DPS Better Engineered Solutions

The Biologicalisation of Medicine and Manufacturing

William Whitford

Global Solutions Leader, DPS Group

3D-Printing and Biofabrication

Boston, 17-18 August, 2020

DPS Group

- A leading global Architectural, Engineering and Consulting Company
- Advanced therapeutics focus
- 2000 People in 15 offices worldwide

DPS Offices

Alliance Partners

Agenda

- Biologicalisation
- Digital manufacturing
- Bio-inspired constructions
- Bioproduction, botany and bioprinting
- Biocentrism and the biocentric universe

Everyone wants “Natural” and “Green”

It’s healthy, romantic and sustainable

- But, natural systems can be
  - Sluggish
  - Inflexible
  - Unstable
  - Inefficient
  - Expensive

Ecosystem services: natural environment benefits

From Wikimedia Commons, the free media repository

19th Century style manufacturing problems

Many industrial reactions leave toxic waste

Powerful and efficient but rely upon

- Transition / heavy metals
- Much heat and pressure
- Organic solvents
- Halogenated
- Caustics
- POPs

From Wikimedia Commons, the free media repository

POP: persistent organic pollutant

Biologicalisation

Biological transformation in manufacturing

- Integration of bio-inspired principles
  - Principles, structures, resources
  - Functions and materials
- With Industry 4.0 tool and methods as
  - Industrial internet of things (IIoT)
  - Machine learning
- And modern chemistries
  - Next-gen molecular biology
  - Nano and ‘omics understandings
- For sustainable manufacturing
  - Technologies
  - Materials

Gaining traction in literature

Peer-reviewed journals

"... integration of biological and bio-inspired principles, materials, functions, structures and resources for intelligent and sustainable manufacturing technologies and systems…"

G. Byrne, et al., Biologicalisation: Biological transformation in manufacturing, CIRP Journal of Manufacturing Science and Technology, Volume 21, May 2018, Pages 1-32 (2018)

"Further inspirations taken from biological systems are adopted for machining centers and drive a biological transformation of manufacturing machines."

Konrad Wegener, Thomas Gittler and Lukas Weiss, Dawn of new machining concepts:: Compensated, intelligent, bioinspired.

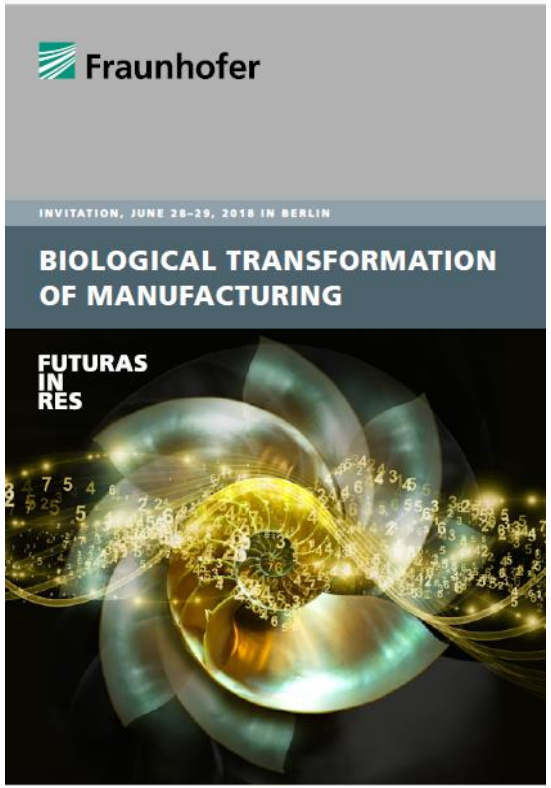
Blogs and forums

Industry embrace and incorporation

Activity is growing

Last summer, Fraunhofer-Gesellschaft of Berlin

- Sponsored *Biological Transformation of Manufacturing*
- "Go back to nature" initiatives for decades
- Emphasis now upon
  - Bio-integrated through novel technologies
  - Manufacturing efficiency and sustainability
  - Modern digital, automation and nano-techniques



Natural to biologialised manufacturing

Moving from original to intensified

- Biological

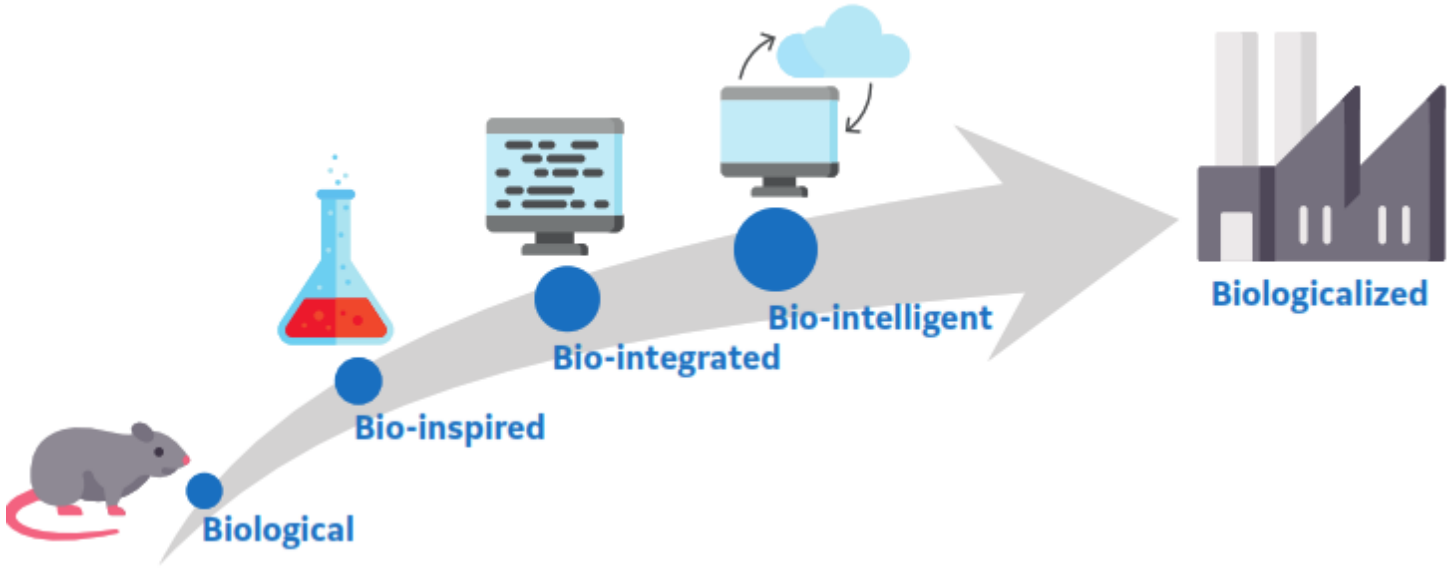
  Animals, plants, bacteria, fungi, functions and natural systems
- Bio-Inspired

