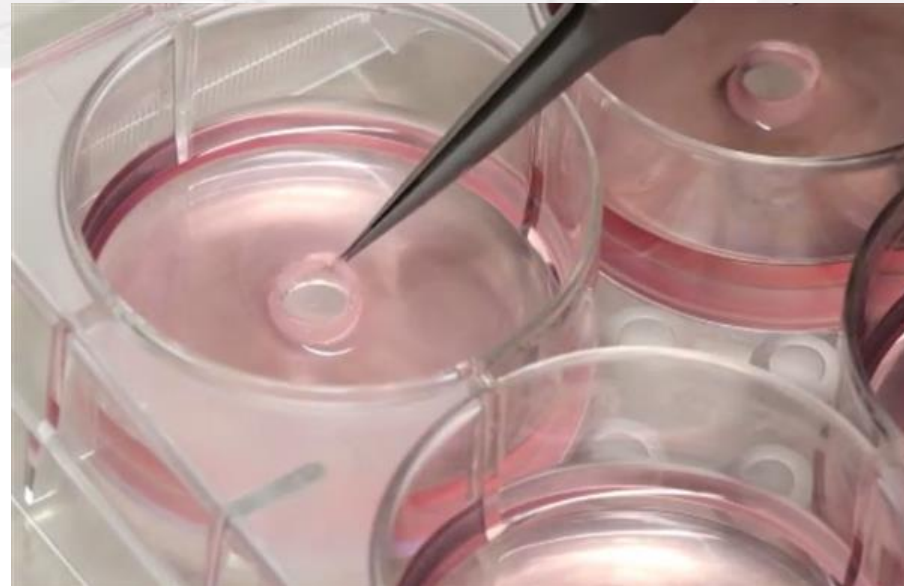


Handheld 3D printer



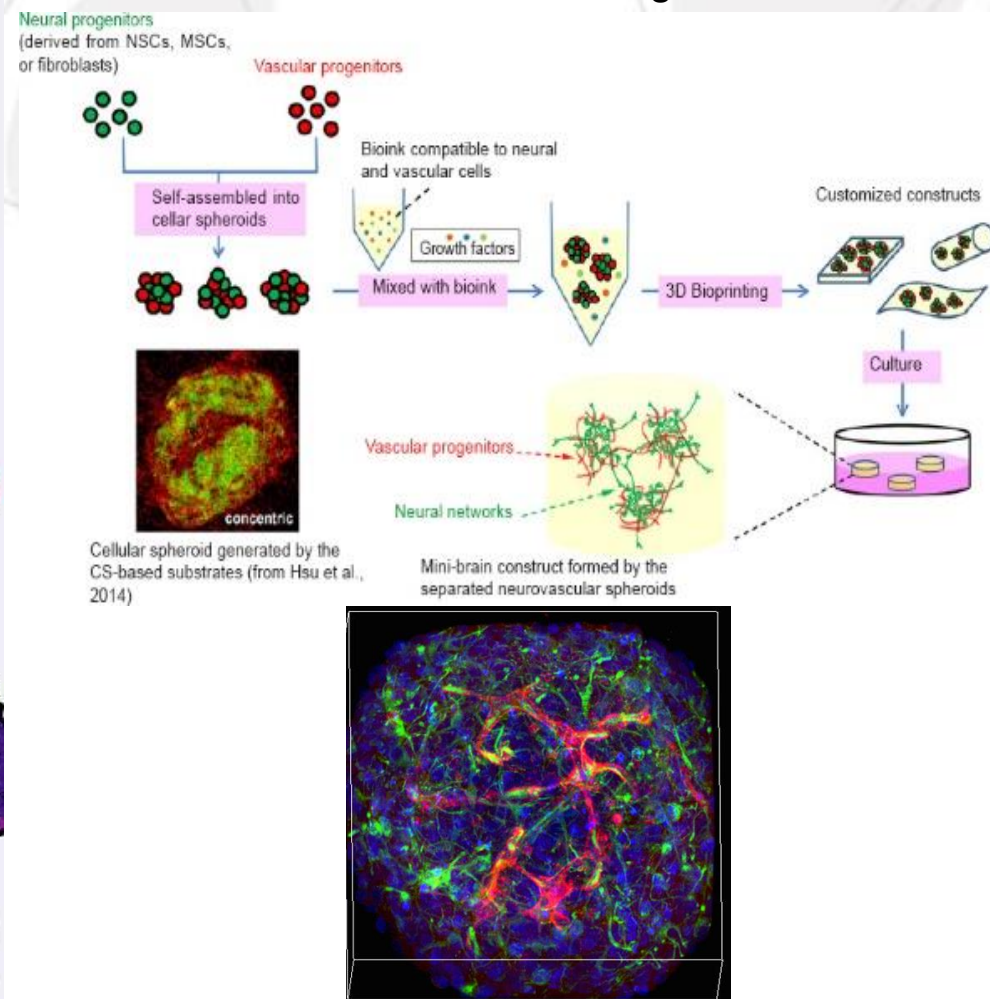
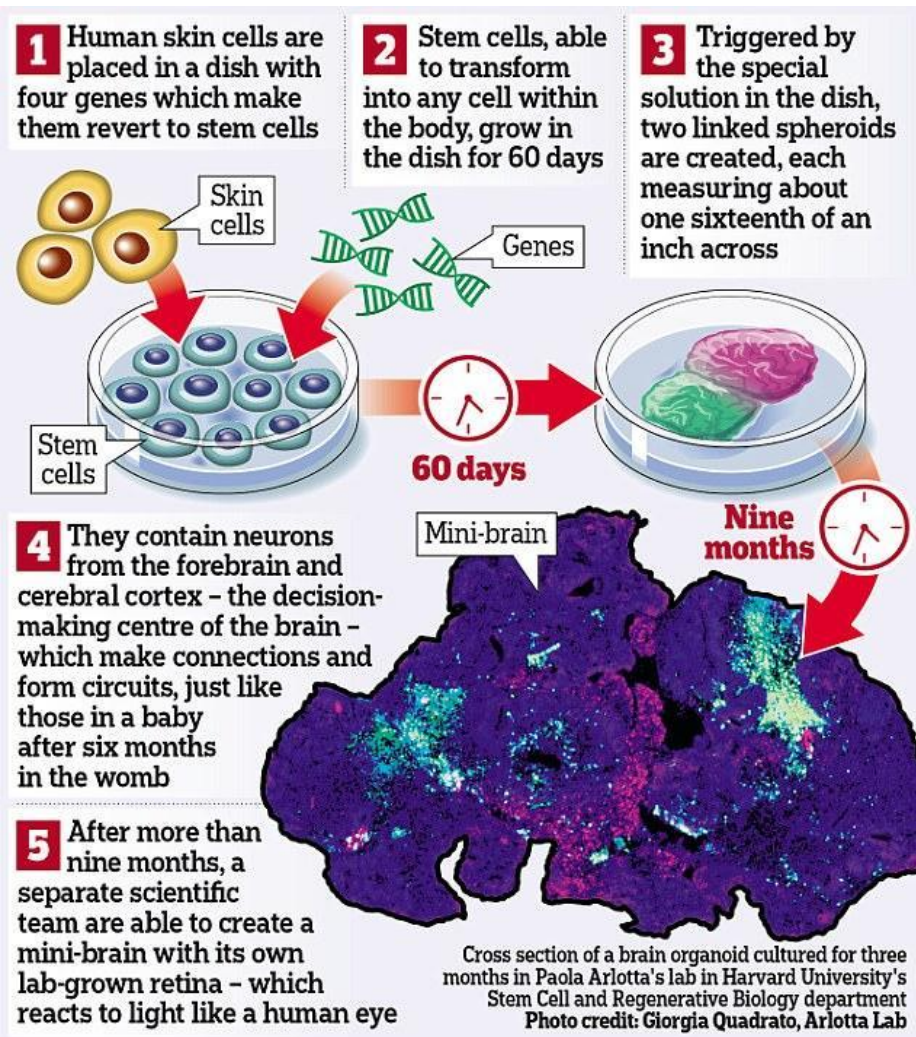
3D Printing Blood Vessels

- Scientists are developing flexible materials to 3D print blood vessels



Using 3D bioprinting to produce mini-brain

Han and Hsu, Neural Regen Res, 2017





organovo®

organovo®

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ExVive™ Human
Tissue Models &
Services for Research

