The applications and impacts of automation to the accessibility of engineering synthetic biological devices

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I declare that the work presented in this essay is my own and that it has not been submitted for assessment on any other module. I have not used any generative AI tool to write this essay.

***Abstract*—Development of synthetic biological devices widely involves the development and integration of genetic circuits, and heavily relies upon the Design-Build-Test-Learn cycle, for which technologies such as CAD and robotics are employed in order to offload tedious or humanly impractical tasks to systems of software and hardware, such that researchers may be free to focus more towards high-level design aspects. The main applications of automation and their effects are highlighted here, as well as the potential impacts to and of greater accessibility in engineering biological devices. The utility of open-source hardware and software is especially emphasised as a major driving force in the adoption of accessible technologies in this space.**

Keywords: synthetic biology, automation, computer-aided design, robotics, open-source software, biological devices

I. Introduction

Synthetic biology (also known as engineering biology[1], and frequently abbreviated to "SynBio") is an interdisciplinary field of science that applies common engineering principles towards research and development of living systems, especially involving the creation of biological devices or machines—i.e. systems that compose standard biological parts (such as promoters and terminators[2]) to produce complex and predictable behaviours[3].

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The development and usage of information technology in synthetic biology—including key technologies such as machine learning and computer-aided design—has expanded rapidly alongside the growth of the field itself[4]. Among these key technologies, automation of laboratory protocols exists as an area with limited practical application at the present time, while having the future potential to greatly accelerate research and development throughout the field[5].

This essay focusses on the current applications of automation to the accessibility of engineering of such synthetic biological devices, and the impacts thereof—where automation is defined as the use of technology to complete tasks that otherwise would have been performed by human actors. We outline these applications in the stages of the Design-Build-Test-Learn (DBTL) cycle—a standard iterative trial-and-error process for the engineering of biological devices[6]—with a greater focus on the design and build stages, relating to automated design by software tools, and by robotics in physical laboratory procedures respectively.

II. Design automation

There exist a number of tasks in the design stage that are able to be automated by the process of computer-aided design (CAD) tools, in a similar way to the process of designing electronic circuits[4]. The majority of these tools, including Cello[7], iBioSim[8], j5[6], Trumpet[9], SynBioCAD[10], and GenoCAD[11], are open-source software developed to facilitate the creation of genetic circuitry in biological devices.

Cello, for example, allows the user to specify logic circuits in Verilog, a high-level hardware description language, which is then compiled to give DNA sequences to exhibit the defined behaviour, having been demonstrated to be able to produce circuits performing majority voting[12] and to create environmental biosensors[7]. This therefore, in theory, avoids the need to consider the genetic machinery that would be required to implement a certain logic circuit, instead allowing the scientist to focus entirely on the high-level logical behaviour of the device.

This automation is a great boon towards elevated accessibility in research and development in the field, for a number of reasons—not the least of which being its lowering of the barrier to entry towards designing genetic circuitry, by virtue of allowing even non-experts to implement combinatorial logic without prior knowledge of implementation details, such as how best to ensure orthogonality and modularity in a biological logic gate[7]. Furthermore the open-source nature of the software removes prohibitive licensing and monetary expense, allowing individual researchers and community labs to gain access to the software, whilst also contributing towards the reproducibility of experiments by ensuring that the software being used will still be available a significant time into the future, and verifiably behaves as is expected.

Swartz[13] however argues a lack of transparency, learnability, and usability in open-source software in sciences, while Heron et al.[14] similarly posit that open-source software is unlikely to be able to "realistically provide a coherent strategy for user documentation and long term support". As applied to synthetic biology, this is prominent in the sphere of genetic circuit CAD tools, with tools such as iBioSim having its issues page on GitHub functioning as its only user support, contributed towards by volunteers[15], and those such as GenoCAD with no system of support whatsoever[16]. Heron et al. are dismissive of community-based user support however, stating it to be "based primarily on hope", though this claim lacks sufficient evidence to be considered absolute—there exist innumerable open-source software projects with sufficient and extensive documentation for example, such as the GNU Compiler Collection[17] and Blender[18], two open-source projects with a vast wealth of documentation and support forums. It would not be unreasonable therefore for it to be a realistic goal for similar tools in the biological CAD space to attain comparable user friendliness and accessibility.

TABLE I
LEVELS OF AUTOMATION IN SYNTHETIC BIOLOGY AS DESCRIBED BY STEPHENSON ET AL.[5]

Level	Description
0: No automation	All experimental processes designed, performed, and analyzed by human
1: Researcher assistance	Specialised instrument automates a single task tedious or impossible manually
2: Partial automation	Multiple steps in workflow or entire sub-workflow automated, human responsible for monitoring/data and remaining portions of workflow
3: Conditional Automation	Most elements of workflow are automated physically with integrated software support; human responsible for some tasks and connections between modules
4: High automation	Entire workflow is automated and connected via hardware and software; capable of iterative experimentation; human intervenes only in case of failure
5: Full automation	System performs all tasks under all conditions; human sets goals and receives results only; no attention or intervention required during execution

III. PHYSICAL LABORATORY AUTOMATION

Stephenson et al.[5] describe a 6-level system (see table I) for the classification of automation in synthetic biology workflows, with level 0 being a complete lack of automation, all labour being performed by humans; and level 5 being full automation without human intervention. They characterise the current state of physical laboratory automation in synthetic biology by describing a number of technologies currently in use, and the levels of automation at which they operate.