  Materials, surfaces, media, pathways, chemistries, catalysts
- Bio-Integrated

  Design, processes, assemblies, reactions, equipment, facilities
- Bio-Intelligent

  Systems, organization, supply chains, global circular economy

From natural to engineered



Natural to biologialised medicine

Natural to ex vivo living or synthetic systems

- Biological (original)

  Organisms, organs, tissues functions and natural systems

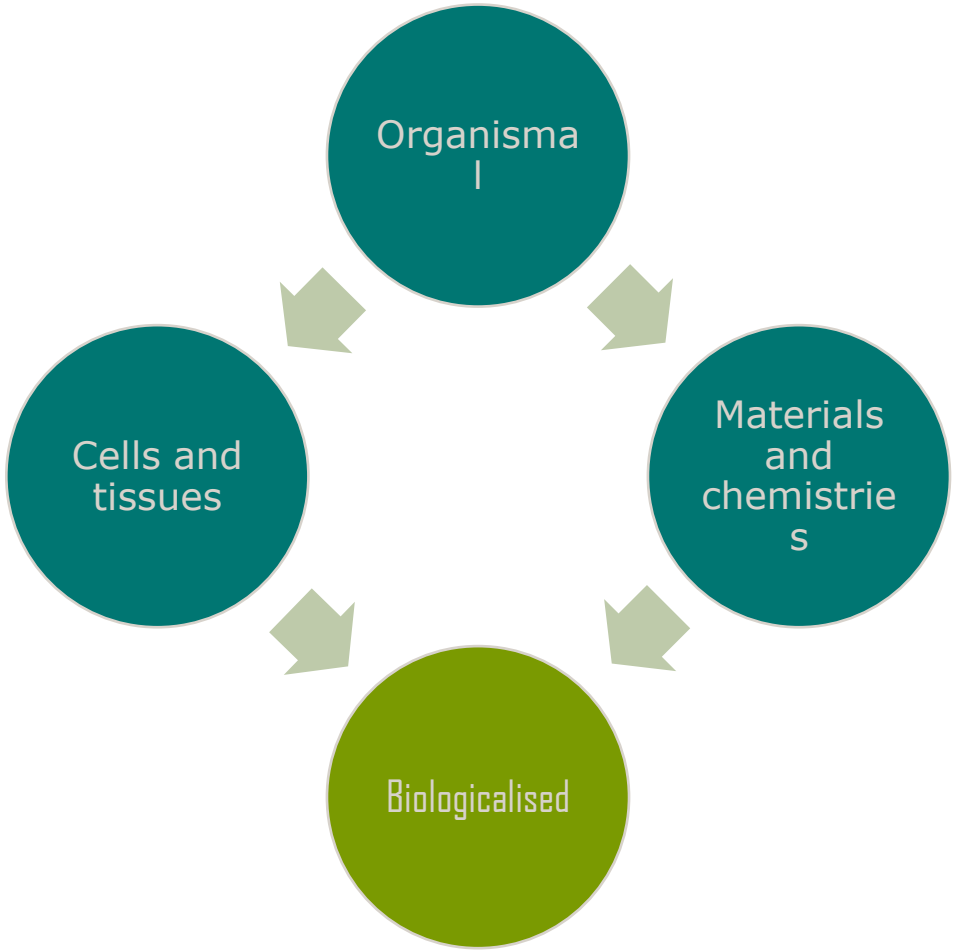
- Bio-Inspired I

  Materials, surfaces, media, pathways, chemistries, catalysts

- Bio-Inspired II

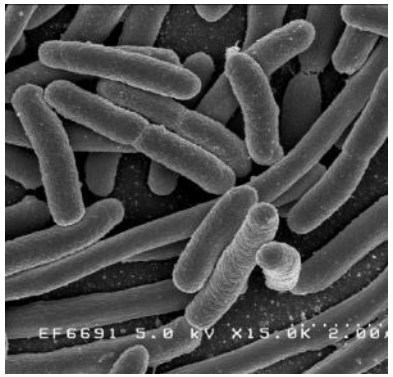
  Cell assemblies, recombinant cells, Bioengineered assays and therapies

Beginning with nature- evolving to bio-inspired



Efficient, sustainable solutions from two directions

Many chemical reactions leave toxic waste



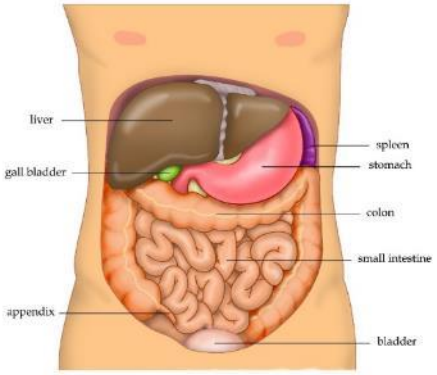
Wiki: Rocky Mountain Laboratories

Chemical reactions

Biologicalised

Natural tissues

Many natural activities lack control and efficiency



Tvanbr - Own work, Public Domain

From poisons to promotors

Chemotherapy

Non-specific intracellular poisons to inhibit mitosis, cell division

Drugs	Acronym
Cyclophosphamide, methotrexate, 5-fluorouracil, vinorelbine	CMF
Doxorubicin, cyclophosphamide	AC
Docetaxel, doxorubicin, cyclophosphamide	TAC
Doxorubicin, bleomycin, vinblastine, dacarbazine	ABVD
Mustine, vincristine, procarbazine, prednisolone	MOPP
Cyclophosphamide, doxorubicin, vincristine, prednisolone	CHOP
Bleomycin, etoposide, cisplatin	BEP
Epirubicin, cisplatin, 5-fluorouracil	ECF
Epirubicin, cisplatin, capecitabine	ECX
Methotrexate, vincristine, doxorubicin, cisplatin	MVAC
Cyclophosphamide, doxorubicin, vincristine, vinorelbine	CAV
5-fluorouracil, folinic acid, oxaliplatin	FOLFOX

