Using 3D Printing as a Research Tool for Materials Discovery

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Summary: In this perspective, we highlight some significant advances in polymer additive manufacturing and bioprinting over the past few years, with an eye toward future applications of 3D printing technology as a research tool for the discovery and design of new materials. While chemistry has taken a central role in advancing the capabilities of 3D printing in factories and hospitals, we believe its profound but overlooked impact may be as a research tool in the laboratory. High throughput discovery techniques are used in many fields, including drug discovery and biochemistry. 3D printing will play a similar role in the discovery of new materials by acting as a rapid testing platform for artificial intelligence and machine learning tools that will not only guide the design of the materials but also provide insights into how they can be transitioned from the lab to production-scale manufacturing.

Introduction - 3D printing is a transformative technology that has promised to change our lives, our health, and the way we make things. From a manufacturing perspective, it offers the possibility to produce diverse products using a single instrument. 3D printing – also referred to as additive manufacturing – can produce parts with less waste and, in many cases, using less energy, making it potentially reducing costs and environmental impact relative to traditional manufacturing methods. Over the years, the development of 3D printing as a manufacturing tool has seen remarkable strides by enabling the fabrication of customized dental prosthetics and sports equipment. Since the filing of the original patent for polymer 3D printing technology in 1987 by Charles Hull, it has gained a broad capability to produce materials made from common, inexpensive plastics such as acrylate resins and acrylonitrile-butadiene-styrene (ABS), to advanced materials such as polyether(ether) ketone (PEEK) or bioplastics like polylactic acid (PLA). In the last decade, 3D printers have been used to make life-saving implants,[1] broaded the scope of art, design, and architecture,[2] and most recently, filled gaps in the supply chain for hospitals during the coronavirus pandemic.[3] This technology not only redefined the manufacturing paradigm but has also ushered in a new era of entrepreneurship with a wide range of startup companies that use 3D printing to produce new products, including parts for high-performance automobiles, stylish sneakers, and even 3D printers themselves.

While 3D printing has become a catch-all term for the process of additively manufacturing objects from custom 3D designs, the machines that accomplish this process rely on a variety of very different technologies. Extrusion-based 3D printers use hard, thermoplastic filaments or soft shear-thinning pastes as their feedstocks, which are forced through printing nozzles to build objects layer-by-layer (Figure 1A).[4-7] Vat photopolymerization printers build each layer by converting liquid monomers into thermosets or elastomers using photoinitiated radical polymerizations (Figure 1B).[8-10] Each of these printing methods possesses unique advantages, encompassing operational costs, user-friendliness, the quality of the printed parts, and the choice of the printing material, which can include many types of materials ranging from metals, to polymers and even chocolate.

In this discussion, our focus will be on polymers that can be utilized in 3D printing techniques such as extrusion and vat photopolymerization. Our primary emphasis on polymers due to their versatility, ease of use, and widespread adoption in the 3D printing industry. It is expected that the concepts discussed here could be applicable to other 3D printing technologies that involve metals, ceramics, and various hybrid materials.

The explosion of inexpensive 3D printers on the market has democratized polymer manufacturing in ways that could not have been envisioned just a few years ago. Polymer 3D printers that use extrusion or photoprinting technology can be purchased for costs similar to a common inkjet or laser printer. While this widespread availability opens the door for hobbyists to produce custom components, it has also made these tools readily accessible to researchers in academic laboratories. Creative users have found ways to make new lab tools,[11,12] or structural models for educational purposes.[13,14] Given 3D printers' ability to dictate processing conditions in a highly parallel and general way, we posit that these instruments can also act as a discovery tool for fundamental research. It may seem unusual to look at a 3D printer in the same way as an NMR spectrometer or a scanning electron microscope in a research laboratory; in fact, it is common to think of 3D printing to be the end product of materials development, rather than an integral part of the development pathway. While the products are often valuable, 3D printed objects provide well-structured macroscale samples that can be used to validate the hierarchical design of functional materials, connecting the bottom-up assembly with the top-down fabrication. This approach is widely used in natural materials, producing porous but rigid bone structures, stretchable but tough skins, and responsive muscles. 3D printing allows researchers to emulate natural systems' multiscale and multifunctional integration[15] across the nano-to-macroscale. In recent years, 3D printers of all varieties have become nearly ubiquitous at academic institutions alongside tradtional research tools, and while these more traditional tools can provide fine molecular and atomic scale information about the materials we make, 3D printers act as a “disruptor” in the traditonal materials discovery workflow. With little cost, and a low learning curve, synthetic chemists can test macroscale implementations of their molecular scale creations, and engineers can create structures and designs using a broader range of materials than ever before. In this perspective, we will discuss ways in which the design of new polymers has enabled 3D printers to access new applications and industries – and how we think that *future directions* in polymer design will be driven by 3D printing technology.

