OPINION

MATERIAL MATTERS

Synthetic biology: The search for a biological periodic table

By **Marcia C. Barbosa**

What will be the next revolution in materials science? If you search on the Internet, you will find possible answers such as nanomaterials, 2D materials, biodegradable materials, sustainable materials, metamaterials, advanced polymers, quantum materials, smart materials, energy-storage materials, space exploration materials, and bioinspired materials. Even though this list comprises areas in which we are already working, it does not respond to the question of "where should we go?" Maybe understanding how we evolved could help in shedding some light in answering this question.

Throughout human history, the ability to manipulate new materials has been closely intertwined with advances in basic science and technological production. For the general population, it is the technological breakthroughs that become visible and have a direct impact on daily life. Materials science serves as the crucial bridge connecting fundamental scientific knowledge to the products we use in our everyday lives.

The principles of thermodynamics and chemistry laid the foundation for the first Industrial Revolution (mid-18th century to the early 19th century), underpinning inventions such as the steam engine, spinning jenny, and cotton gin. However, the true acceleration of these industries was made possible by the development of remarkable new materials: a more efficient fuel source derived from coke made from charcoal, the production of steel, and the synthesis of the first aniline dyes from coal. Materials science played a critical role in the fuel, the engine, and the manufacturing process.

Due to the steam engine, it became possible to achieve large-scale iron production initially using charcoal. Iron was not a novelty, having been known for more than 3000 years. The decline in charcoal production prompted the search for an alternative energy source, leading to the use of coke from coal. The efficiency of coke allowed for the conversion of iron into steel in the absence of air. Naturally, this transition was not without challenges, as impurities in the coal posed technical difficulties that ultimately drove further advancements. This textbook history suggests that this technological transition was only feasible because of a fundamental understanding of heat transfer, chemical reactions, and rudimentary concepts of matter, all thanks to individuals who discovered processes for manipulating solid materials to produce steel with minimal impurities.

During the second and third Industrial Revolutions, the use of oil and gas as energy sources followed by advancements in quantum mechanics and developments in organic and inorganic chemistry paved the way for the manipulation of a diverse range of solid-state materials, of particular relevance to semiconductors and nanomaterials. In this "holy grail" for new technologies, the periodic table was the source for searching for a specific material when a property was on the radar. Additionally, there was widespread utilization of petroleum-based materials through polymer science. As new energy sources emerged and the semiconductor industry gained momentum, production rates increased significantly, resulting in a substantial upsurge in waste generation. However, this rapid production, driven by scientific advancements and the introduction of new materials, did not come without drawbacks. At present, global waste production stands at approximately 2.1 billion tons, with a projected increase to 3.2 billion tons by 2050, with one-third originating from highly industrialized countries.[1] The reliance on petroleum-based materials has contributed to the accumulation of 242 million tons of plastic waste. Although recycling has emerged as an alternative, the process of recycling requires energy, resulting in an additional billion tons of carbon emissions.

In order to circumvent this continuing catastrophic scenario for the environment, we need not only to create new affordable, efficient, and sustainable sources of energy but also to create a new production ecosystem, which produces efficiently but with less waste.

In recent years, synthetic biology has emerged as a tool not only for creating artificial life but also for engineering materials based on biology.[2–4] These new materials were designed for implementation within health and agriculture systems.[5–7] In principle, materials based in biology would be more suitable for applications in life sciences where out-of-equilibrium phenomena are ubiquitous. However, in attempting to replace oil-based chemical reactions by sustainable production it has become clear that they could serve as an option to create new model systems[8,9] This strategy will probably replace petroleum-based materials with biologically designed systems. The challenge in using biological

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systems as a substitute for traditional chemical reactions and solid-state materials is that while the science behind the design of traditional materials has been well-established in previous Industrial Revolutions, bio-based materials still lack a consolidated scientific foundation to support their use. There is no equivalent of a periodic table for bioprocesses.