https://en.wikipedia.org/wiki/Chemotherapy

Adoptive Immunity

Antibody-mediated immunity

Cell-mediated immunity

And more…

Many medical applications

Nature inspired chemistries, technologies and products

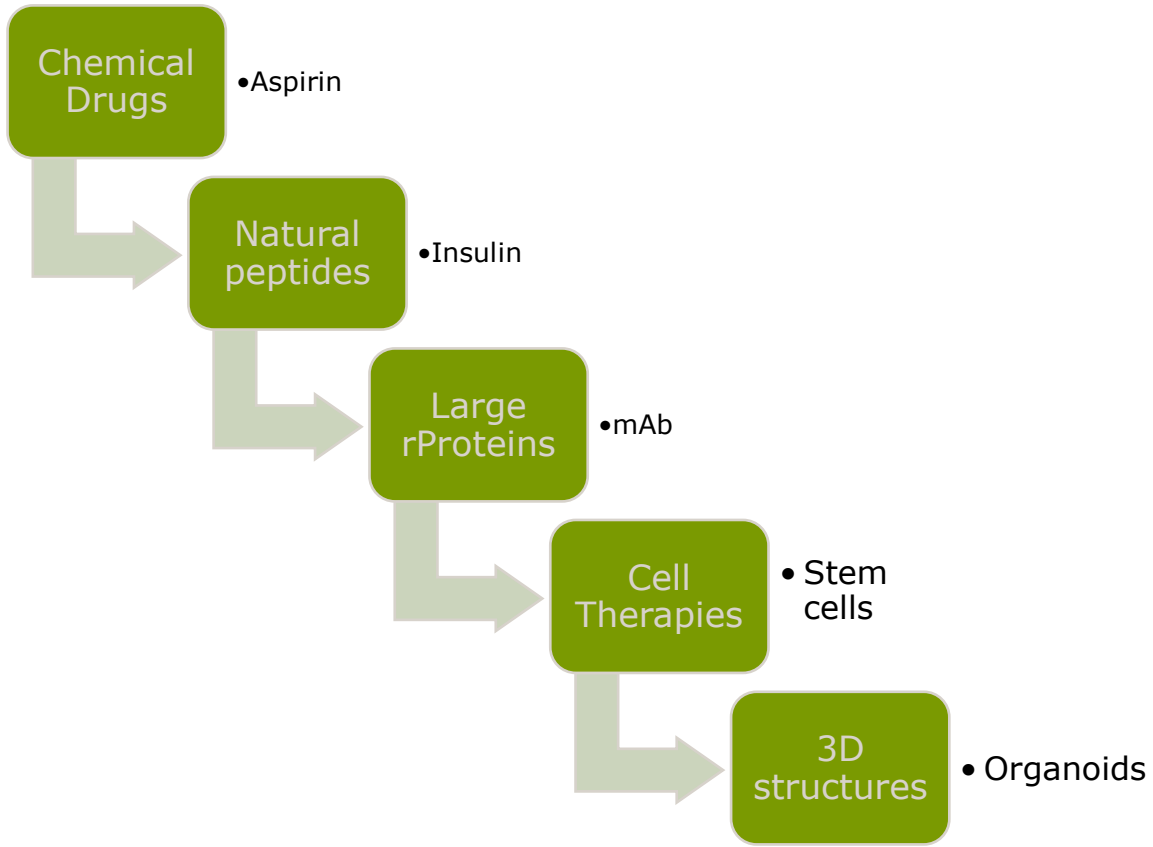
- Materials
- Surfaces / structures
- Assays and diagnostics
- Therapeutic development
- Final entity / therapy designs
- Drug manufacturing processes
- Product handling / shipping / surveillance

Cell-based activity in medicine

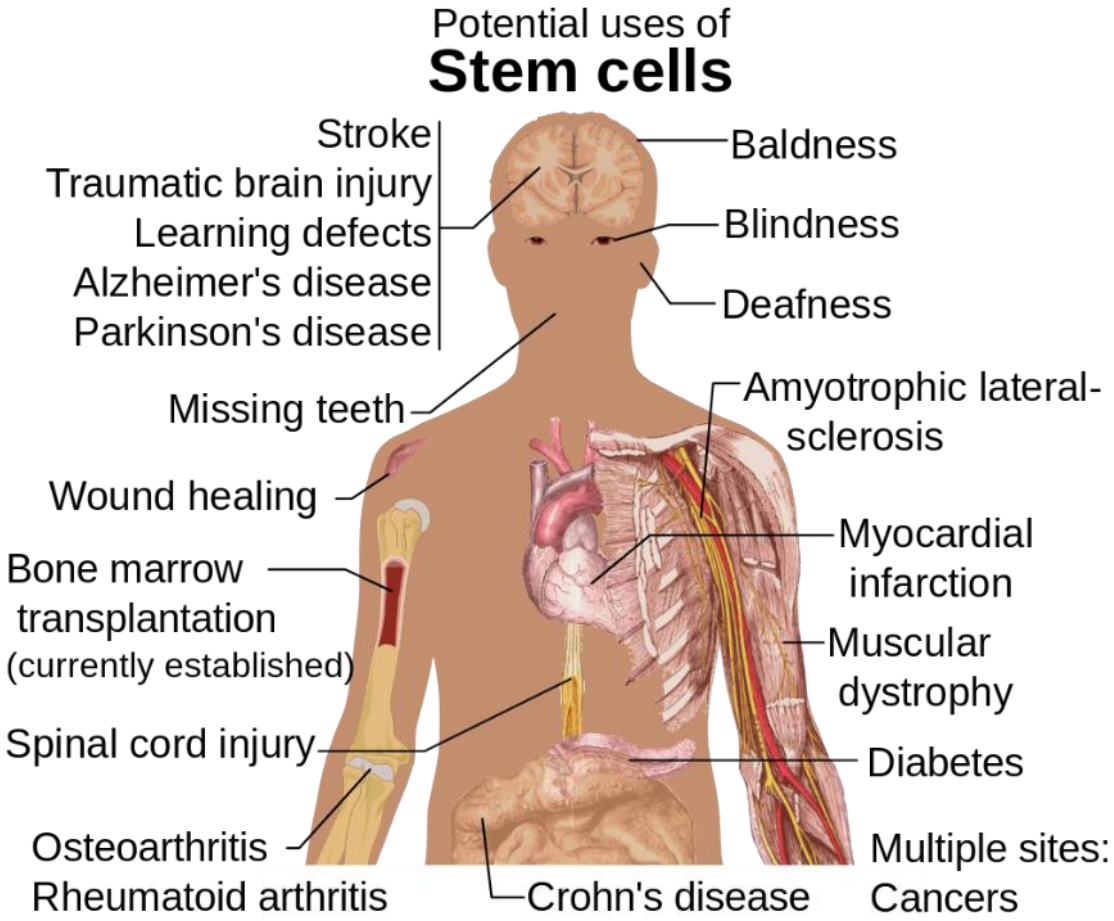
- T and B cell based therapies
- MSC, iPSC based therapies
- Biomanufacturing
- Exosomes as vectors
- Bioprinted tissues for therapy
- Bioprinted drug screening assays
- Bioprinted structures for diagnostics

