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REVIEW ARTICLE

Using Modular Robotics to Accelerate the Design-Build-Test-Learn Cycle in Synthetic Biology: A Review

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ABSTRACT: Synthetic biology involves using genetic tools to develop novel biological parts, systems, or organisms, and it depends on the iterative Design-Build-Test-Learn cycle. Manual execution is profoundly slow and prone to error/non-replicability. Integration of modular robotics significantly enhances this cycle as a result of 4 primary advantages, which are higher throughput, cost efficiency, precision, and flexibility. The adaptability and reconfigurability of modular robots make them exceptionally suited to the ever-changing and iterative nature of the DBTL cycle in synthetic biology. This review explores how modular robotic solutions enable accelerated iteration of the Design-Build-Test-Learn cycle in synthetic biology. Research studies in this field have relied on large-scale integrated experimentation platforms, such as biofoundries or self-driving labs (which is the pinnacle of current technology), to investigate how the DBTL cycle can be optimised. They have applied various modular robotic components, such as liquid handlers, robotic arms, and plate readers, to perform and interpret experiments at a large scale, whilst running algorithmic frameworks.

KEYWORDS: Biomedical Engineering, Synthetic Biology, Design-Build-Test-Learn Cycle (DBTL), Modular Robotics, Precision in Synthetic Biology, Biofoundries, Automation.

Introduction

A 2024 BCC business report forecasts the synthetic biology research field to grow from $19.3B to $61.6B in 5 years, at a staggering compound annual growth rate of 26.1%.[1] One of the catalysts for this surging growth is the use of biofoundries. They are large, centrally automated synthetic biology laboratories, integrated using modular robots. Synthetic biology is a bioengineering branch involving the formulation and development of novel biological parts, systems, or organisms by manipulating genetic tools. The Design-Build-Test-Learn (DBTL) cycle is a core part of this process. This is because biological systems are complex and multifaceted, so researchers have predominantly relied on a top-down, iterative approach to achieve desired results in this field. The DBTL cycle is a systematic engineering plan used in synthetic biology to develop biological systems according to desired requirements. It begins with the design of a genetic circuit, followed by the physical construction in a host organism. The result is then tested to analyze its limitations, and the data collected is used to learn from the results.[3] This knowledge is then applied to the next iteration of the cycle, creating a continuous feedback loop that is used for the development of novel products or solutions.[4]

Modular robots excel at the repetitive and physical aspects of the 'build' and 'test' phases of the cycle, which helps generate a substantial number of prototypes quickly and test them rapidly using task-specialized robots.[5] This paper explores how modular robotic solutions enable accelerated iteration of the Design-Build-Test-Learn cycle in synthetic biology. Specifically, this paper aims to address the literature gap by analyzing the benefits of "modular" robotic solutions (rather than generic lab automation) in synthetic biology, as they are extremely advantageous in this field due to their capabilities to be dynamically reconfigured to suit a vast array of specifications.

There is an urgent and significant need to accelerate experimental cycles in synthetic biology, including but not limited to its immense potential for quick disease treatment (even resolving future pandemics like COVID-19),[6] and sustainable chemical manufacturing solutions,[7] to reduce the effects of global warming. Implementing modular robotic systems can radically reshape the field of synthetic biology, provided that current challenges in their integration and rapid data analysis are addressed.

Review methodology

Literature for this review was collected primarily through the databases of PubMed, Google Scholar, and direct searches in publisher platforms, mainly Nature and ACS Publications. The keywords "modular robotics," "synthetic biology automation," "DBTL cycle," and "biofoundry integration" were searched. Additional sources were located using 'snowballing' from the reference lists of key review articles, which involved identifying more relevant papers by exploring the reference lists and citations of key articles already found. The cited publications are mainly from 2015 to 2025, indicating the rapid evolution of modular automation during this time period. However, two key studies from 2012 were also used because they provide foundations that continue to have strong implications and are cited extensively in current research. Only peer-reviewed academic articles and an authentic business report were included, and any preprints, opinion pieces, and non-technical reports were excluded.

