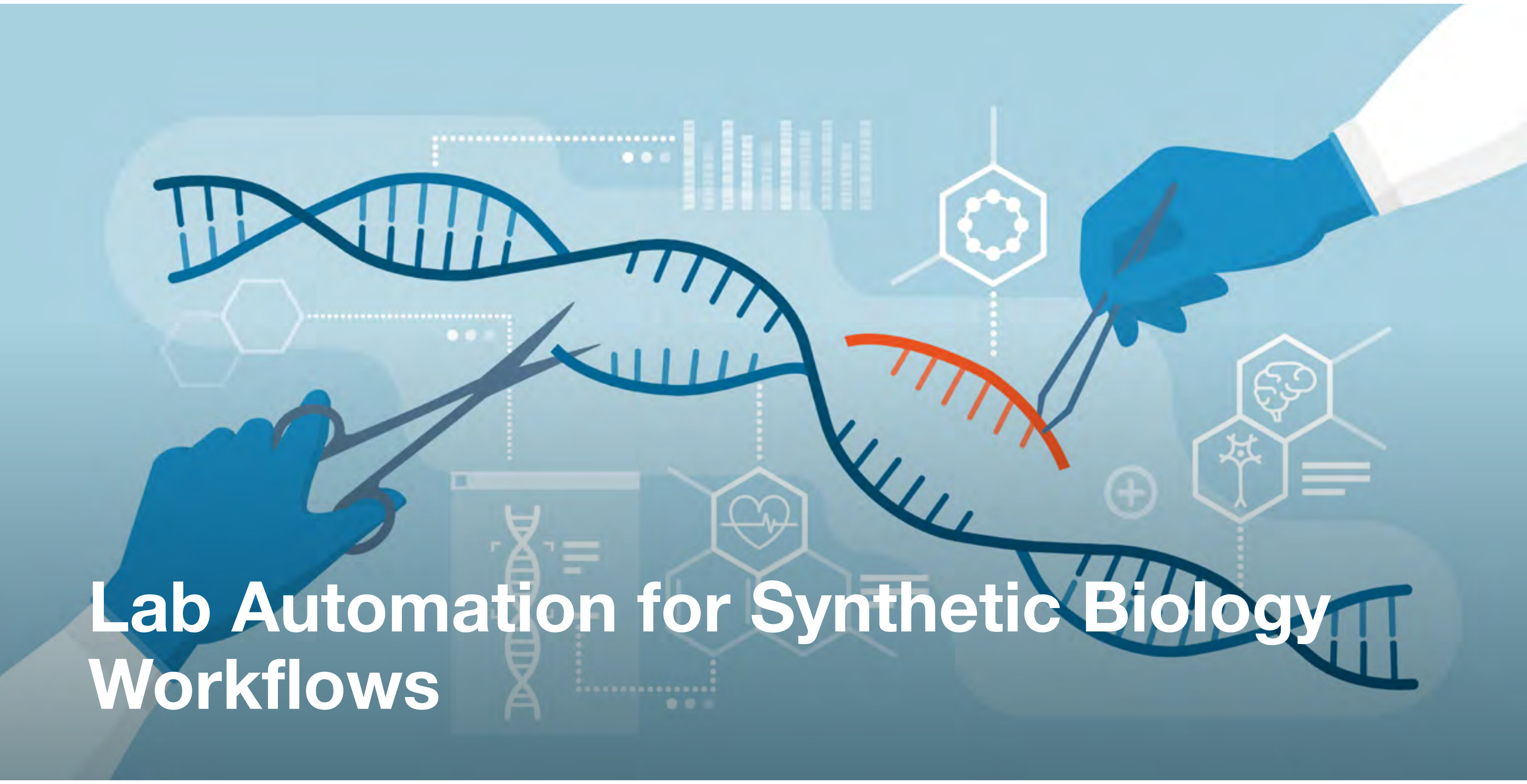

Lab Automation for Synthetic Biology Workflows

Synthetic biology is an exciting field that aims to build novel biological entities and redesign existing biological systems by applying principles of design and engineering. Mirroring how work is completed in engineering, synthetic biologists look to meet specific performance criteria for their engineered systems through the design and assembly of core components. For synthetic biologists, these core components can include elements like genetic circuits, metabolic pathways, and enzymes. Unlike traditional engineering fields, which are commonly more linear and predictable, synthetic biologists face challenges due to the complexity and limited understanding of biological systems. Hence, their research process often involves multiple design, build, test, and learn (DBTL) cycles.