Improving 3D Printing with Polymer Chemistry – Despite the immense promise of 3D printing technology to revolutionize everything from large-scale manufacturing to regenerative medicine, the technology presently has many limitations. One of the biggest hurdles is the fact that many of the most readily available commodity polymers were not designed to be used with 3D printers. For example, parts produced through extrusion printing of conventional thermoplastics often exhibit macroscale defects at the interfaces between layers, reducing their mechanical strength – especially in comparison with parts made from the same material using conventional injection molding. On the other hand, not all materials can be used with vat photopolymerization, since the resins need to be photocured. In other words, the range of the materials compatible for vat photopolymerization printing remains much more limited.

Although addressing these problems may seem like a daunting challenge, polymer chemists have developed a vast toolbox of chemical approaches that can be used to overcome this challenge. Self-healing polymer designs can produce extrusion-printed parts with mechanical behavior similar to those formed by molding (Figure 2A).[16] Similarly, high-quality multifunctional 3D-printed hydrogels are highly demanded for biomedical uses. By using molecules that are connected together as rings threaded through a necklace, also known as polyrotaxanes, 3D-printed stimuli-responsive hydrogels with enhanced mechanical properties have been produced (Figure 2B).[17]

Innovations in polymer chemistry are also pushing the limits of what kinds of materials are considered “printable.” For example, the 3D printing of polydicyclopentadiene was enabled by the creation of a temperature-sensitive ring-opening metathesis catalyst, allowing for the resin polymerization along a consistent front only after the resin has been extruded from a cold nozzle (Figure 2C).[18,19] Polyimides, which are high-temperature engineering plastics widely used in the aerospace industry, are introduced as 3D printing materials through vat polymerization followed by post-printing treatment (Figure 2D).[20]

Remarkable progress has been achieved in overcoming the challenges associated with biocompatibility and fabrication speed in the realm of 3D printing. To shift the photocuring wavelength away from the harmful UV range and increase the light penetration depth, visible and near-infrared photocatalysts have been specifically designed for vat photopolymerization. Advances in photocatalyst design allow for radical polymerizations to be carried out using visible, or even near infrared light (Figure 2E).[21] Improvements to manufacturing-scale printing have been driven by the implementation of polymer membranes that are semi-permeable to oxygen, enabling a continuous printing process[22] (known as CLIP) that can help make the speed and scalability of 3D printing competitive with other manufacturing methods (Figure 2F). 3D printers can also be used to optimize reactions in ways beyond directly performing the chemistry. One recent example of this concept was the use of 3D printers to make specially designed reactionware to enable more efficient synthesis of several pharmaceutically relevant chemical compounds.[23] Though the 3D printer did not perform the chemical reactions themselves, it provided a way to rapidly manufacture specially designed equipment to make this process possible. Mechanochemically active polymers can also be 3D printed now, further expanding the scope of damage-detecting and stimuli-responsive materials.[24]

While the most prevalent and commercialized forms of polymer 3D printing involve the production of plastic parts and prototypes, bioprinting elicits great excitement in the scientific community and the public due to its potential to produce customized medical devices, tissue, and eventually organs for patients. In particular, bioprinting is a type of 3D printing technology, but uses bio-inks, which are materials that support the viability of living cells. With the explosion of advances in bioprinting technology, the prospect for producing unlimited spare parts for humans feels like a distinct possibility. To achieve this promise, researchers have, once again, dived into the fundamental toolbox of chemical design to create materials that can provide a friendly and healthy environment for cells and tissue to survive the printing process.