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DOI: 10.36838/IJHSR89.97

Application of modular robotics in synthetic biology workflows

Modular robots are flexible, reconfigurable machinery capable of performing manual tasks, significantly reducing the need for human input. Notably, up to an extraordinary 89% of research tasks can be segmented into smaller manual tasks or steps within a protocol, such as liquid operations, labware movement, or sample collection, that can be performed by integration of commercially available robotic hardware.[8] The scope of literature work in this field usually deals with automation levels 5 and 6,[9] as they can assist in carrying out multiple experimental steps consecutively without human intervention, making them strategic for biofoundries. Automation level 5 refers to static machines/workstations, like centrifuges and spectrophotometers, that are designed for one specific task.[9] Whereas automation level 6 (most commonly used in life sciences research) refers to flexible workstations that can be reconfigured according to changing tasks, like a motorised stage microscope.[9]

One of the most time-consuming steps in the “build” phase of the cycle is combining DNA parts to create new genetic assemblies. This is because DNA parts and enzymes are generally processed in microliter or even nanoliter ranges and require exceptional precision.[10] Liquid handling modular robots can be utilized here as they specialize in manipulating small volumes of liquid and perform precise pipetting, serial dilutions,[11] and reagent mixing. Their specialization is crucial for tasks like DNA assembly, where exact concentrations of DNA fragments and enzymes are required to build a new genetic circuit, in extremely precise measurements, due to a higher rate of error propagation.[12] To add, different biological reagents (examples: buffers, DNA, enzymes) have different viscosities, which affect pipetting speed and accuracy.[10] Modular robots can seamlessly be calibrated for these evolving requirements.

Microplate readers are another key modular component, with their primary function to rapidly detect biological or biochemical reactions by measuring certain physical variables, namely absorbance, fluorescence, or luminescence. They enable accelerated testing and data collection as they allow samples in multiples of 96, 384, or even 1536 to be gauged simultaneously in plates. When integrated with modular robotic systems of automation levels 5 or 6, plates can be automatically loaded and unloaded after simultaneous rapid testing, with minimal human intervention, enabling a highly efficient, continuous workflow.[9]

Furthermore, robotic arms with multiple degrees of freedom serve as the central transport modules that seamlessly connect workflow stages in a biofoundry. Degrees of freedom essentially refer to the variety of independent movements that a robotic arm can perform. In a biofoundry, ‘N’ unit operations are constrained by high degrees of freedom robots, forming N^P theoretical configurations in a workflow of P steps.[13] Thus, the increase in dynamic capability is exponential. A crucial case study to be examined is the iBioFAB (Illinois Biological Foundry for Advanced Biomanufacturing).[14] It is a successful biofoundry with over 20 specialized modules, including liquid handlers, thermal cyclers, plate readers, and incubators. The 6-degree-of-freedom robotic arm operating on a 5-meter rail is a highlight of the mechanism, demonstrating the significance of modular interconnectivity. The biofoundry has minimized costs by enabling high-volume efficiency, exemplifying the phenomenon of economies of scale. This is evidenced by the fact that it has built up to 1000 TALEN constructs per day at less than $3 each, which is a 99.7% reduction in what it might cost using manual methods.[15] Remarkably, iBioFAB has also performed multiplex genome-scale engineering of *Saccharomyces cerevisiae* in a fully automated manner, at more than 10 times the efficiency of a single person without automation.[15] (Although the throughput of a single person may not be a fair comparison.)

Key strengths of modular robotic solutions in synthetic biology

Table 1: The summary table depicts the limitations of manual workflows that modular automation addresses in a concise, tabular format.

Benefit	Automated Workflow	Manual Workflow
High Throughput	Processes many samples rapidly	Limited sample processing capacity
Reduced Manual Labour & Long-Term Cost Efficiency	Minimal hands-on effort, cost-effective over time	Labour-intensive, costs increase with scale
Scalability & Flexibility	Easily scalable and adaptable to new tasks	Difficult to scale, limited flexibility
High Precision & Replicability	Consistent, accurate, and highly reproducible	Variability due to human error

High throughput and speed:

Integrating modular robotics into synthetic biology offers the key benefit of allowing higher throughput experimentation than manual methods, accelerating the overall pace of development as seen in Table 1. In this context, high throughput refers to the ability to perform a large number of operational procedures in a shortened duration. This effect was demonstrated by Saini *et al.*, who created a platform for automating multiplex biochemical assays by incorporating integrated liquid handlers and detection modules.[4] Notably, they were able to perform the ADP-Glo assay on this platform with five 384-well microplates in 2 and a half hours, compared to the manual performance of this task, which would have taken 3-3.5 hours. This equated to a remarkable 20 - 40% improvement in cycle time.