Despite how complex and unpredictable biological systems are, the workflows common to researching these systems, such as building and testing plasmids or building genomes, are generally standard and repetitive. This combination of unpredictable science with standard and repetitive workflows and unpredictable outcomes can make research laborious, low throughput, and expensive. These challenges make synthetic biology a field prone to and fit for laboratory automation.

Laboratory automation can directly address these challenges as it is proven to reduce human errors as well as increase the speed, precision, and accuracy of experiments. Laboratory automation also increases the variety and number of experiments that can be completed simultaneously.[1,2] Considering the advantages that lab automation has delivered in these core areas of research, synthetic biology and lab automation are natural partners with successes having been demonstrated by early adopters.

In this article, we discuss lab automation in the context of the DBTL workflow and explore how researchers at biofoundries are currently applying lab automation to accomplish their goals. We will also highlight the latest innovative lab automation options that can be applied to common workflows in the synthetic biology lab for optimization of the DBTL cycle.

Laboratory automation and the DBTL workflow

Laboratory automation, defined as the use of largely autonomous and reprogrammable equipment, has not surprisingly been limited to associations with physical hardware such as robotic movers, platforms, and devices. In the laboratory, increasing capabilities related to automated sample management, machine learning (ML), and artificial intelligence (AI) has started to shift this hardware centric view to a more holistic view which incorporates both hardware and software.

For synthetic biology, adopting this view brings tremendous advantages for successful implementations of the DBTL cycle. This paradigm shift allows researchers to not only look for integrated devices that can be used for building and testing, but also a complimentary software suite for designing and learning. In summary, automated sample management and AI/ML techniques enable systems to analyse, learn, and improve whereas lab automation hardware generates the high-quality, repeatable, unbiased data required to successfully train these systems.[3]

Researchers who have been successful with this approach have published powerful articles demonstrating these benefits. For example, Hamedi Rad *et al*. have conducted ground-breaking proof of concept work on the lycopene biosynthetic pathway to demonstrate full automation of the DBTL process for biosystems design. Their BioAutomata platform designed and executed experiments as well as conducted data analysis to optimize this pathway in an iterative manner. Through ML a mutant was identified which produced a 1.77-fold higher lycopene titre than the best mutant found from random sampling. Advantageously, this demonstrated how ML is not biased, and a system connected to the web of knowledge may be able to learn from published data in real-time.[4]

How biofoundries are implementing automation for their synthetic biology needs

Over the past years, research institutions have been establishing core laboratories or biofoundries to expand their biotechnology and synthetic biology development capabilities.[5,6] These biofoundries are diverse and can have multiple specialities. For example, genome foundries can build DNA or genetically reprogram organisms for academia as well as help industry with research and development and production. As a result of this diversity,

Figure 1: The Thermo Scientific™ inSPIRE™ Platform at the Concordia Genome Foundry in Montreal, QC. Canada © Concordia University, photos by Marc Bourcier.

groups such as SynBioBeta and the Global Biofoundry Alliance have formed to create an innovation network of researchers sharing a passion for synthetic biology as well as coordinate activities worldwide.[5]

Biofoundries are typically extensively automated and can carry out a range of functions needed for bioengineering and synthetic biology. Their automated facilities are usually highly flexible and can be used for a variety of workflows such as, but not limited to, extracting DNA, manipulating DNA, vector assembly, transformation and plating of bacteria or yeast, fragment analysis, colony PCR, PCR and qPCR, and colony picking.