Small molecule → Cell therapy → 3D structures

Evolution of therapies



Cultured cells in diagnostics and medicine



Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.orBy Mikael Häggström, used with permission. - All used images are in public domain., Public Domain, https://commons.wikimedia.org/w/index.php?curid=6638034

Animal cell-based solutions

Cellular influence at ESACT 2019

Biologicalization: Cell and nature-based digital manufacturing

Bill Whitford
GE Healthcare Bio-Sciences AB, Björkgatan 30, 751 84 Uppsala, Sweden

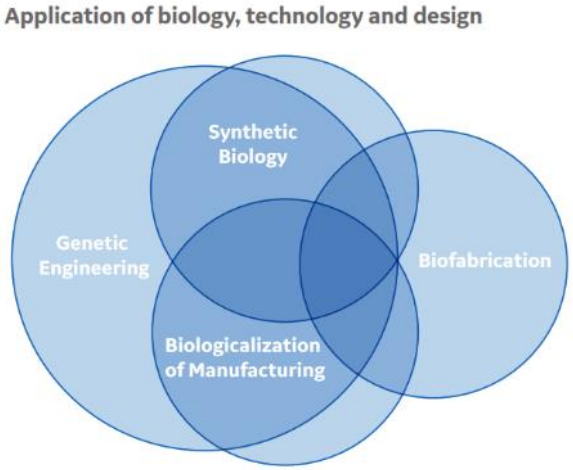
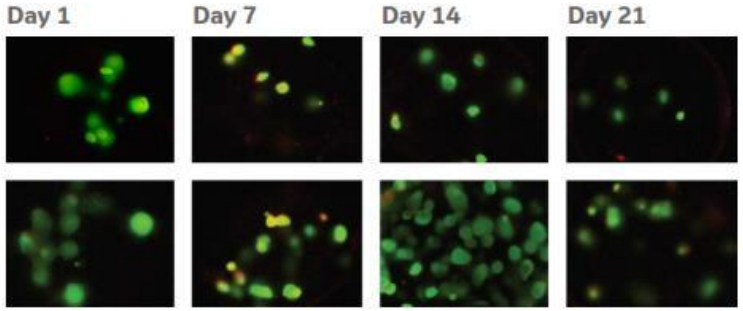


Fig 2. Relationship of some new technologies to biologicalization.

3D printed iPSC-derived cardiomyocytes



(B)

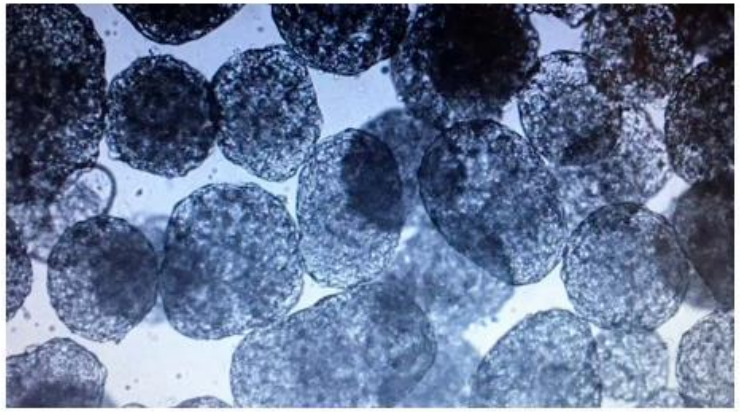


Fig 3. Assays of spheroids of iPSC-derived cardiomyocytes over time.
Images by express permission of CELLINK.

Courtesy CELLINK, WWW.CELLINK.COM

Digital Manufacturing

Industry 4.0 in bio-inspired manufacturing

Cyber-physical approaches, as described in Industry 4.0

- Advanced computer data storage, hard- and software
- Industrial internet of things (IoT), model-based control
- Cloud-based information techniques, machine learning
- Artificial intelligence and autonomation
- Newer MES / automation in production

FOCUS ON... MANUFACTURING

The Era of Digital Biomanufacturing

William Whitford

The digital revolution in manufacturing began with an explosion in monitoring, analytics, and new computing capabilities. Combined with such advances as artificial intelligence (AI), automation, and robotics, they are changing our concepts of manufacturing in general — from product development and factory operations to materials supply. This evolution also connects product and process designers and leaders in manufacturing engineering. Digital manufacturing (DM) isn't a dream or a concept on some advanced developer's design table; it's occurring now and will change industry forever (1, 2).

For many years, manufacturing plants have been generating more and better data than ever before. But some companies have begun harnessing the resulting sea of information to gain valuable insights that can lead to greater efficiencies, productivities, and

WHAT IS DIGITAL MANUFACTURING?

- Explosion in monitoring, analytics, and new computing capabilities
- Artificial intelligence, automation, and robotics operating now
- From product development to materials supply to factory operations
- Connectivity among operations, design engineers, and academic leaders
- Small-molecule drug manufacturers exploiting for continuous processes

The digital concept

Similar concepts presented in many forums

- Digital transformation of industries (DTI)
- Digital plant maturity model (DPMM)
- Cyber / physical production systems
- Next-gen biomanufacturing
- Enterprise adaptive control
- Smart factory technology
- Digital biomanufacturing
- Fully automated facility
- Factory of the future
- Smart bioprocessing
- Biopharm 4.0
- Industry 4.0
- Society 5.0

Whitford W, BioProcess Int. 15(3) 2017:12–18
Courtesy www.bioprocessintl.com

Biological transformation

Modern digitalization + bio-inspiration

Biological transformation (biologicalisation)

- A harmonisation of digital manufacturing principals with biological systems, structures and chemistries
- A transformation of the entire value chain
- Dependent upon
  - The application of bio-inspired principles and materials in synergy with digital technology, equipment, facilities

- Klaus Schwab, *World Economic Forum Geneva*

  "…the digital revolution… is characterized by a fusion of technologies that is blurring the lines between the physical, digital, and biological spheres."

