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Biologicalisation: A nature-based digital manufacturing revolution

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Biologicalisation in medicine and manufacturing: A nature-based digital revolution

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Abstract

Industry 4.0 is changing manufacturing concepts (1). Biologicalisation uses 4.0 principles in concert with biological and bio-inspired materials, chemistries and functions to support efficient and sustainable manufacturing. From product design to development and production, biomimetic product implementations and bio-integrated manufacturing systems embody this biological transformation of manufacturing (2). This process applies to both manufacturing and medicine.

Processes, chemistries and supply chains are being enhanced by the harmonization of newer digital manufacturing principals and applications, and advanced process understandings, with biological systems and materials. This is enabling streamlined product designs and providing efficient, clean and robust production that better supports sustainable, circular and global economies.

Progress in our understanding of biological elements, phenomena, substrates and chemistries enables this revolution. In fact, a 2018 Nobel Prize winner in Chemistry year, Frances H. Arnold illustrates this. She invented systems directing the engineering of enzymes now routinely used in development of such tools as catalysts in manufacturing [Figure 1]. This technology supports the sustainable manufacturing of such diverse product as renewable fuels and pharmaceuticals [*3*].

Natural → Synthetic → Biologicalised

The history of acetic acid (HOAc) manufacturing illustrates our evolution from biological, to synthetic, to bio-integrated (or biologicalised) manufacturing.

The German method of production was a very early and natural means of production that percolated an alcoholic solution through a tower of wood shavings harboring *Acetobacter*. In the next approach, HOAc was generated synthetically, using energy-demanding processes employing chlorinated hydrocarbon intermediates, much energy and troublesome waste.

Today the biologicalisation of the process, through genetic engineering and digital biomanufacturing techniques, is promising a more sustainable means of production. Benefits here include lower energy requirements, metals-free aqueous waste and the possibility of using such low-cost and green carbohydrate sources as organic municipal wastes and agriculture residues.

We see here that an engineered application of first-generation biological systems (the German method) was too slow and inefficient; The 19th century way of chemical synthesis is energy and toxic material dependent; While current initiatives of melding molecular and synthetic biology with digital biomanufacturing promise the design of an bio-inspired, efficient and sustainable solution.

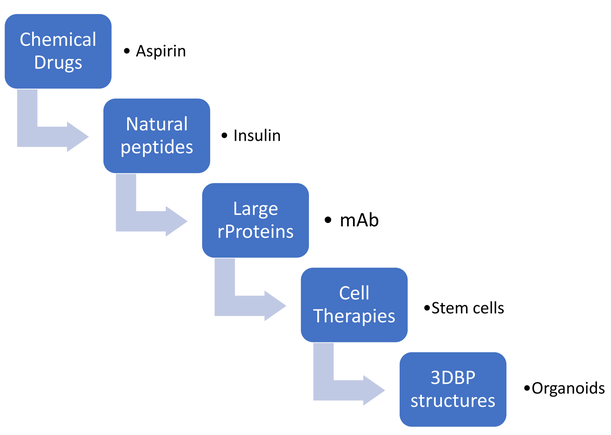
Digital biomanufacturing

Sampath Kandala, director of digital product management and partnerships at GE Healthcare says of a bioreactor digital twin: “The twin is trained with the assistance of mechanistic and statistical models, and real-time machine learning from the bioreactors operation-- such as temperature, pH and mixing speed, and cell density. It is more able to predict how the process will progress. For instance, you can obtain insight into cell density, product titer or glucose and lactose consumption. That makes it possible to detect faults in the process much earlier”. [https://www.c2w.nl/partnercontent/the-digital-future-of-bioprocessing/item 20066]. GE Healthcare already has a digital twin of a single-use mixer at production scale and is now developing a twin of a bioreactor for the improvement of drug development as well as the prediction of large-scale production events.

Cell-based biologicalisation in medicine

Cell-based medical systems begin with such biomanufacturing methods as the fermenter and bioreactor-based production of such pharmaceuticals as therapeutic enzymes and MAbs. The success of such cell-based therapies as tisagenlecleucel, an FDA-approved CAR T-cell therapy for B-cell lymphoma, illustrates the next step. 3D bioprinting and newer microfluidics, in e.g., replacing whole animal-based assays, can generate *ex vivo* cell-based systems that provide gains in analytical power as well as in environmental sustainability. Some cyber-physical cellular constructions are now employing 4.0 principals in both their design and generation as well as placement and operation.

Evolution of cell-based medical biologicalisation



Introduction

The biological transformation of manufacturing begins with the incorporation of bio-inspired systems materials, chemistries, and catalysts. This can be supported by structures, enzymes, metabolisms and cells. It continues with bio-integrated process design – from equipment and assemblies to resources, processes, and facilities. Finally, it develops bio-intelligent systems and supply chains feeding a global, circular economy [Figure 1]. Biologicalisation is another term used for this use of excerpted biological pathways, as well a entire plants, bacteria and animal cells.

As much as biology, it is based upon Industry 4.0 tools, algorithms and methods. This includes advanced computer hardware and software; industrial internet of things (IIoT); advanced data handling and automation; artificial intelligence; predictive modeling and machine learning (4).

Industry 4.0 goals specifically include sustainable enterprise manufacturing. They apply to systems in product design and development, process analytics and manufacturing– as well as to post-commercialization surveillance (4). So, bologicalisation is more than only cellular systems or biomimetic chemistries. It includes application of such modern digital techniques as advanced process monitoring, the IIoT, Cloud applications, AI and model reference adaptive control.

Figure 1.

Nobel Prize: Chemistry

For efficient engineering of enzyme function toward diverse scientific and manufacturing goals.