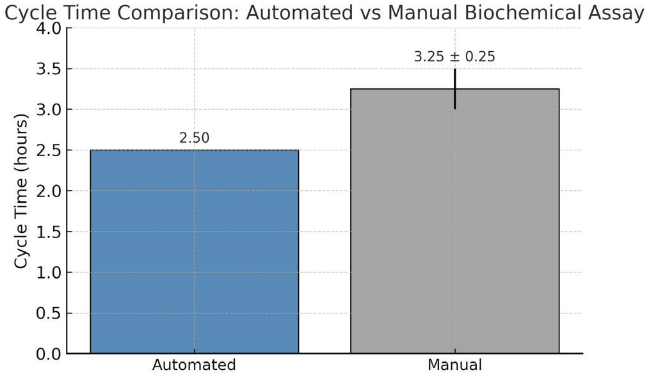

Figure 1: Bar graph depicting cycle time comparison for biochemical assays using the two methods (Data source: Saini *et al.*)

The 20-40% improvement in cycle time can be visually observed in Figure 1. Furthermore, the error bar highlights that the time taken to perform this assay using manual methods is highly variable and imprecise. This aspect will be discussed further in the paper.

One of the main reasons for this markedly higher level of efficiency when using integrated modular robots is the reduced manual interruption. Manual interruptions present two main challenges, namely cumulative delays,[4] and inconsistency; the latter will be further discussed in the paper. A study comparing the workflow efficiency and maintenance requirements for five automated clinical instruments for the diagnosis of STIs highlighted that those platforms requiring multiple manual interventions, specifically two return visits per 96-test batch, encountered close to one hour of hands-on time, which doubled for a second run and even prolonged operational work into the next work shift.[16] Such is the effect of individual delays, which accumulate over time across workflow stages, resulting in high aggregated time loss.

Moreover, advances in automated DNA assembly as a result of integration with modular infrastructure allow thousands of unique DNA fragments, such as oligonucleotides, to be assembled simultaneously, which is another key driver of high throughput in synthetic biology.[17] Thousands of unique DNA fragments can be synthesised in a single production batch, which are then transferred by liquid handling modules to genetic assembly workflows, where specific protocols like Golden Gate can be performed in parallel reaction wells.[18] The simultaneous development and testing of these genetic constructs accelerates the process by an immense order of magnitude.

Time constraints are inherent in life science experiments.[19] Another reason why modular robotic systems excel over manual methods is the potential for optimal workflow scheduling. In essence, it is the accurate execution of interconnected experimental tasks at calculated timings that is critical for the kind of precision and time constraints that synthetic biology experiments can present.[19] The time constraints caused by the duration of the interlinked experimental steps in synthetic biology are defined as time constraints by mutual boundaries (TCMBs), and they are dramatically reduced by automation.

Reduced Manual Labor and Long-term Cost Efficiency:

Another critical strength of modular robots in the "build" phase of the DBTL cycle is that they can be programmed to construct prototypes far more efficiently than manual labor counterparts.[5] Synthetic biology researchers are estimated to spend more than 50% of their working time in constructing DNA molecules,[20] demonstrating a highly inefficient use of skilled human capital. Integrating modular robotics into biofoundries allows these highly qualified researchers to focus more on the analytic aspects of the cycle,[20] namely 'Design' and 'Learn' phases, whereas specialized robots can focus on efficiently carrying out the 'Build' and 'Test' phases.