- GE's PREDIX platform: digital manufacturing now

Bio-inspired reactions / constructions

Biological to synthetic to bio-integrated

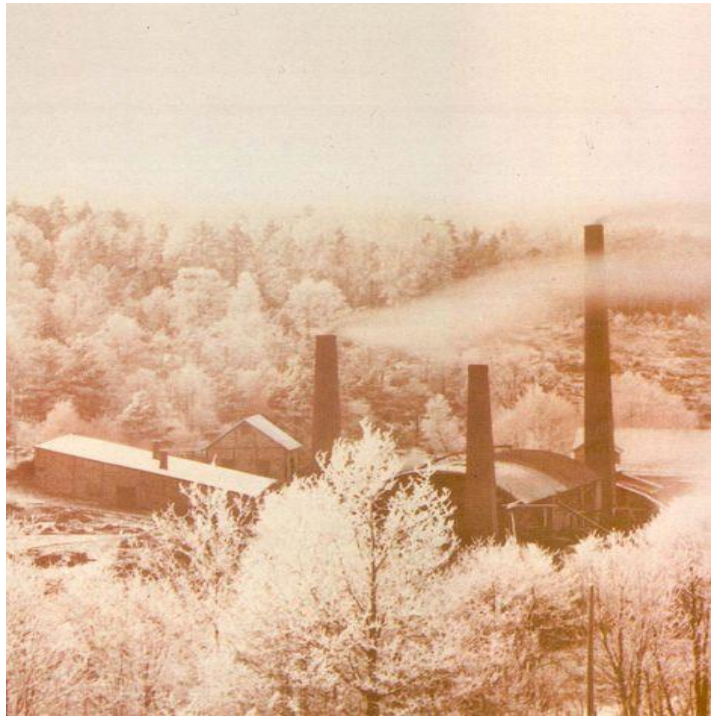
A common historical scenario

German Method of acetic acid manufacturing

- Alcohol-containing feed percolated through wood shavings
- Aerobic fermentation to alcohol by bacterium
- Collection of a solution of acetic acid at the bottom

Synthetic generation from rather inorganic compounds

- Chlorination of carbon disulfide → carbon tetrachloride → pyrolysis to tetrachloroethylene → aqueous chlorination to trichloroacetic acid → electrolytic reduction to acetic acid
- Typical 20th century manufacturing approach



Perstorp 1884 acetic acid purification plant

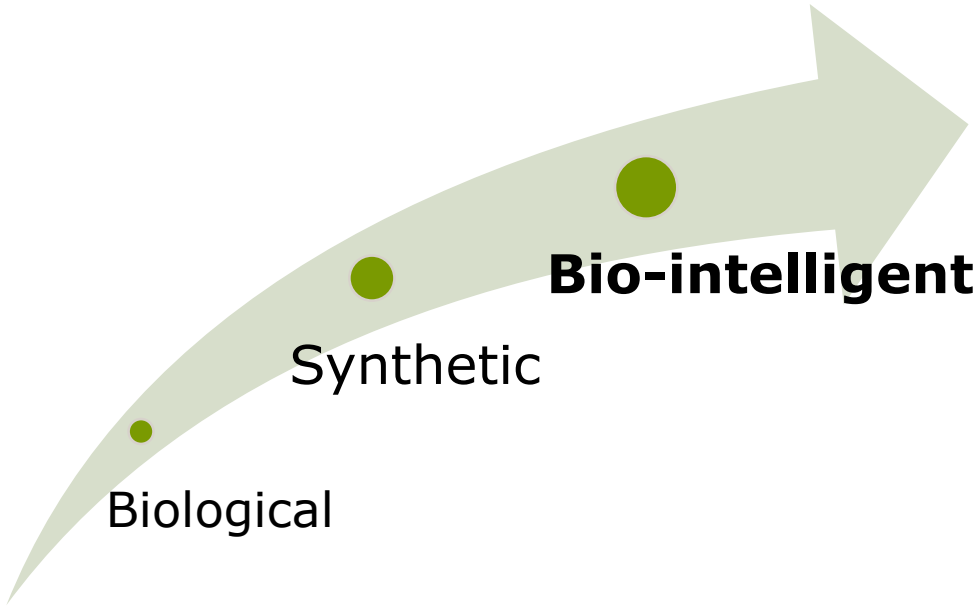
Wimvandorst on en.wikipedia

A common progression in manufacturing

A common historical scenario

Today we are seeing biologicalisation

- Engineered bacteria expressing new alcohol dehydrogenases
- Digital manufacturing-based advances in fermentation
- Lowering manufacturing energy requirements
- Supporting low-cost carbohydrate source use
- $C_2H_4O_2$ from organic and agricultural waste



Bio-integration of pathways and processes

A 2018 Nobel Prize in Chemistry winner

- Frances H. Arnold, Caltech Professor
- Invented systems for directed evolution of enzymes
- Now used in such tools as catalysts in manufacturing
- Eg, environmentally friendly manufacturing of pharmaceuticals and renewable fuels
- Only the fifth woman to receive Chemistry prize

Wikimedia commons: Beavercheme2 - Own work

Bioproduction, botany and bioprinting

Biosensors

Developing biosensors

- Employ recognition capabilities of biological systems
- Combine them with physicochemical transducers
- Deliver simple diagnostic systems in diverse applications
- Commercial applications in e.g., biochips, and wearable sensors

Keynote Lectures included

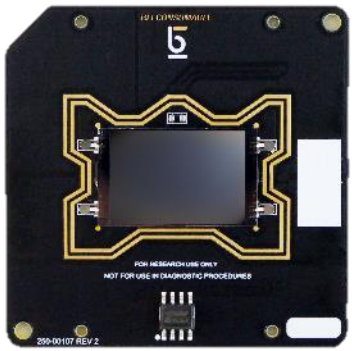
- Biosensing through high-affinity artificial protein binders from computationally simulated epitopes
- From in-vitro to in-vivo: Silicon technology for healthcare
- From sensing to bionics: A view of current trends and future prospects