Similarly to in the design stage, the provision of open-source software here is a great benefit to improving accessibility. Unlike in the design stage however, the build stage not only requires software, but also requires hardware; an especially pertinent technology described is the use of robotics for liquid handling, for example. A liquid handling robot transports volumes

of liquids to and from specific containers, to automate the same task that would otherwise take large amounts of tedious, impractical and potentially unreliable manual work[19]. There exist both proprietary and open-source solutions in this space (see table II), performing a variety of functions including pipetting, sample preparation, and microplate washing. The provision of open-source hardware here is, similarly to that of open-source software, highly beneficial towards improving accessibility. Stephenson et al. note the existence of DIY approaches to liquid handling such as the MiLab OpenLH, OTTO, FINDUS, PHIL, and Sidekick robots, through the use of technologies including "3D printing, CNC milling, laser cutting, and affordable microcontrollers". These utilise open-source software for programming, though Stephenson et al. neglect to discuss the potential challenges associated with specialised skills being required to effectively build DIY systems and the potential lack of reliability and/or reproducibility of such a system, if constructed improperly or if documentation regarding instruction is lacking. It is however briefly mentioned that "investments in time are often more justifiable than investments in cost", which, though no examples are given to evidence this, is evident from the prohibitive costs of typical commercial systems[20].

Hardware is unlike software in that its development requires much more expensive equipment and physical materials, as well as a large amount of time to design and manufacture, and so it may be argued that commercial production of hardware systems for liquid handling may be the most effective method for providing automation to as wide a range of researchers as possible—so as to fund its development and optimisation. This is a large issue in open-source hardware, where there is little funding available to support developers, especially where the added value of such a system over existing proprietary solutions is unclear[14].

TABLE II
COMPARISON OF HARDWARE FOR BUILD AUTOMATION

Name	Application	Open-source software?	Open-source hardware?
Opentrons OT-1[5]	Liquid handling	Yes	Yes
Opentrons OT-2[6]	Liquid handling	Yes	No
Metafluidics[21]	Microfluidics	Yes	Yes
Gilson PipetMax[22]	Pipetting	No	No
Gilson GX-241[22]	Liquid handling	No	No

IV. CONSEQUENCES OF RISING ACCESSIBILITY

By increasing the accessibility of these forms of biotechnology, the engineering of such biological devices becomes increasingly easier for individuals, of whom a significant majority may be untrained in laboratory safety or lacking in ethical consideration. Already we have seen experiments of questionable safety performed in small-scale community laboratories, such as Atkin's[23] successful DIY gene therapy for the treatment of lactose intolerance, and Licina's[24] development of night-vision eyedrops. In future it is likely for there to be a significant growth in the availability to perform such research to an increasing number of non-expert individuals and small organisations.

With the increase in accessibility, it is a matter of course for there to be a large increase in genetic data and research containing sensitive data such as human individual genetic profiles. This then prompts further consideration as to the ownership and protection of genetic data—whether such data is subject to copyright, could be considered personal information, or should be able to be patented, sold, or freely distributable. Grishin, Obbad, and Church[25] argue a potential case for the enabling of discrimination based on collected genomic data, which may be used for targeted advertising—a clear invasion of privacy, and with regards to the engineering of biological devices especially, it would be feasible for the development of devices performing logical calculation to affect only specific genetic groups, for example.

The ethical issues surrounding biological devices are of course numerous, raising questions such as whether the technology may be more easily used for nefarious purposes such as biological terrorism or warfare[26], and as such gives rise to concerns regarding regulation of access. Especially with the prominence of open-source in this space, it is both infeasible and undesirable to entirely restrict public access to

automation for synthetic biology, for a multitude of reasons. Douglas and Savulescu[26] posit that there is a dual-use dilemma in that greater accessibility has the potential for both great harm and great good. There exists however, the argument that while terrorists and nation-state threat actors have no reason to acknowledge any manner of prohibitive legislation, individuals and organisations who would otherwise be able to engineer novel and unique medicines that would be otherwise unavailable to them, are prevented from doing so, thus rendering the legislation largely ineffective towards its intended purpose. By providing open-source hardware and software, genomics data needs not pass through a third party, thus bypassing the aforementioned potential privacy concerns regarding processing of personal data, therefore it would be largely detrimental in several ways for legislation to prohibit public access.

V. Conclusions

A number of methods for automation in the process of engineering biological devices exist throughout the DBTL cycle: in the design stage CAD tools for the design of genetic circuits are deeply integrated with current laboratory protocols, whereas in the build stage high monetary costs have resulted in slower growth in prominence of robotics for automation. Provision of open-source software and hardware is widespread in the field, allowing for much greater accessibility to both individuals and organisations, however the lack of motivation for funding open hardware has been detrimental to further adoption.

We conclude that the prevalence of open-source in synthetic biology is a large driving force in the increase in accessibility, along with which there comes into being the requirement for greater consideration towards protection of individuals' rights to the participation in research and development of biological devices, thus prompting the need for further discussions surrounding legislation with regards to the DIY biology/biohacker movement, as well as regarding privacy and intellectual property concerns relating to the large volumes of genomic data being produced and processed.

We further conclude that it would be infeasible to entirely limit access to these technologies, due in part to the prevalence of open-source—and therefore for there to not be an overwhelmingly net negative effect arising from the dual-use dilemma, it must not come to pass that individuals are prohibited from the engineering of biological devices. Further consideration is needed to determine potential solutions for the mitigation of malicious usage and unintentional damage attributed to both amateur and professional research.

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