Economies of scale are an economic phenomenon observed when the per-unit production cost falls, as a result of increased production (efficiency). In the context of synthetic biology, it is observed that when automated biofoundries improve productivity, allowing more constructs to be built in less time without increasing proportional labour costs.[21] The DNA-BOT, developed by researchers in Imperial College London, is an economically viable, automated DNA assembly platform, showcasing this effect.[21] The researchers assessed its operation by assembling 88 simple genetic constructs. The result was an impressively low cost of \$1.50 - \$5.50 (which is an estimation) per construct, while maintaining high accuracy. This resulted from using significantly cheaper open-source hardware (Opentrons OT-2 liquid handler), running at reduced volumes for efficiency (at the scale of μLs), and parallel processing of multiple batches, in a 96 plate well format, which would not have been possible with conventional manual methods.

Scalability and flexibility:

The need for seamless scaling of development and testing according to emerging requirements is critical in synthetic biology, which modular robots can critically address. A paramount example is the high-throughput, automated SARS-CoV-2 testing platform developed by Michael *et al.* during the peak of the COVID-19 pandemic.[6] The team implemented a full-cycle automated workflow for SARS-CoV-2 RNA detection from patient samples. This included robotic liquid handlers for sample processing and automated platforms for RT-qPCR, RT-LAMP, and CRISPR-Cas13a assays. It was a potent solution to address the rapid surge in demand for SARS-CoV-2 testing at the time. The modular design allowed for easy expansion of capacity by adding more robotic units, based on ever-changing requirements. The platform was installed in NHS diagnostic laboratories, which increased testing volume by a significant 1,000 samples per day. For context, the average turnaround time for processing 94 samples manually is approximately 2 hours and 28 minutes.[6] Even assuming manual testing could be conducted 24 hours a day at this rate, the modular system would still be able to sample roughly 9.3% more per day than manual screening, demonstrating a radically higher processing rate, driven primarily by the scaling of modules.

Additionally, the study also specifically emphasized the need for diagnostic test workflows to "be open and modular". This was because modular automation platforms allow for flexibility between different reagents and protocols depending on availability, and, during that time period, certain testing reagents were scarce due to very high demand.[6]

A further strength of modular robotic systems is the ability to be easily reprogrammed and physically reconfigured to meet the specifications of new protocols or tasks. Leading synthetic biology corporations, like Ginkgo Bioworks®, have leveraged this property of modular robots to sustain a business model where bespoke organisms or enzymes can be engineered for applications specific to a client firm[22] (formally known as cloud laboratories)[15].

High precision and replicability:

Synthetic biology constructs are designed for specific real-world functions that must work consistently under replicable conditions. If results vary unpredictably, bioengineered systems may fail in real-world applications, leading to serious concerns about safety and financial losses.[23] Therefore, replicability is imperative in synthetic biology. A meta-analysis revealed that upwards of 50% of preclinical life sciences research is effectively irreproducible, in turn causing almost $28 billion dollars' worth of losses in the US alone.[24] Poor reproducibility would mean that promising research could not translate into real-world impact, significantly inhibiting progress in the field.[25]

In genetic circuits, the intended functions inscribed by sequences aligned on a DNA molecule depend on two factors, namely their precise ordering and the specific structural interactions between them.[26] Thereby, undesired molecular interactions can occur because of the inherently necessary spatial micro-clustering of synthetic components, which can compromise their whole function.[26] Hence, there is an enhanced requirement for precision in synthetic biology, more so than in other fields.

Modular robots excel at performing iterative cycles, whilst ensuring they are performed at consistently standardised conditions.[27] Recently, this was demonstrated by RoboCulture, a fully automated modular robotic platform, which performed an autonomous 15-hour-long yeast culture experiment.[28] It used a vision and force feedback, and a modular behavior tree framework to monitor and execute experimental steps. Real-time decisions were made autonomously, strictly using definitive optical feedback set points. This framework ensured that each experimental step was performed exactly the same way across runs, elevating the consistency of results.