To ensure the success of bioprinting, soft materials such as shear-thinning hydrogels are developed to provide a 3D environment for cell and tissue growth. The shear stress generated during the bioprinting process— by forcing the cells in the printing matrix to flow through a syringe or needle and then expand to fill the desired printed voxel— often reduce cell viability. To address this problem, Heilshorn and co-workers developed a hydrogel capable of shielding the cells from these stresses using a dual crosslinking strategy (Figure 3A).[25] The unique ability of 3D printers to create materials with complex internal structure such as voids and cavities, makes them ideal for reproducing the intricate architectures found in organs and their corresponding vasculature. Another challenge arises because many of the hydrogels used for tissue growth are too soft to be self-supportive. To address this issue, Lewis and co-workers[26] designed a system where a simulated extracellular matrix (ECM) is used as a matrix for the printed vasculature materials that simultaneously provides a supportive mechanical and biological environment for the tissue scaffolds (Figure 3B). Feinberg and co-workers developed a method that induces a gelated form of collagen through a rapid pH change induced by the print head (Figure 3C).[27] This enables the direct bioprinting of collagen as the simulated ECM material.

Precise mechanical control over biomaterials is key to their effectiveness in tissue growth. Burdick and co-workers used a well-known supramolecular host-guest pair, β-cyclodextrin and adamantane, to produce healable and 3D printable hyaluronic acid hydrogels that maintain their shape and mechanical properties over extended periods of time (Figure 3D).[28] While regenerative medicine has been a central research focus in bioprinting, others have imagined its use for other applications in biotechnology. Nelson and co-workers have developed a 3D printable hydrogel matrix containing yeast, which enables continuous fermentation processes to produce ethanol without significant degradation of the polymer matrix or the embedded viability of the yeast (Figure 3E).[29] Though each of these examples uses bioprinting to solve different problems, all of them used a fundamental polymer design tool, such as stimuli responsiveness or supramolecular host-guest recognition, to create new materials that can work seamlessly with 3D printing technology.

Looking to the Future*: *Improving Materials Chemistry with 3D Printing – In many areas of chemistry, researchers strive to develop a clear and fundamental understanding of how to make molecules for specific applications from the bottom up – often referred to as "rational design". However, in practice, this is not always a practical or productive approach. In drug discovery, even in cases where the mechanism of action for a small molecule drug candidate is well understood, the complexity of whole biological systems can limit the effectiveness of this strategy. High-throughput techniques, such as combinatorial chemistry[30] and automated flow synthesis[31] can produce large libraries of compounds that can be used to build a clearer picture of the mechanism of action.

Similarly, the development of advanced polymers with highly tailored properties poses an equally complex and daunting challenge due to the myriad compositional and processing details that must be chosen and tested experimentally. Given this expansive parameter space, new paradigms that seek to generate data quickly and more efficiently are of high value. Traditionally, polymer samples are prepared at the microgram to gram scale on wafers or as macroscopic test coupons, which limits the scale at which experimental campaigns can take place (Figure 4A). A major breakthrough that represents high throughput experimentation (HTE) of polymers in the ability to prepare libraries of samples using of a doctor blade approach for realizing films combinatorial polymer libraries.[32-34] Known as flow coating, this approach used an accelerating doctor blade to obtain orthogonal gradients in thickness and composition.[35] Once prepared, the gradients can be locally probed to map properties of interest (Figure 4B). While this approach has been used to study a variety of polymer properties,[36] its widespread use is limited by the restrictions it places on the processing conditions and the need to locally measure composition/thickness in order to confidently label data.

HTE methods for 3D printing have also been employed to discover new printable polymer inks for applications in drug delivery,[37,38] tissue engineering,[39] and even catalytic polymer composites.[40] In principle, there are many possible ways to implement HTE methods to study materials in these areas, however, 3D printers can create materials in many differerent shapes and geometries as well as different compositions. In applications where accessible surface area or feature thickness play as much of a role as the polymer composition (*e.g.,* catalyst kinetics, biodegradation), 3D printing tools add a new dimension to high-throughput materials discovery.

In contrast with HTE methods that seek to generate large libraries of samples, a more recent experimental paradigm is the use of a self-driving lab (SDL), which comprises the iterative selection and testing of samples without human intervention (Figure 4C).[41] While the total throughput in terms of samples prepared may be lower than HTE, the use of all available knowledge to select each experiment can result in faster generation of important samples and knowledge. While SDLs have been employed in a variety of fields, of particular relevance to polymers are systems for spin-coating polymer blends and measuring their properties for example in terms of hole mobility or adhesion.[42,43] In comparison with grid-based searching, SDLs have demonstrated 30× reduction in the number of experiments needed to identify high performing samples.[44] Such systems even outperform iterative selection by human experts.[45] Illustrating the promise of this approach, there are efforts ongoing to develop large-scale SDLs that combine polymer synthesis and detailed characterization for a complete polymer research effort.[46]