3D Human Tissues for
Medical Research &
Therapeutics

THERAPEUTIC TISSUES

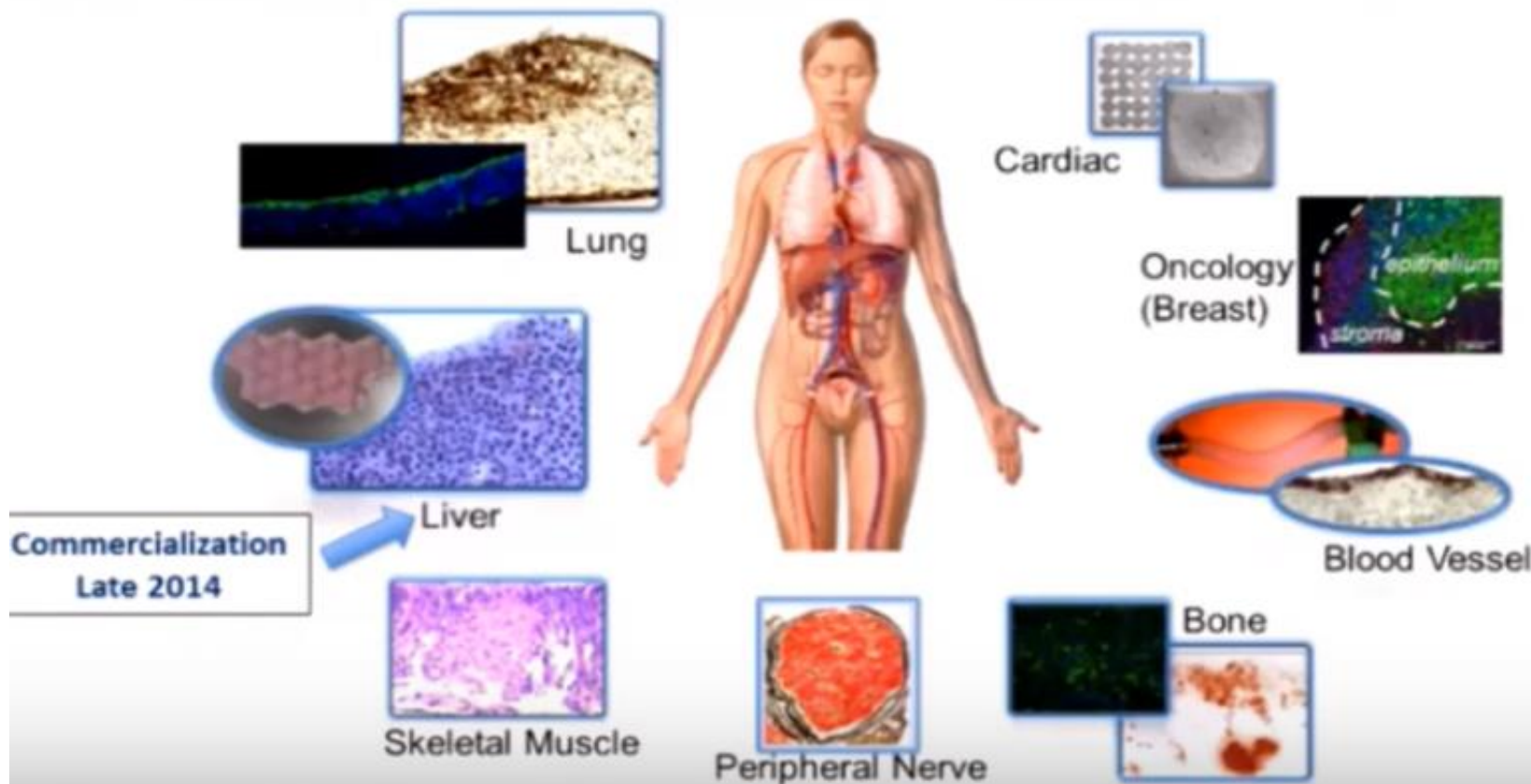
T O M O R R O W

TISSUE TESTING SERVICES