Notwithstanding the challenge of not having a table of biological processes as a guide for their utilization in materials, much progress has been made so far.[4] One notable example is the biotransformation of agro-industrial waste, such as sugarcane bagasse, corn stover, and forestry waste, into biorenewables, including fuels, chemicals, and materials. One of the key steps in this biotransformation process involves the depolymerization of these lignocellulosic materials, which is typically achieved through biocatalysis in biorefineries.[10] Complex enzyme formulations, commonly referred to as enzyme cocktails, are developed to facilitate the deconstruction of these wastes. These cocktails are essential but also represent a significant portion of the overall costs. The identification of the most efficient enzymatic package capable of dissolving lignocellulose remains a challenge due to the lack of a comprehensive database of these enzymatic processes and their synergistic effects, beyond the sheer structural and chemical complexity of such material.

Where to look for new enzymes? The answer to this question is nature. If the idea is to find an enzyme to “digest” lignocellulose, the natural place to start the search is the herbivores. Monogastric herbivores are organisms with only one stomach that are capable of digesting cellulose in their diet by symbiotic bacteria. Recently, researchers have realized that some of them exhibit intestinal microbiota capable of obtaining energy from lignocellulosic materials. One particular case is the capybaras since they have included sugarcane in their diet for decades due to the increase of plantation in the area they live, possibly leading to an evolution/adaptation of their microbiota to digest the fibers. In order to understand how the capybara can obtain energy from sugarcane fibers, researchers utilized integrated multi-omics approaches, functional enzymology, site-directed mutagenesis, several biophysical techniques, and state-of-the-art synchrotron tools.[11,12] These researchers elucidated how the microbial community and their enzymatic systems operate and outperform the recalcitrance of lignocellulosic materials to generate monomeric sugars to be further converted into short-chain fatty acids, an energy source for the host.[13]

Novel bacterial species have been discovered, which are highly competent in lignocellulose processing and harbor a complex enzymatic machinery adapted to the main carbohydrates present in sugarcane such as heteroxylans.[13] Consequently, enzyme cocktails could be enhanced with enzymatic components from these taxonomic novelties to boost the use of lignocellulose in biorefineries, impacting the production of second-generation ethanol from agricultural biomass, for instance.

This example highlights the potential that biological processes can offer to the production of new materials and energy in an ecosystem with less waste. However, this transition faces two challenges that need to be resolved before this becomes as common as the use of petroleum-based materials.

First, we still know very little about our biodiversity, especially in more isolated regions such as tropical forests and the Antarctic continent. For example, Brazil boasts one of the planet’s largest biodiversities, featuring six distinct biomes: the Amazon, Pantanal, Caatinga, Cerrado, Atlantic Forest, and Pampa.[14] In addition to the flora and fauna, these regions are home to a colossal and hidden universe of microorganisms, estimated to include as many as 1 trillion microbial species on Earth, with the vast majority of them not being culturable in a laboratory.[15] Despite the implementation of several international databases of microbial life, such as the nonprofit American Type Culture Collection (ATCC)[16] and the Global Biodiversity Information Facility (GBIF),[17] biodiversity remains the “new world” waiting to be discovered.

The search for specific enzymes or metabolic pathways is not a trivial task. Unlike nonliving matter, where the search within materials with similar properties can be facilitated by the periodic table, no such easy roadmap exists for living matter. Magnificent efforts have been made toward elucidating microbial life on Earth, such as the Human Microbiome Project[18] and Tara Oceans,[19] but multiple biomes remain underexplored, including many found in Brazil.

The development of a multidimensional framework in which researchers could navigate to search for genetic information, specific enzymes, or metabolic pathways to address specific issues is still missing, and it will require a deep understanding of some form of universality in biological processes.

Finally, even if we catalog all the planet’s biodiversity and design a multidimensional biological periodic table, the large-scale production of biomaterials is an essential challenge that will likely only be solved with the production of synthetic life.[20]

The endeavor of synthetic biology and eventually synthetic life will require much input and knowledge from the materials research community, from the business sector, and governments, with a vision similar to the Industrial Revolutions and the courage that led us to explore space. It is time for this first-order phase transition to take place now.