While it is clear that SDLs can provide tremendous acceleration and are being used for polymer research, additive manufacturing is itself ideally suited to perform a role in the synthesis of materials. Indeed, 3D printers have already been incorporated into SDLs to, for example, fabricate polymer components in an effort to maximize their ability to absorb mechanical energy (Figure 4D).[44,47] This example takes advantage of the structural freedom afforded by 3D printing. In addition to structural details, many types of additive manufacturing allow one to control facets of the processing that can be crucial in determining polymer properties. However, the majority of the work to date has focused on adjusting such processing parameters to maintain consistent outcomes.[48,49] A powerful future direction is the use of the processing control afforded by 3D printing to function as an avenue to more generally study processing-property relationships through the use of an SDL. One example is the use of jet printing 3D printing as a way of mixing resins to determine the property gamut available to mixtures which has been realized in a high-throughput active learning-guided format.[50] These examples pave the way for future work in which SDLs are developed that allow composition and processing parameters to be autonomously explored to discover new materials formations.

Sustainable Plastics Powered by 3D Printing – Creating effective and sustainable plastic materials is one of the biggest challenges facing polymer chemists (and humanity) in the coming years. Through collaboration, creativity and hard work, polymer chemists and engineers have produced vast libraries of materials that are either derived entirely from biorenewable feedstocks, or that can be recycled effectively on small scales into materials of equal (or sometimes even better) value and mechanical quality.[51] Unfortunately, translating these innovations from laboratory scale to industrial scale where they can have great impact remains a major stumbling block. In fact, even this pathway is no longer linear as manufacturing technologies are diversifying to include more energy and material efficient techniques. Despite these advantages, the materials used in

3D printing often have the same molecular composition as those used in conventional polymers, meaning that they still have the same problems regarding where they come from (petroleum) and how they are disposed of (landfill, incineration, or as unmanaged waste). For 3D printing to achieve its promise as a sustainable technology for manufacturing in the future, it must also be able to manufacture products using sustainable materials. In many cases, these greener materials are far too costly to replace their petroleum sourced counterparts on the market. Since small, desktop 3D printers operate in similar ways to those that are used in larger scale manufacturing, we envision a process where research scientists can design new materials with a holistic philosophy that addresses issues in sustainability, function, and scale-up manufacturing. In fact, sustainable polymer technologies have already begun to transition to compatibility with 3D printers,[52,53] and researchers are beginning to consider the operation of the 3D printer itself in life-cycle analyses of manufacturing efficiency.[54]

Validating Machine Learning and Artificial Intelligence Tools with 3D Printing – Artificial intelligence (AI) and machine learning (ML) advancements have sparked significant breakthroughs in the field of materials design and discovery, transforming how we approach the engineering of new materials[55-57]. Machine learning, in particular, has become an invaluable tool for accelerating material property predictions, and optimizing properties to cater to specific requirements[58-62]. This expeditious method allows for a quicker iteration cycle in the design of materials, shortening the timescale from initial concept to the final product.

Integrating ML with 3D printing adds another layer to this process. The synergy between the two opens up possibilities for validating ML models swiftly through experimental testing. Given the inherent ability of additive manufacturing to fabricate intricate designs with relative ease, it proves to be an excellent tool for creating complex designs conceived through ML and optimization processes[63-66].

An illustration of this integration comes from the development of architected materials with improved mechanical properties[67-72]. Researchers have harnessed the power of AI and ML tools to design these robust materials, with 3D printing then used for actual fabrication. The validity of the ML models and the performance of the newly developed materials were subsequently confirmed through experiments. By leveraging these technologies, researchers have been able to create architected materials with tailored mechanical properties. Beyond mechanical properties, additive manufacturing also provides a platform for validating ML models pertaining to a wide range of other properties. For instance, the biological compatibility of materials, vital for medical implants and prosthetics, can be swiftly evaluated[73,74]. The acoustic properties of materials, crucial for applications in noise dampening and sound insulation, can also be rapidly assessed[75]. Electrical properties of materials, fundamental for electronics and energy storage applications, can be gauged with greater ease and accuracy[76]. And these are just a few among the many other properties that can be validated through this symbiotic relationship between ML and 3D printing. Advances in AI and ML also enables real-time adjustments and automated detection of part quality in the additive manufacturing process[77-81]. This would make the process more efficient and could allow for the manufacturing of materials with customizable, location-specific properties.