The iGEM Interlab Study conducted in 2016 is an organized multi-lab analysis involving over 70 participating teams globally to investigate the experimental precision of fluorescent protein expression measurements from standardized genetically engineered *E. coli* constructs, with each team using a standardised method and base materials.[29] It was found that 17% of data points were outliers, and that the imprecision of generating reliable data in synthetic biology is largely due to the measurement variability between the researchers handling the instruments. The study also emphasizes that automating laboratory protocols using robotics would advance precision and consistency in synthetic biology, just as it has done so in other emerging fields.[29]

Addressing Integration and Data Processing as Primary Limitations

Among the several limitations of implementing modular robotic systems in synthetic biology, two limitations consistently emerge as the most significant:

i. the difficulty of achieving seamless hardware–software integration across heterogeneous modules,

ii. and the need for high-volume data processing for effective DBTL learning.

Achieving seamless hardware-software integration is critical for reducing systematic errors, along with enhancing reproducibility and scalability of the cycle. Digital biofoundry instruments, such as incubators and sequencers, tend to use discrete and vendor-specific APIs, command protocols, and data formats.[30] This makes it tedious to unify workflow hardware and software components efficiently and without errors. Attempts to address this bottleneck involve the implementation of an "orchestrator,"[30] which is an independent software infrastructure that commands robotic devices, continuously monitors execution, and validates data flows, unifying this layer with heterogeneous hardware modules. Interface standardization could also likely tackle this hurdle.[31] Kim *et al.* propose a structural framework enabling interface standardization by separating the biological design plan from device control and creating common unit operations that independent hardware modules can map to (known as the abstraction hierarchy).[31] This is achieved by a simplified four-level framework that decomposes overall design goals to standard device steps, therefore reducing the need for bespoke interfaces.

The implementation of modular robotics enables accelerated iteration in the design, build, and test phases of the cycle; however, a key limitation remains in the high-volume data processing and analytics needed to complete the "Learn" stage of the cycle.[30] Actionable design improvements from huge datasets need to be learnt and implemented efficiently to close the loop, as it is an iterative cycle.[32] Recent work on biofoundry orchestration[30] and abstraction hierarchy[31] has highlighted that, without significant computational and informatic advancements, the Learn phase becomes a rate-limiting factor despite rapid throughput. It is inherently the weakest supported step of the cycle, because of the tendency to be non-systematic.31 Modern machine learning advancements are increasingly addressing this concern. For example, Automated Recommendation Tool (ART)[32] is a machine learning tool that uses probabilistic modelling techniques to guide quick and relatively more accurate, synthetic biology design iterations in each cycle. Another key advantage of this tool is that it also quantifies uncertainty in a particular design iteration by showing a full probability distribution for the expected response. This could potentially be transformative as data is expensive to collect, and a success probability is shown to drive researchers' decisions.

Conclusion

As exemplified by experiments like TALEN genetic constructs in iBioFAB developed at a staggering 99.7% reduced cost, modular robotics progress presents a paradigm shift for synthetic biology, enabling radically higher efficiency than before. Historically, significant advancements in any engineering discipline, be it electronic engineering, computer science, or others, have been driven by breakthroughs that enable rapid prototyping and testing. Evidently, modular robotics presents such a breakthrough for synthetic biology. Continual progress in the field of robotics, owing to the progression described by Moore's Law, has developed their capabilities enough to tap into the previously inaccessible bio-molecular scale. With the successful integration of advanced Artificial Intelligence (AI) and Machine Learning (ML) in modular robotics, even the "Design" and "Learn" phases of the DBTL cycle can be significantly advanced, leading to true automation in this field. This will enable synthetic biology to reach its promised potential.

Evidently, the 4 primary advantages of implementing modular robotics in synthetic biology, namely higher throughput, cost efficiency, precision, and flexibility, are not only separate benefits in this process, but also mutually reinforcing. The advantages are complementary to each other, creating a potent reinforcing cycle, substantially driving progress in this field. Further research must focus on addressing comprehensive AI and ML integration into biofoundry automation, more robust modular component standardisation (both hardware and software), and efficient data processing infrastructures to fully enable closed-loop automation of the DBTL cycle in synthetic biology.

■ Acknowledgments

I want to thank Dr. Devin Carroll and the Indigo research team for helping me refine my research paper and being my mentors throughout this writing process. I attest that the ideas, writing, and graphics in this paper are entirely my own.

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