Frances H. Arnold

Linus Pauling Professor of Chemical Engineering, Bioengineering and Biochemistry at Caltech

4D bioprinted models replace animals

Madeline Lancaster is Group Leader, MRC Laboratory of Molecular Biology. Her projects include work on a 4D model of brain tissue where cells spontaneously self-organized to form a structure resembling the human brain. These “cerebral organoids” are an *in vitro* replica of the complexity and structure of the developing brain. These organ-like structures can be used to model human disease. Animal models used in studying brain development have many limitations, including the lower complexity and lack crucial components in the brains of rats and mice. Cerebral organoids are valuable in not only studying mechanisms and treatments of neurological disease but also in completely replacing some animal studies [Figure 3]. Dr. Lancaster was winner of LMB’s Cell Biology Division 3Rs Prize, which had been sponsored by GlaxoSmithKline (GSK) [6].

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

Advantages over live animals or their tissues begin with their economy, efficiency and modifiability. They are also more controllable, amenable to multiplex monitoring and, finally, are more humane. We refer to such cell-based systems as “biologicalised”, due of the human engineering required.

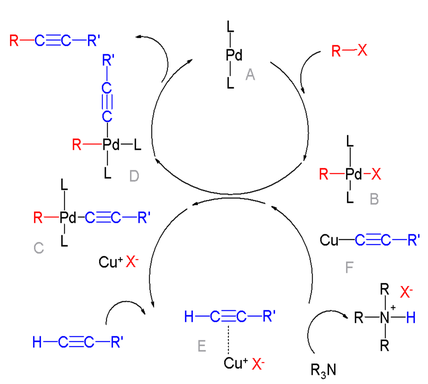
Biomimetic-structure based biologicalisation

Lipitor is a success story of small-molecule biologicalisation. Pfizer had previously improved Lipitor manufacturing in ways that reduced organic waist by 65% [7]. Yet, the remaining 35% remained an issue. For example, the methanol and tetrahydrofuran in the process is a problem in disposal

R. Heck, E. Negishi, A. Suzuki took the 2010 Nobel Prize in Chemistry for Palladium-based carbon couplings in aqueous solutions. Reactions can occur at room temperature and in water/acetonitrile and water/toluene biphasic mixtures-- or even in neat water.

Bruce Lipshutz (UCSB) has a further improvement that uses a self-assembling surfactant in an aqueous medium [8]. The micelles produced mimic a living cell in sequestering reactions and components from the general environment. This system can support many common reactions, including carbon cross–couplings at room temperature. Such structured reactions require only parts per million transition metals in an organic solvent-reduced / -free environment [Figure 4].

Figure 4. Biologicalisation of carbon couplings



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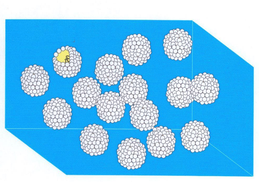

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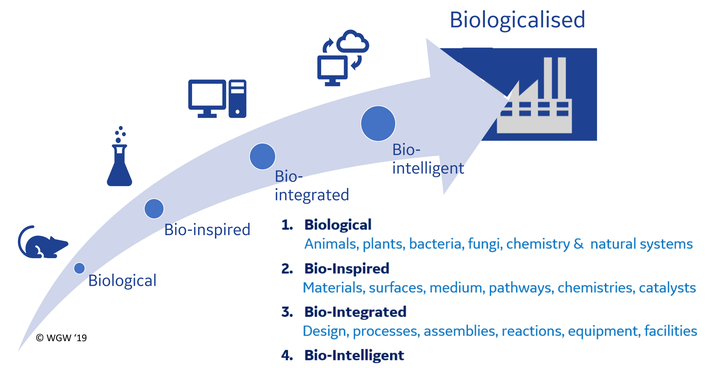
Figure 2. Natural to biologicalised



Relationship of major fields

The relationship of the many contributing technologies in this new approach to manufacturing is complex. It begins with the field of genetic engineering, a classic means of bio-design that develops new products with the original style of genetic modification using restriction endonucleases and cloning – and is guided by both heuristics and our imagination. Improvements here yielded synthetic biology, highlighting the building of new bio-based materials, parts, and devices by including advanced biochemistry, digital algorithms, and *in silico* model guidance.

Biofabrication in this context is a new and little-discussed approach to bio-based raw material design and sourcing by understanding, adapting, and re-designing natural materials (5). Biofabrication includes custom manufacturing techniques such as 3D bioprinting. It is opening the door to more effective medical treatments and assays– and providing tools to help in drug screening and pharmaceutical development.

The biologicalization of manufacturing adopts these technologies, along with 4.0 methods.

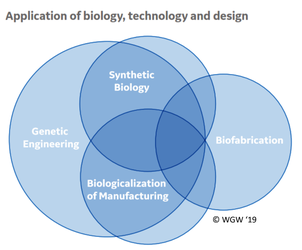
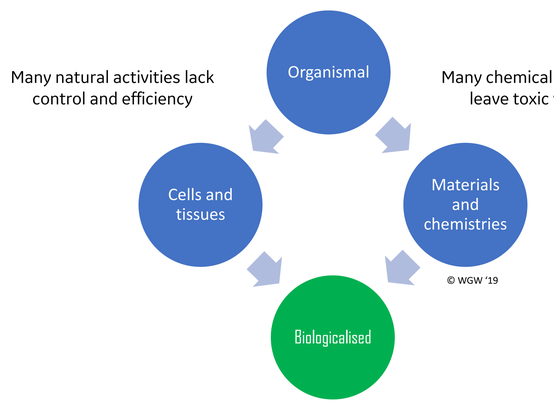


Figure 3. Beginning with nature– evolving to bio-inspired



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