Recently, three-dimensional (3D) printing has revolutionized manufacturing and made rapid prototyping possible. With this new manufacturing technique, it is now possible to design and create complex, intricate objects that are impossible to produce through any other means. The rise of 3D printing and the dwindling cost of the required hardware have been a boon to hobbyists and “makers” who can create objects in a matter of hours using cheap starting materials. These opportunities have also attracted the attention of many chemists due to the possibility of creating labware that may be cheaper or offers better performance than commercially available products as well as custom labware that simply isn’t commercially available.  

Notable examples range from simple microscopes\textsuperscript{2} to complex microfluidic systems,\textsuperscript{3} and even data visualization aids.\textsuperscript{4} In this issue of ACS Central Science, Cronin and co-workers report software\textsuperscript{5} that enables chemists to 3D print bespoke “reactionware” as part of their effort to make digitizing chemistry more accessible.\textsuperscript{6}

By using labware tailored to a specific synthetic route, referred to as “reactionware”, the labor required for multistep syntheses can be substantially reduced.\textsuperscript{7} The authors have previously demonstrated the use of the reactionware concept to synthesize a variety of compounds.\textsuperscript{8} Three-dimensional printing makes this possible since the cost compared to, for example, custom glassware is so much lower. However, one of the chief challenges in creating custom 3D-printed parts is that they must be designed using computer-aided design (CAD) software, and most chemists lack the knowledge to use it. The Chemical Synthesis by Computer Aided Design (ChemSCAD) software has emerged from the Cronin group as a possible solution to this dilemma.

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Using ChemSCAD, a chemist with access to a 3D printer can print the reactionware necessary for their synthesis. Notably, the reactors are not designed from scratch to fit the...
The software uses a series of templates (Figure 1) and takes the required synthetic operations and reaction parameters as inputs. The module is chosen based on whether it will be used simply as a reaction vessel or for various filtration or purification operations by inserting one or more filters during printing. Similar heuristics are used to select the module’s top, such as selecting a top with an inlet for reactions that require an inert atmosphere or in vacuo solvent removal. The software also includes different choices for the bottom of the module and connectors based on the reactor’s place in the process and any requirements for connection to external apparatuses. In essence, the ChemSCAD reactors can be designed based on a set of rule-of-thumb considerations including the actions to be performed, the scale of the reaction, the physical state of the reagents and products, the reaction’s air or moisture sensitivity, and the potential for gas formation during the reaction.

The true innovation revolves around treating chemical synthesis in much the same way as the software for designing the reactionware in which it is performed. The designs for the 3D-printed reactors, along with information about the reaction and its outcome, obtained from analytical instruments (e.g., HPLC, NMR, MS, etc.), can be stored in a database. This database can be used for version control, but it can also be used to optimize the 3D-printed reactor in order to more efficiently synthesize the target molecule. One could even imagine supplying this data to a machine learning (ML) algorithm, so that a self-driving lab could autonomously optimize the process.

To demonstrate the usefulness of their new software, the Cronin group used reactionware, which was 3D printed from ChemSCAD designs, to synthesize three simple and well-known active pharmaceutical ingredients (APIs). Namely, the antiviral ribavirin and the narcolepsy drug modafinil were synthesized in good yield and with purities of over 95%. In addition, the chemotherapy drug lomustine was synthesized in both batch and flow using the flow reactor template included in ChemSCAD.

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However, there are challenges to using 3D printed labware. Although polypropylene, from which the reactionware is currently printed, is compatible with many chemicals, strong acids and organic solvents can still pose a problem.9 Further, high-temperature reactions may be out of reach as polypropylene melts at ca. 160 °C. These technical limitations have more to do with the materials from which the reactionware is printed than the concept itself. Eventually, technological advances could make 3D printed labware made of more chemically and thermally resistant materials including glass, ceramics, and fluoropolymers such as polytetrafluoroethylene (PTFE) more accessible.10 One important challenge of the reactionware concept is that it likely cannot be used for a synthetic route that requires more than a rudimentary chromatographic separation. Another important consideration for widespread use of 3D printed labware, which is often overlooked at the early stages of research, is the potential wastefulness of single-use or iteratively designed reactionware—we are well aware that our over-reliance on disposable and short life cycle products has led to significant climatic and environmental consequences.

Despite the aforementioned considerations and challenges, 3D-printed reactionware, which the ChemSCAD software makes easier to design than before, holds much promise for accelerating chemical research by reducing the amount of human labor required. In the future, one could imagine reactionware designs being shared when reporting synthetic methods or deposited in a database similar to crystallographic data.
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