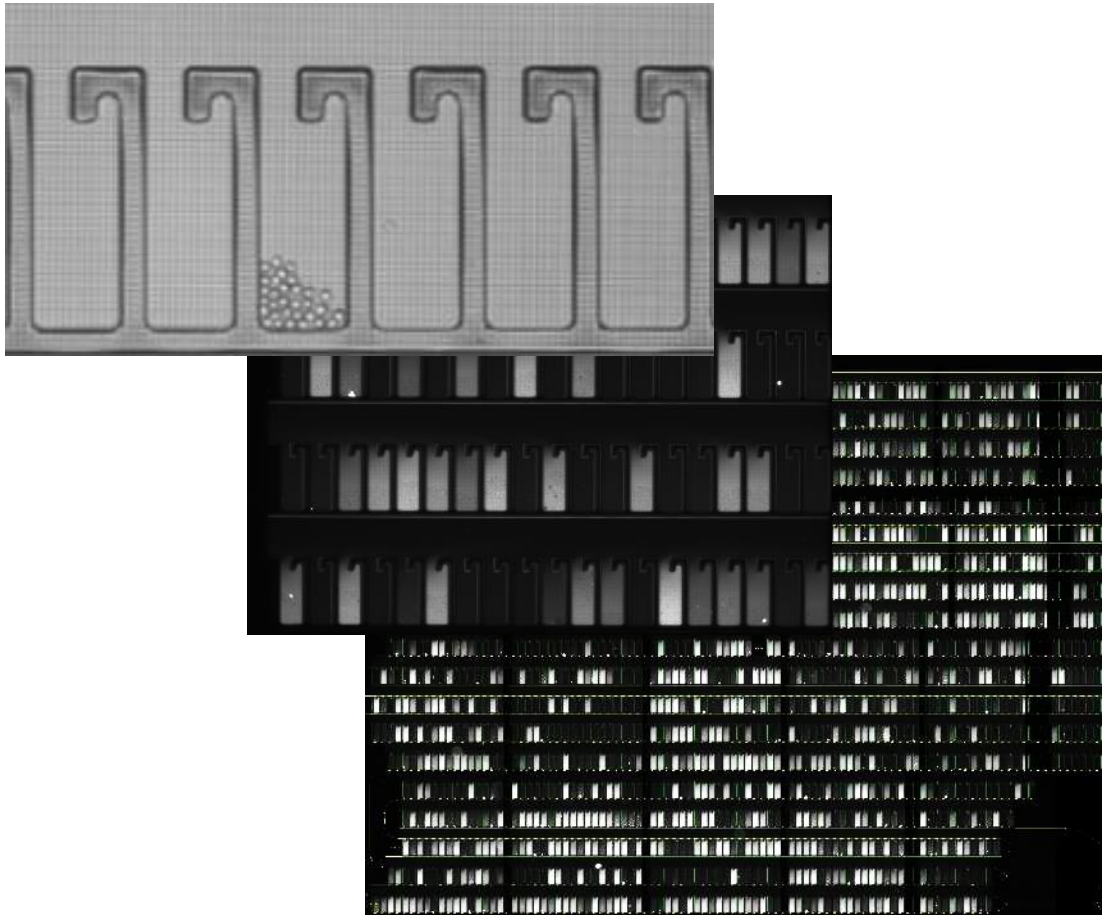
Automated cell selection and screening

Example: Berkley Lights

Beacon CLD

- Automated screening of 1000s of cells
- Early product enabling Digital Cell Biology
- Many potential workflows on nanofluidic chips
- Growth, phenotype and selection and recovery
- Digital microscopy and optical tweezers supported





Biomimetic 3D printing of materials and meta-materials

Example: 3D printing PLA and β-TCP scaffolds

- Polylactic acid (PLA)
- Tricalcium phosphate (β-TCP)
- Incorporated in various hydrogels
- Assists tissue repair and regeneration

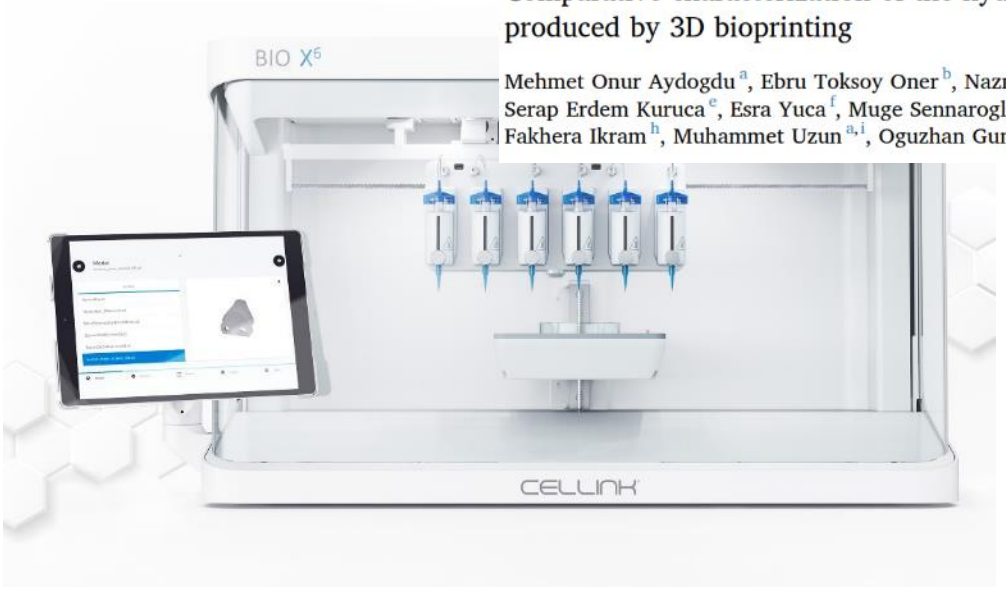
Contents lists available at ScienceDirect

Bioprinting

journal homepage: www.elsevier.com/locate/bprint

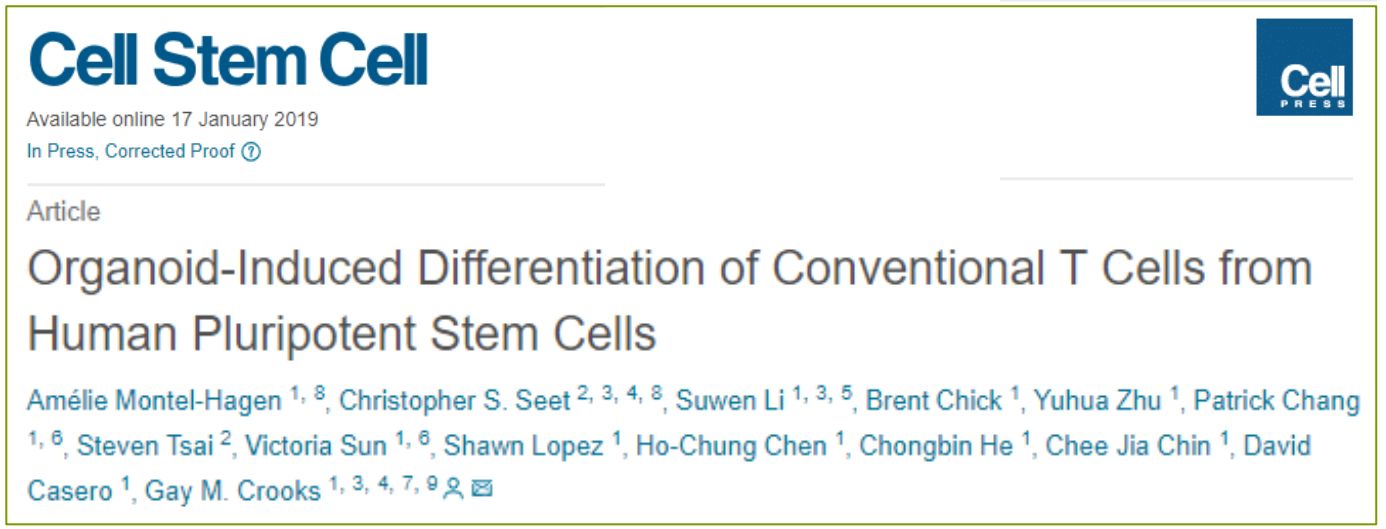
Comparative characterization of the hydrogel added PLA/β-TCP scaffolds produced by 3D bioprinting