For instance, the Concordia Genome Foundry has extensively implemented robotic instrumentation through adopting a configurable and compact infrastructure. One of the innovative platforms selected by the Concordia Genome Foundry for automating their workflows is the Thermo Scientific™ inSPIRE™ Collaborative Laboratory Automation Platform (Figure 1).[1,7] The Concordia Genome Foundry leverages their highly automated research platform for DNA assembly techniques including Golden Gate assembly, CRISPR/Cas9, and yeast recombination. They also provide RNA-Seq library preparation for Next Generation Sequencing. By automating notoriously labour-intensive lab procedures, the Genome Foundry has been able to eliminate bottlenecks in their research cycles.

Other foundries such as the Edinburgh Genome Foundry and Illinois Biological Foundry have implemented large automated systems that span an entire room. These highly automated platforms also provided by Thermo Fisher Scientific feature 6-degree-freedom articulated robotic arms and tracks to transfer microplates among more than 20 instruments integrated on the platform. These sorts of larger systems can be used to rapidly assemble DNA and offer the wide range of protocols mentioned above as a service.

Overall, the diversity of equipment used in these biofoundries can range from small to large fully automated systems depending on the research goals and workflows. For example, large liquid handling devices are commonly viewed as the workhorses of automation as they are well suited to address some processes and workflows. However, to create an unattended fully automated operation of a complete workflow, a robotic arm can be used to integrate this liquid handler with centrifuges, labellers, reagent dispensers, thermal cyclers, microplate heat sealers, plate seal removers, and shakers. Ultimately, the best implementation comes down to how a researcher would define their success.

Choosing the right hardware and software to automate the DBTL cycle, in your synthetic biology lab

While many biofoundries have successfully automated their workflows, there are naturally many considerations that need to be made before making this investment. To evaluate what would be the right hardware and software solution, one question that may be worth asking is: "What technologies have other synthetic biology researchers been successfully using?" Here, we highlight some of the latest automation technologies that researchers are using in this field provided by Thermo Fisher Scientific.

Thermo Scientific inSPIRE Platform

Figure 2: The Thermo Scientific™ inSPIRE™ platform integrated with various instruments including the Thermo Scientific™ Cytomat™ Automated Incubator Series. These instruments are placed on tables, platforms, and shelves integrated around the central frame containing the Thermo Scientific™ Spinnaker™ XT Microplate Robot and controlled by the Thermo Scientific ™ Momentum ™ Workflow Scheduling Software.

The inSPIRE platform (Figure 2) is the world's first collaborative laboratory automation platform. This platform provides an interactive, intuitive, and easy to use solution recommended for automating synthetic biology workflows, especially for researchers looking for a compact and configurable solution. In the synthetic biology space, this platform, is currently being used to automate processes such as (but not limited to) vector assembly, colony PCR and QA/QC steps.

The compact and vertical orientation of the platform allows for a space conscious and flexible solution. The platform consists of a central frame with the Thermo Scientific™ Spinnaker™ XT robot as the mover for transferring samples between instrumentation. The Spinnaker XT coupled with the powerful Thermo Scientific™ Momentum™ software has made the inSPIRE platform a dependable lab automation solution. The central frame with the Spinnaker XT at the core supports the configurable infrastructure of the inSPIRE platform allowing a variety of instruments to be easily accommodated around the central frame. An extensive catalogue of modular components allows researchers to build the best solution for their workflows, simplifying the process from a complex manual protocol to automated workflows. These hardware components are discussed in detail below.

Thermo Scientific SmartShelf

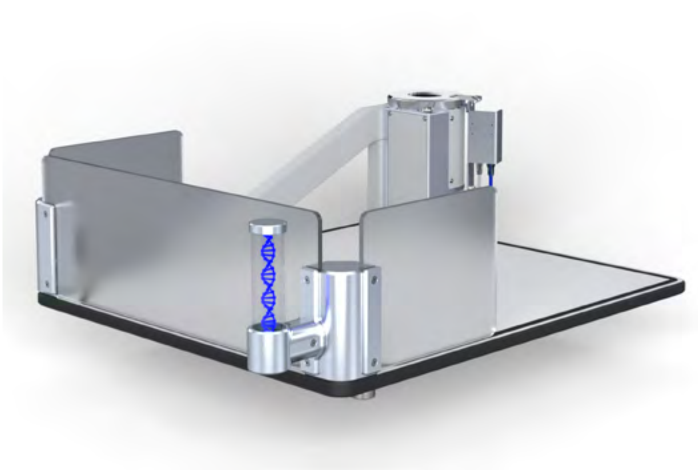

Figure 3: The Thermo Scientific™ SmartShelf can support devices of up to 110 lb/50 kg and contains built-in power and communication ports.