As such, the intersection of AI, ML, and 3D printing is a frontier that holds enormous potential. By allowing for rapid design, fabrication, and validation of new materials with tailored properties, this integrated approach is set to change the future of materials science and engineering. Exciting new outlooks in this field is in the fabrication of sustainable and eco-friendly materials. As environmental concerns become increasingly critical, AI and ML can be used to design and optimize sustainable and eco-friendly materials. They can help in the discovery of materials that are not just high-performance but also have a low environmental impact. 3D printing, with its potentially material-efficient process, also aligns well with this trend. These emerging trends offer exciting opportunities for future research and application.

Conclusions **–** As an emerging technology, 3D printing has found its way into the hands of a broad range of users, from educators, to hobbyists, to manufacturers, with the full extent of its impact yet to be seen. We believe that 3D printing will have a similarly powerful effect on how researchers design new materials and collaborate with one another. The ongoing expansion of 3D printing into the field of materials discovery represents the concerted efforts by chemists and engineers to find new ways to solve big problems. Polymer chemists are racing to perfect designs for plastics that lie at the – so far, undiscovered – interface of sustainability and practicality. Bioengineers are seeking new polymers that can survive the complex mechanical and immunological environments required to grow tissue, bone, and treat disease. 3D printing tools can replicate the manufacturing process that polymer chemists need to validate their experimental designs and rapidly move them towards large scale implementation, *and* provide the highly individualized fabrication capability needed to rigorously test biomedical devices. Due to the tremendous promise of this emerging area, we expect that it will have a transformative impact on both the 3D printing community and, increasingly, other facets of materials science.

Declaration of Interests **–** The authors have no competing interests to declare.

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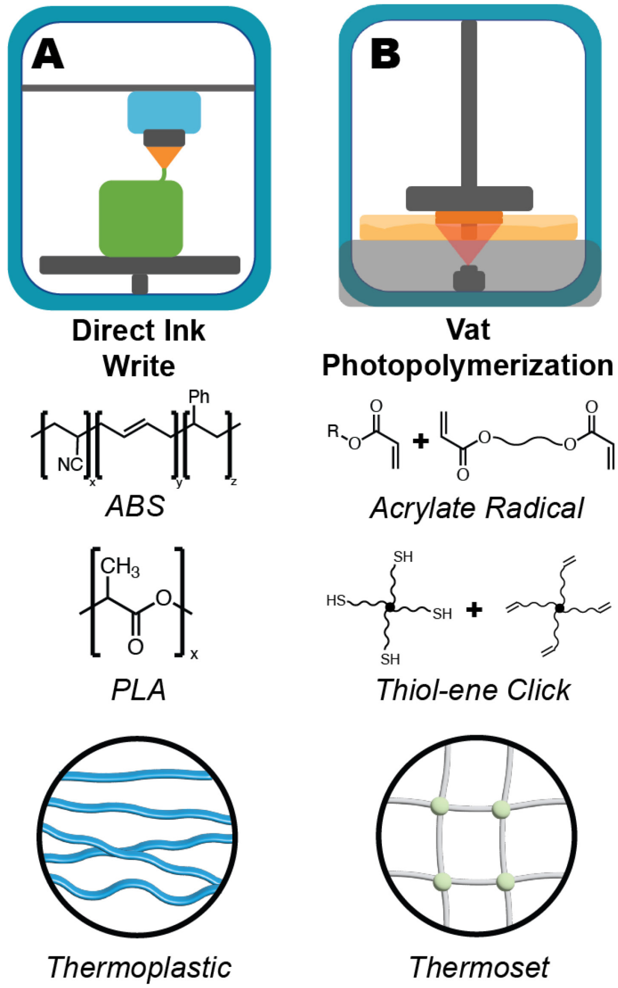

Figure 1. Common techniques used for research-scale polymer 3D printing. A) Extrusion printers use pre-synthesized thermoplastic polymers, which can be melted and shaped by extrusion. **B)** Photoprinting techniques produce crosslinked, or thermoset, polymers during the printing process, typically using rapid, radical polymerization reactions.