Endnotes

1. S. Kaza, L.C. Yao, L.P. Bhada-Tata, F. Van Woerden, *What a Waste 2.0: A Global Snapshot of Solid Waste Management to 2050*, Urban Development Series (World Bank, Washington, DC, 2018). http://hdl.handle.net/10986/30317

2. S.A. Benner, A.M. Sismour, Synthetic biology. *Nat. Rev. Genet.* **6**, 533 (2005). https://www.nature.com/articles/nrg1637

3. R. Kwok, Five hard truths for synthetic biology. *Nature* **463**, 288 (2010). https://www.nature.com/articles/463288a

4. C.A. Voigt, Synthetic biology 2020–2030: Six commercially-available products that are changing our world. *Nat. Commun.* **11**, 6379 (2020). https://www.nature.com/articles/s41467-020-20122-2
5. X. Chen, M. Gentili, N. Hacohen, A. Regev, A cell-free antibody engineering platform rapidly generates SARS-CoV-2 neutralizing antibodies. *Nat. Commun.* **12**, 5506 (2021). https://doi.org/10.1038/s41467-021-25777-z
6. R.U. Sheth, V. Cabral, S.P. Chen, H.H. Wang, Manipulating bacterial communities by *in situ* microbiome engineering. *Trends Genet.* **32**(4), 189 (2016). https://doi.org/10.1016/j.tig.2016.01.005
7. E.W. Weber, M.V. Maus, C.L. Mackall, The emerging landscape of immune cell therapies. *Cell* **181**(1), 46 (2020). https://doi.org/10.1016/j.cell.2020.03.001
8. Y. Choi, S.Y. Lee, Biosynthesis of inorganic nanomaterials using microbial cells and bacteriophages. *Nat. Rev. Chem.* **4**, 638 (2020). https://doi.org/10.1038/s41570-020-00221-w
9. Y. Cui, Engineered phages for electronics. *Biosens. Bioelectron.* **85**, 964 (2016). https://doi.org/10.1016/j.bios.2016.05.086
10. C. Filiatrault-Chastel, S. Heiss-Blanquet, A. Margeot, J.-G. Berrin, From fungal secretomes to enzymes cocktails: The path forward to bioeconomy. *Biotechnol. Adv.* **52**, 107833 (2021). https://doi.org/10.1016/j.biotechadv.2021.107833
11. L.M. Fonseca, L.S. Parreiras, M.T. Murakami, Rational engineering of the Trichoderma reesei RUT-C30 strain into an industrially relevant platform for cellulase production. *Biotechnol. Biofuels* **13**, 93 (2020). https://doi.org/10.1186/s13068-020-01732-w
12. E.A. de Lima, F. Mandelli, D. Kolling, J. Matsusato Souza, C.A. de Oliveira Filho, M. Ribeiro da Silva, I. Lobo de Mesquita Sampaio, T. Lopes Junqueira, M. Ferreira Chagas, J.C. Teodoro, E.R. de Morais, M.T. Murakami, Development of an economically competitive *Trichoderma*-based platform for enzyme production: Bioprocess optimization, pilot plant scale-up, techno-economic analysis and life cycle assessment. *Bioresour. Technol.* **364**, 128019 (2022). https://doi.org/10.1016/j.biortech.2022.128019
13. L. Cabral, G.F. Persinoti, D.A.A. Paixão, M.P. Martins, M.A.B. Morais, M. Chinaglia, M.N. Domingues, M.L. Sforca, R.A.S. Pirolla, W.C. Generoso, C.A. Santos, L.F. Maciel, N. Terrapin, V. Lombard, B. Henrissat, M.T. Murakami, Gut microbiome of the largest living rodent harbors unprecedented enzymatic systems to degrade plant polysaccharides. *Nat. Commun.* **13**, 639 (2022). https://doi.org/10.1038/s41467-022-28310-y
14. United Nations Environment Programme (UNEP), *Megadiverse Brazil: Giving Biodiversity an Online Boost* (UNEP, Nairobi, February 29, 2019). https://www.unep.org/news-and-stories/story/megadiverse-brazil-giving-biodiversity-online-boost
15. K.J. Locey, J.T. Lennon, Scaling laws predict global microbial diversity. *Proc. Natl. Acad. Sci. U.S.A.* **113**(21), 5970 (2016). https://doi.org/10.1073/pnas.1521291113
16. American Type Culture Collection. https://www.atcc.org/
17. Global Biodiversity Information Facility. https://www.gbif.org/
18. Human Microbiome Project. https://commonfund.nih.gov/hmp
19. Tara Oceans. https://fondationtaraocean.org/en/home/
20. J.W. Szostak, D.P. Bartel, P.L. Luisi, Synthesizing life. *Nature* **409**, 387 (2001). https://doi.org/10.1038/35053176

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