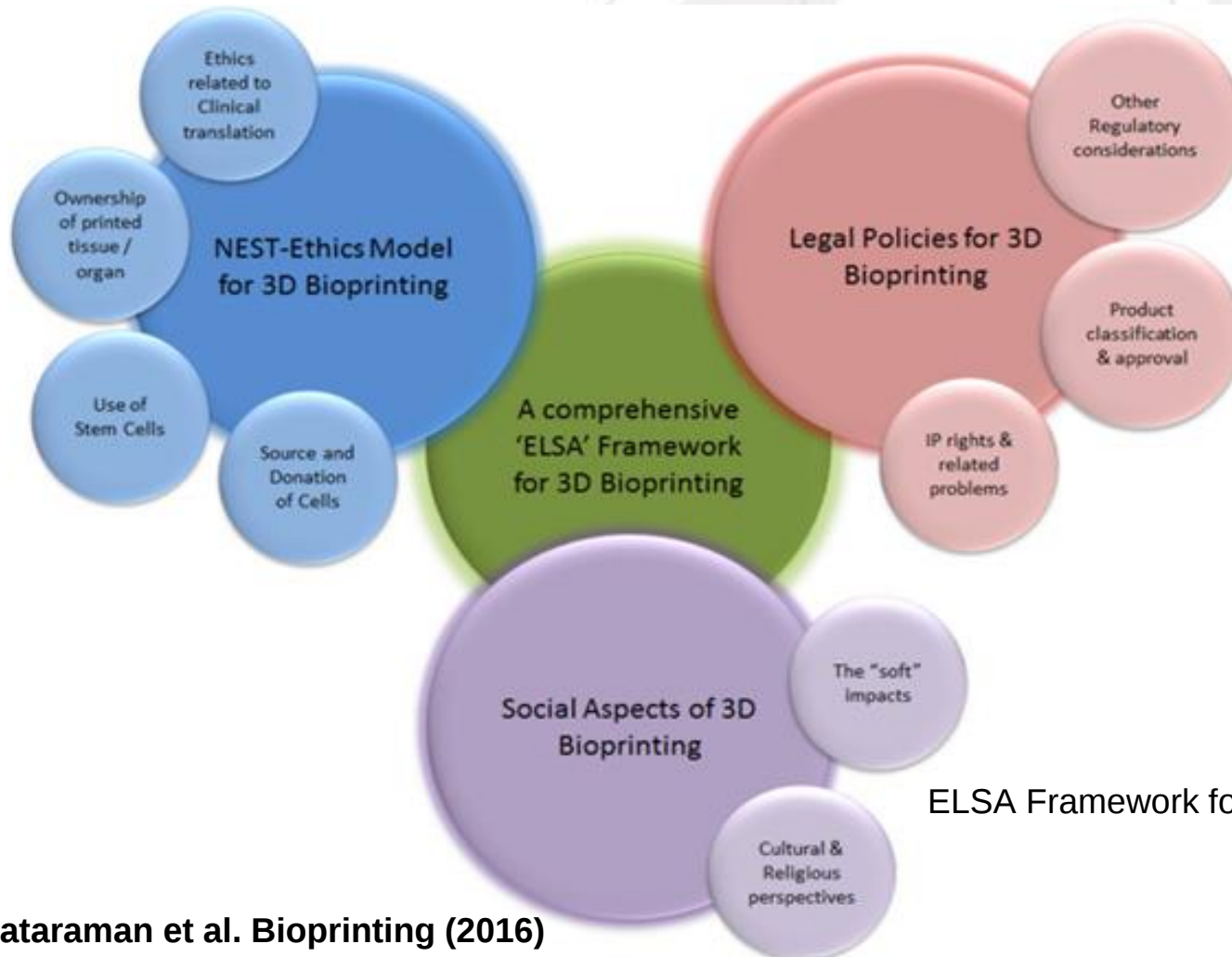
T O D A Y



Tissues from throughout the body
Organovo technology has bioprinted successfully



Aspectos legais, éticos e sociais ??