A catalogue of tables, platforms, SmartSlides, SmartShelves, and accessories can be selected to allow scientists to configure the right end-to-end solution required for their automated workflow. Some of these configurable components such as the SmartShelf (Figure 3) leverage SmartHandle technology. This provides an 'at-a-glance' health status indication for each instrument, along with touch control for easy instrument access. This allows researchers to access an instrument for manual use and just as easily return it to the automated system when done. It is a useful feature when high value instruments need to be "shared" between the automated system and researcher for manual work.

Thermo Scientific Spinnaker XT Robot

Figure 4: The Thermo Scientific™ Spinnaker™ XT robot is the central mover to the inSPIRE platform, and it is responsible for microplate transportation between all instruments on the system.

The Spinnaker XT robot is a one-of-a-kind 4-axis SCARA robot, with an integrated camera that allows for a simple vision-based teaching method, self-correcting capabilities, and powerful sample tracking (Figure 4). The robot's height, as well as infinite rotation, enables access to an expansive workspace. It also provides user-friendly features such as flexible plate handling, an integrated regrip station, de-lidding and built-in error recovery. These are a few of the many features which combine to make the Spinnaker XT robot a precise and reliable option for researchers looking to automate a range of instruments.

Thermo Scientific Cytomat Incubators

Figure 5: The Thermo Scientific™ Cytomat™ 2 C-LiN Series is a mid-capacity incubator that couples automated plate handling with an ideal storage and incubation environment for various cell lines (mammalian, yeast, bacterial etc.).

With more than 50 years of experience in CO_2 incubator technology, the Cytomat series ensures a safe and reproducible process through unsurpassed temperature uniformity and stability. It is designed for fast and flexible integration compatible with a wide variety of cell types and different plate capacities. The robot accessible Cytomat series has features such as precise humidity control, expanded temperature range, automated decontamination routine, TRUE orbital shaking and CO_2 Control to support high capacity and quality cell growth. All in all, these features make Cytomat the ideal solution for your automated incubation needs when designing and testing in synthetic biology.

Thermo Scientific Momentum Software

Figure 6: The dashboard interface to the Thermo Scientific™ Momentum™ Workflow Scheduling software. Momentum has two interfaces: the general interface for accessing the full scope of features in a format suitable for complex tasks and the dashboard interface for a simplified and streamlined display.

The Momentum software is built on 20 years of proven success in system integration automation providing researchers with an easy to use and powerful dynamic scheduling software (Figure 5). Synthetic biologists who have selected Thermo Fisher Scientific automation for their workflows use the Momentum software to run their system. This software provides a dynamic and intuitive solution featuring drag and drop process creation and event-driven scheduling as well as capability to support more than 350 instruments.

The latest version of the Momentum software enables connections between your lab automation and a larger digital ecosystem. This includes a Unite module and RESTful API. Unite connects Momentum to external applications, such as LIMS (laboratory information management systems), ELNs (electronic laboratory notebooks), and other platforms to extract, use, duplicate, manipulate, format and store data. In addition, the RESTful API enables third-party applications to request work and query the status of various containers. These links can support the integration of various AI and ML tools and can assist with closing the loop in the DBTL cycle.

In conclusion, with the range of options available, automating your synthetic biology workflow has never been easier. Researchers can either automate their laboratories or use the services available in biofoundries to assist with building novel biological entities or redesigning existing biological systems. As a result, synthetic biology is a rapidly evolving field leading the way in innovation with the help of automation at every step of the DBTL cycle.

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