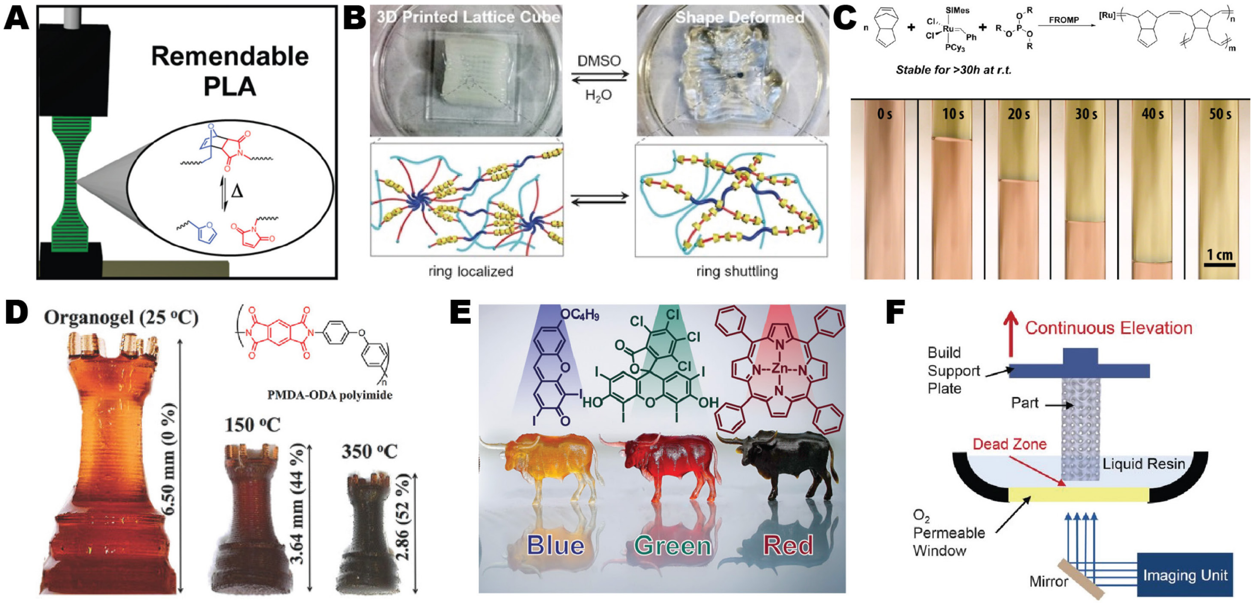

Figure 2. Examples of polymers and monomer formulations designed specifically to work with 3D printing technologies. A) A self-healing polymer that can repair filament adhesion defects *in situ* during an extrusion printing process. Adapted with permission from ref 16. Copyright 2016 American Chemical Society **B)** A printable hydrogel containing mechanical bonds that can switchably change its shape based on an external stimulus. Figure adapted from ref 17 with permission from Wiley-VCH Verlag GmbH & Co., copyright 2017 **C)** Extrusion printable monomer formulation that can be polymerized using a specially designed metathesis reaction without the need for additional thermal or photochemical input. Adapted with permission from Adapted with permission from ref 18. Copyright 2017 American Chemical Society. Copyright 2018 American Chemical Society **D)** Printing a typically "unprintable" material using monomers that can be converted to the desired polyimide after an orthogonal acrylate radical polymerization that can be easily photoprinted. Reproduced from ref 20 with permission from Wiley-VCH Verlag GmbH & Co., copyright 2017. **E)** Photocatalysts that absorb in the visible region can allow 3D printing with visible light, rather than the less biocompatible, but more commonly used, ultraviolet light. Adapted with permission from ref 21. Copyright 2020 American Chemical Society **F)** Fine tuning the behavior of a radical polymerization reaction by controlled introduction of oxygen as an inhibitor led to a printing process that can be carried out continuously, rather than layer-by-layer, improving the quality of printed plastics. Adapted with permission from AAAS from ref 22, copyright 2015.