Mehmet Onur Aydogdu [a], Ebru Toksoy Oner [b], Nazmi Ekren [a,c], Gokce Erdemir [d], Serap Erdem Kuruca [e], Esra Yuca [f], Muge Sennaroglu Bostan [g], Mehmet S. Eroglu [g], Fakhera Ikram [h], Muhammet Uzun [a,i], Oguzhan Gunduz [a,j,*]



3D natural environment replaces complex media / factors

- Engineered organoids support T cell differentiation from PSCs
- These PSC-derived T cells are similar to conventional T cells
- Naive, antigen-specific T cells can come from TCR-engineered PSCs



Cell Stem Cell

Available online 17 January 2019

In Press, Corrected Proof ⓘ

Article

Organoid-Induced Differentiation of Conventional T Cells from Human Pluripotent Stem Cells

Amélie Montel-Hagen [1, 8], Christopher S. Seet [2, 3, 4, 8], Suwen Li [1, 3, 5], Brent Chick [1], Yuhua Zhu [1], Patrick Chang [1, 6], Steven Tsai [2], Victoria Sun [1, 6], Shawn Lopez [1], Ho-Chung Chen [1], Chongbin He [1], Chee Jia Chin [1], David Casero [1], Gay M. Crooks [1, 3, 4, 7, 9]

https://doi.org/10.1016/j.stem.2018.12.011

Cell-based assays / reactions

Madeline Lancaster, MRC Laboratory of Mol. Bio.

- First brain organoid derived from human iPSC
- First 3D model of the human embryonic brain
- Using human induced pluripotent stem cells
- Spontaneously self-organize into a structure
- Removes many limitations of animal models
- Recapitulate anatomical / functional activity

Courtesy the NC3Rs, https://www.nc3rs.org.uk/about-us

Advantages over animals / tissues

Efficient

Modifiable

Controllable

More humane

Less expensive

Multiplex monitoring

CHAPTER 14

Three-dimensional cell-based assays in hollow fibre bioreactors

John J. S. Cadwell[1] and William G. Whitford[2]

[1] *FiberCell Systems Inc., Frederick, Maryland, USA*

[2] *GE Healthcare, Life Sciences, Cell Culture, Logan, Utah, USA*

Bioprinting generates *ex vivo* systems

Biomimetic systems replace

- Unsustainable features of synthetic chemistries
- Undesired animal systems as well

WILL 3D PRINTED HUMAN SKIN MAKE ANIMAL TESTING FOR COSMETICS OBSOLETE?

BEAUTY FEATURE

dezeen

3D-printed human cells could "replace animal testing"

Marcus Fairs | 7 November 2013 | 7 comments

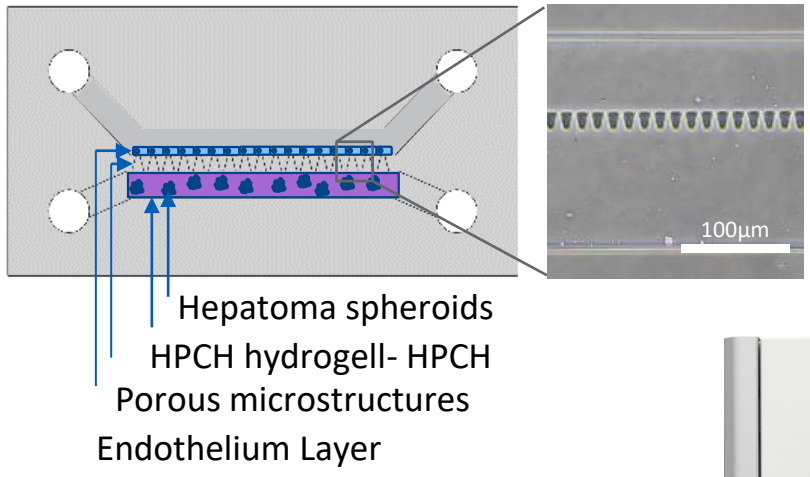
News: 3D-printed human cells could replace the need for animal testing of new drugs within five years, according to a pioneering bio-printing expert at the 3D Printshow in

3D assays better than either 2D *in vitro* or animal

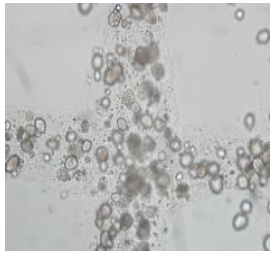
3D bioprinted microfluidic model

- *In vitro* hepatoma model
  - based on 3D printing as well as microfluidics
  - results similar to animal experiments
  - results better than in 2D models
- Power attributed to
  - biomimetic 3D drug transport efficiency
  - microenvironment in the model
- Drug-mediated ADCC effects also observed