ELSA Framework for 3D bioprinting

S. Vijayavenkataraman et al. Bioprinting (2016)

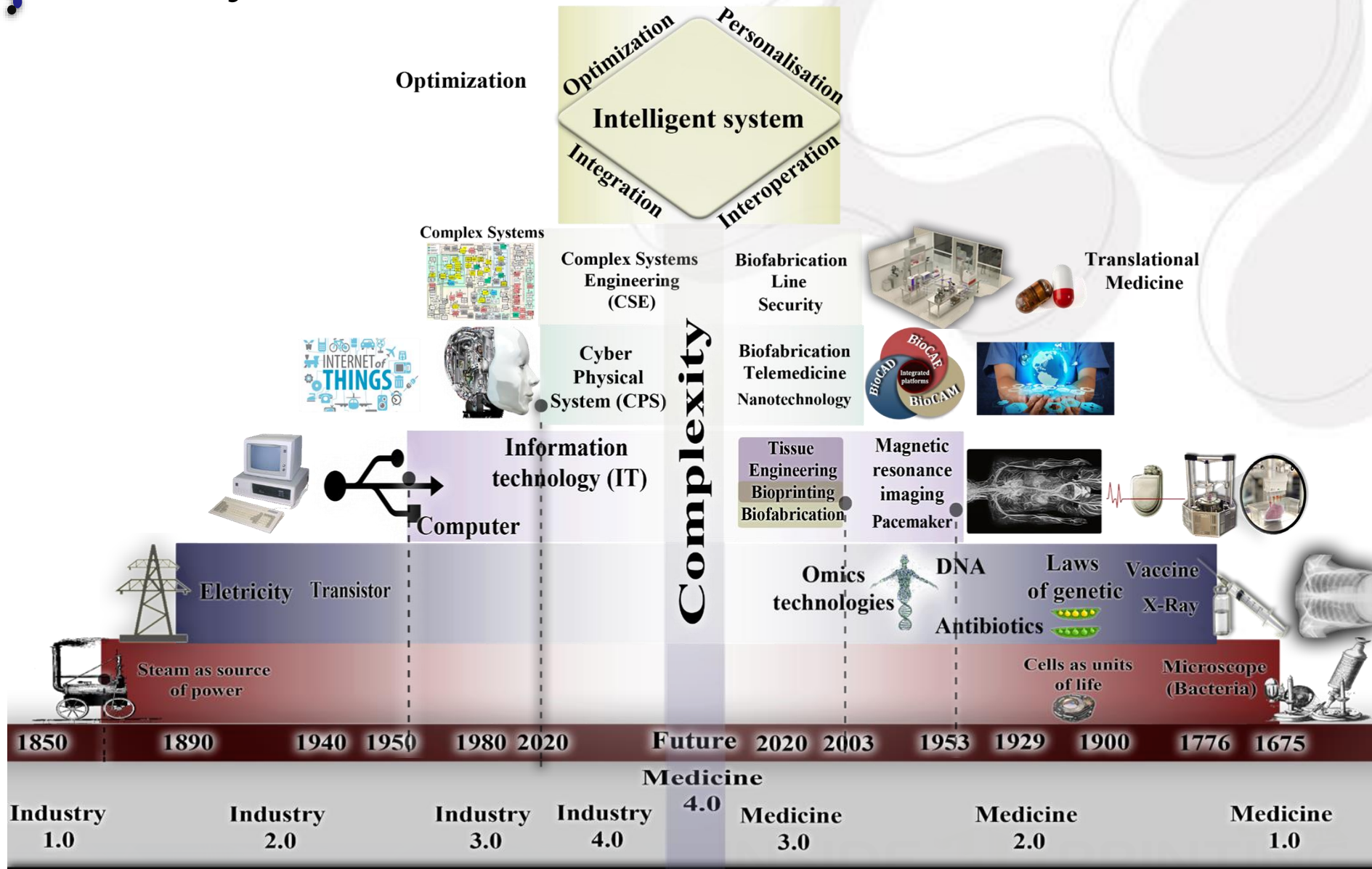


Por que ainda não temos órgãos funcionais “bioimpressos”?

- ✓ **Integration Engineering x Life Sciences;**
- ✓ **Development of new bioreactor for 3D bioprinted tissues;**
- ✓ **Development of bioprintable biomaterials;**
- ✓ **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.**
- ✓ **Development of integrated operational system integration of robotic bioprinters (special software);**
- ✓ **Laws and regulations.**



Industry 4.0 e Medicine 4.0



Biofabricação de Tecidos e Órgãos

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Biofabricação

Biofabricação representa um conjunto de técnicas e métodos da engenharia, biologia, medicina, química, física, computação, ciência dos materiais, entre outras disciplinas, visando a construção e reconstrução de estruturas tridimensionais biológicas que atuarão no tratamento, na restauração e estruturação de tecidos e órgãos.





Thank you for your kind attention!



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