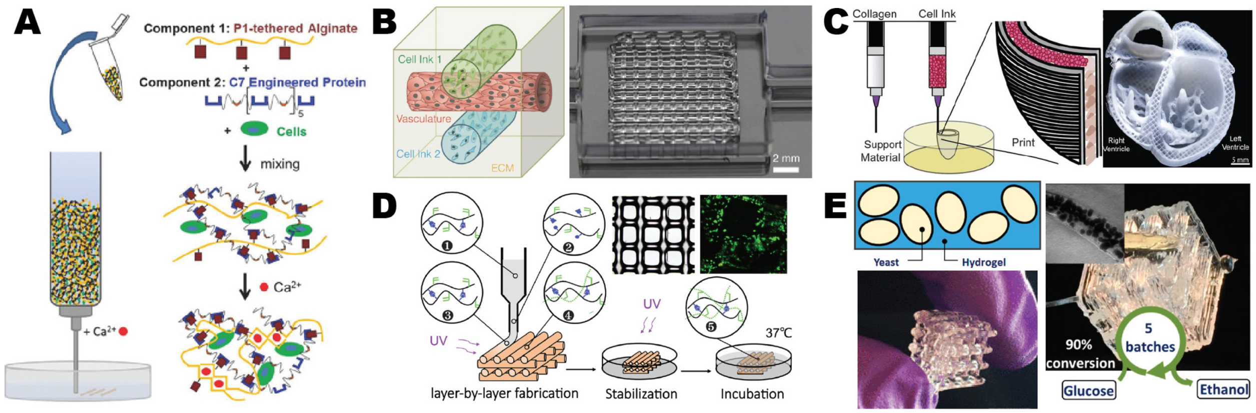

Figure 3. Polymer designs for bioprinting. A) Protecting embedded cells from damage during 3D printing through the use of multi-stage crosslinking. Reproduced from ref 25 with permission from Wiley-VCH Verlag GmbH & Co., copyright 2016. **B)** Bioprinting of vasculature using multiple types of cell-laden "inks" and a shear-thinning support matrix. Reproduced from ref 26 with permission from Wiley-VCH Verlag GmbH & Co., copyright 2014. **C)** A method for making collagen printable using an *in situ* pH controlled gelation technique Adapted with permission from AAAS from ref 27, copyright 2019. **D)** Supramolecular crosslinking of hyaluronic acid gels preserves their structure and mechanical properties over long periods of time. Adapted with permission from ref 28. Copyright 2017 American Chemical Society **E)** Hydrogel encapsulated yeast can be printed into designed shapes while maintaining their abilty to catalyze the production of ethanol from glucose. Adapted with permission from ref 29. Copyright 2018 American Chemical Society

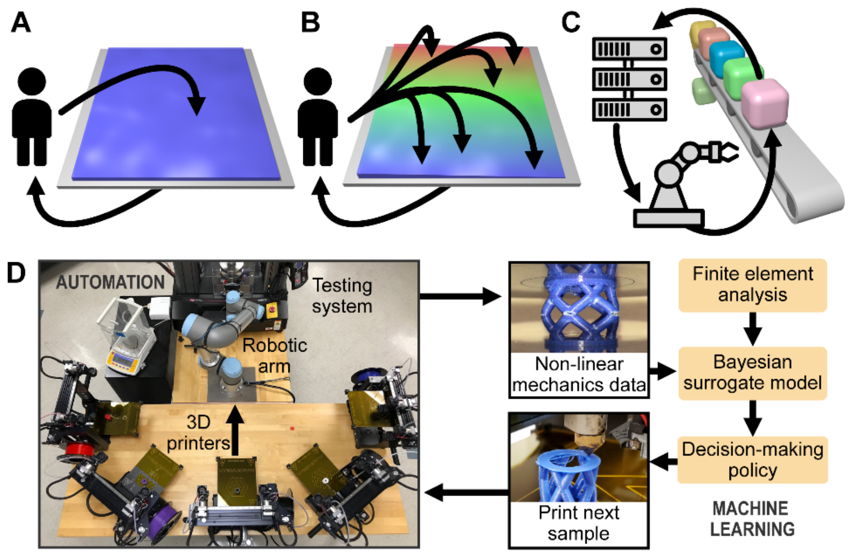

Figure 4. 3D printing for accelerating experiments and self-driving labs. A) Conventional materials research paradigm in which samples are individually selected and prepared by a researcher. **B)** High-throughput experimentation (HTE) of polymers enabled by the generation of combinatorial gradients of polymer films in which thickness and composition are varied across the sample. In this way, different locations may be iteratively selected to proceed efficiently. **C)** Self-driving lab (SDL) paradigm in which samples are sequentially selected, prepared, and characterized in an automated fashion to proceed toward a given goal both rapidly and efficiently. **D)** Example of an SDL that leverages 3D printing to explore structural designs. Here, 3D printers prepare samples that are automatically moved to a universal testing machine to determine their non-linear mechanics. The resulting data is used together with a finite element analysis prior to select subsequent experiments to maximize the amount of energy that is absorbed. Panel D adopted from Gongora et al under a Creative Commons Attribution License.