SunP Biotech ALPHA-CPT1



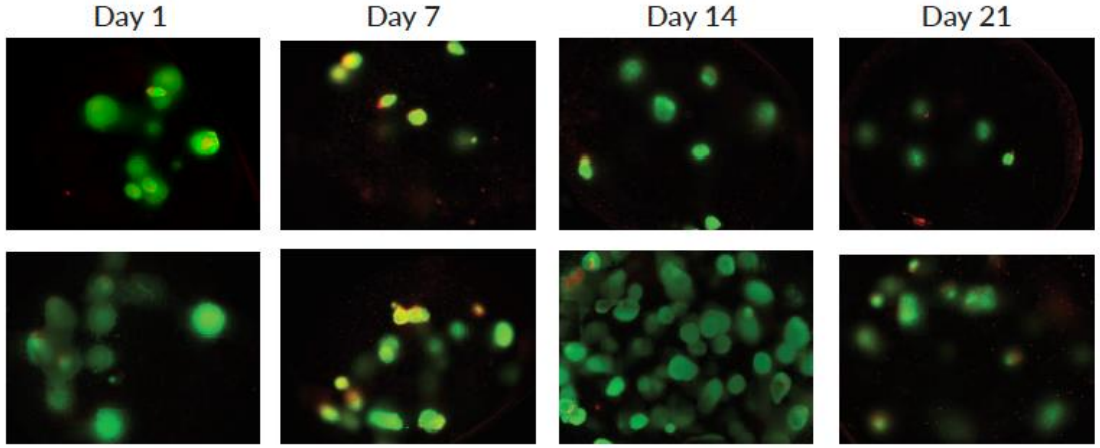
3DP(SMMC)-120h-NC

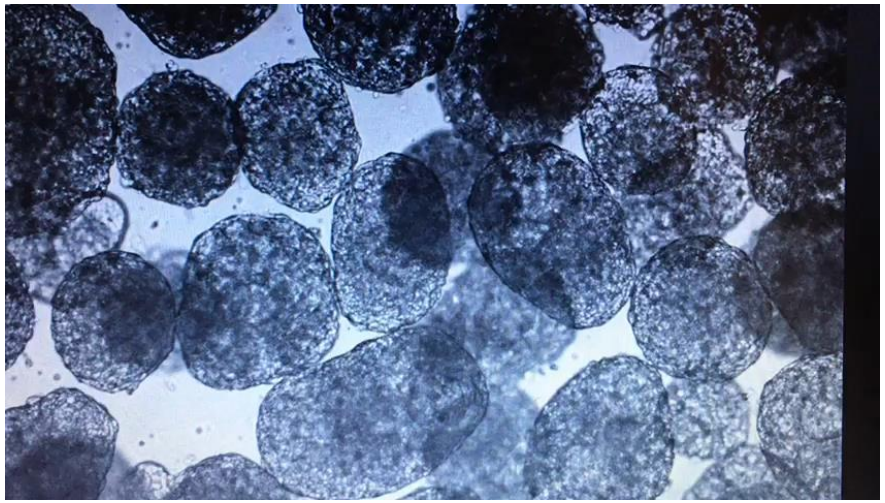


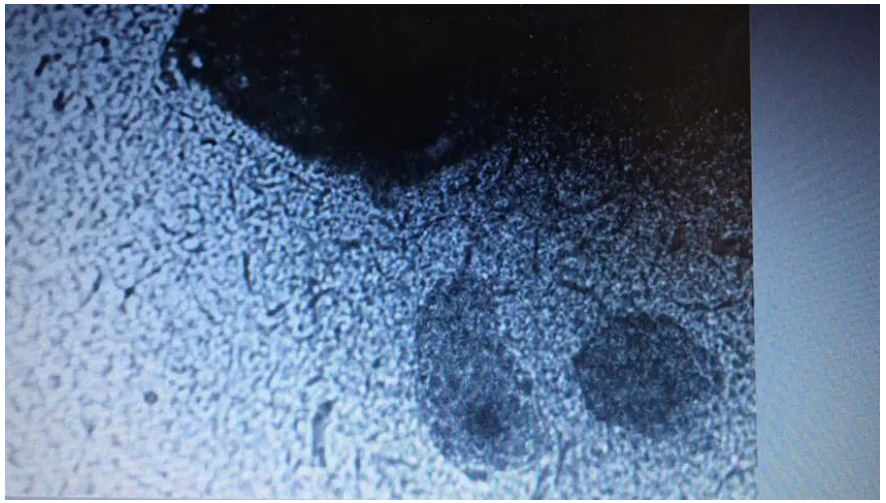
Li Yang, et al, *Biofabrication, under review (credit by Tsinghua and SunP Biotech)*

3D bioprinted heart tissue models

- 3D printed cardiomyocytes
- Cultured human iPSC-derived
- Printed in CELLINK Laminink 521
- Maintain contractility for 12 weeks
- Can replace many synthetic assays







Courtesy CELLINK, WWW.CELLINK.COM

Biologicalisation in Manufacturing and Medicine

In manufacturing

- Promises sustainability and efficiencies
  - Eg, water-based reaction media
- Enabled by many developing initiatives
  - Eg, digital, molecular, and nano
- Implemented by diverse technologies
  - Eg, reactions, enzymes and 3D cultured cells

In medicine

3D printed tissues may keep athletes in action

Courtesy CELLINK, WWW.CELLINK.COM

The ontology of biology….

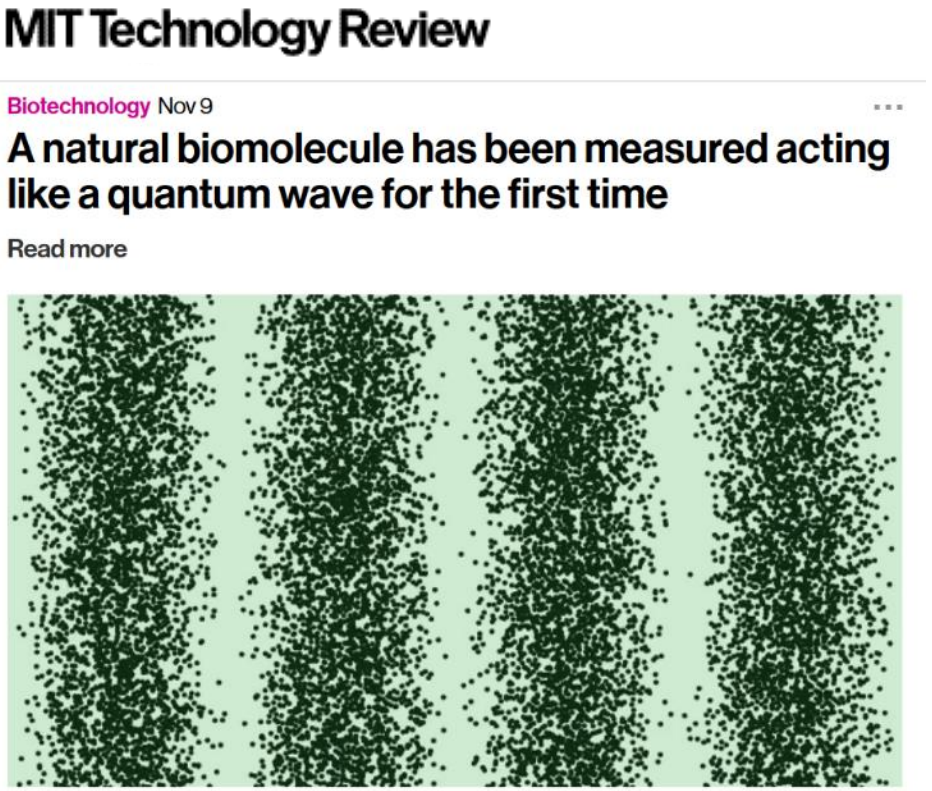
Wave-particle duality demonstrated in a peptide **November 9th 2019**

Armin Shayeghi, U of Vienna

Quantum interference in molecules of gramicidin

(natural antibiotic made up of 15 amino acids)

- Created a beam of ultracold gramicidin molecules
- Measured the interference pattern created when beam interfered with itself
- Implying superpositioning and entanglement of biological molecules



Biocentrism and the biocentric universe

Biocentrism

The centrality of all life in ecological, political and ethical values

Apollo 17 [Public domain]

The Biocentric Universe

Space and time are forms of animal sense perception rather than external physical objects

Non-fee album cover