With all due Maholo, Lab Automation isn’t anthropomorphic

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To the Editor:

Biosciences journals often require rigorous statistical evidence for the data presented, because a substantial proportion of the biosciences literature is not reproducible (http://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970). Yachie et al. propose that LabDroids could form part of a robotic infrastructure that might contribute to improved reproducibility\(^2\). However, reproducible research might be more readily enabled by existing and new low cost automation technologies applied in both individual research groups and centralized DNA Foundries which could be accessible across ‘the cloud’.

Most bioscience experiments move small amounts of liquid from one place to another in such a way that an effect can be measured. Scientists use tools such as adjustable micro pipettes, first launched by Eppendorf in 1961, to move liquids down to the microliter range. Based on similar principles, automated technologies were developed to enable this at higher throughput, driven primarily by the pharmaceutical industry’s desire to screen large chemical libraries for drug leads. The Biomek 1000 tip based liquid handler system was introduced in 1986, and allowed protocols to be programmed so that liquids could be moved around a robot deck depending on the application. Such systems require disposable tips and direct manipulation, but it had been known since the 1920s\(^3\) that a high power acoustic source could eject droplets. The principle was commercialised in instruments such as the Labcyte Echo (first released in 2003), which could reliably transfer 2.5nl droplets at high speed without tips or direct contact with the liquid. Further scaling up was simultaneously enabled by the introduction of 96 (first released by Dynex in 1965), 384 and 1536 well microplates under the same footprint, a standard now known as the ANSI/SLAS standard\(^3\).

Since the tools for automated research are in place, why have most molecular and cellular biology labs resisted the use of automated workflows? Effective automation requires both skills and compromises in approach in order to achieve scalable and reproducible processes. For automation engineers engaged in developing solutions, there are a number of challenges. Firstly, the need to translate existing assays and protocols from tubes (usually eppendorfs) to a microplate format, in a way that not only works, but saves time and is scalable. The ‘rules’ scientists learn when using human-friendly tools in the ‘wetlab’ often do not apply to automation problem solving, as developing an assay using nanoliter droplets in 1536 plates requires a different approach in for example mixing reagents in a well, which may be better executed by a centrifuge rather than repeated aspiration and dispense.

Whilst one could adopt LabDroids as proposed by Yachie et al\(^1\), we argue that the humanoid approach makes an assumption that human useable tools are an optimum solution, and ignores the extensive development of high throughput methods, liquid handling and integrated instrument technologies that can look very different (for instance the Agilent Vspin automated centrifuge is entirely controlled by software) and in some cases leading to methods that would be impossible to do by hand. By focussing on the approach, rather than the optimum way to obtain the same set of data, Yachie et al\(^1\) cannot take advantage of the parallelisation and throughput benefits of redesigning an assay around high density microplates using equipment designed for that purpose. In some cases, not every step of a process is required, or a step can be improved or changed in order to be effective in automated workcells using microplates. Areas of molecular biology that required extensive use of automation was the human genome project in for example large numbers of Solid-Phase Reversible Immobilization (SPRI) processes\(^4\) and such an approach continues into advances in NGS, particularly at the Sanger Institute-EBI Single-Cell Genomics Centre reducing the cost and throughput of the tagmentation reaction for kits such as Nextera (Illumina). Another area is in image based high-content screening (HCS) of biological systems and cells where many properties of individual cells or organisms
can be studied simultaneously. This lead to the development of automated digital microscopy systems and flow cytometry in combination with integrated computer systems for analysis and storage of data. Such systems have been used to carry out chemical genetics and RNAi screens to study many areas of cell biology.

Automation could benefit synthetic biology as the Design-Build-Test-Learn (DBTL) requirements to engineer for example metabolic pathways, assemble and test synthetic genomes or construct new logic-based sensing circuits requires multiple iterations, design of experiments and large amounts of data that is both difficult to manage while requiring the accurate dispensing of combinations of large sets of particular elements at low volumes. An algorithmic approach to programmatically defining the build instructions based on computer aided design opens up the possibility of scale at an unprecedented level. For example, one workflow for BASIC DNA assembly can produce 5,000 to 10,000 constructs per run in our Foundry. Even a small 459 plasmid construction study requires 8097 individual low volume transfers. For an expert ‘wetlab’ researcher (assuming 30s per liquid transfer and no human error) this would take ~68 hours of continuous pipetting work which is unrealistic. By creating such platforms, researchers can focus on developing more creative experiments rather than being constrained by what can be done using manual labour. Given that the DBTL engineering framework is central to synthetic biology, there is also an absolute requirement for robust and reproducible measurements that can inform computational models to guide the design process. Multiple measurements and HT approaches therefore accelerates the design cycle by allowing a broad exploration of the biological design space as well as producing highly reproducible and standardized measurements upon which design decisions are based.

The London DNA Foundry has been established at Imperial College to utilise mature High-Throughput-Screening (HTS) liquid handling technology and apply it to a range of high throughput molecular biology applications required for synthetic biology. We took further inspiration from HTS when designing our automation, as it became apparent in recent years that the pharmaceutical industry preferred smaller more focussed flexible HT workcells rather than single fully-integrated automation systems, with the smaller workcells running automated or semi-automated HT assays. The Edinburgh Genome Foundry has developed a large integrated system for genome scale assembly and testing but with the possibility of running parts of their system independently, whilst the MIT-Broad Foundry have developed highly modular workflows for DNA part assembly, testing and prototyping. The growing establishment of centralized DNA Foundries worldwide is also leading to the development of automation processes and computational tools that can be utilized by researchers in small molecular and cellular biology labs.

The Maholo robot offers another way to reduce labour and increase reproducibility. Maholo is an engineering and technical feat but its development assumes that using human–friendly hand tools is the optimal way to carry out experiments. Maholo can skilfully pick up an Eppendorf tube, open it and use a pipette to manipulate liquid. A non-humanoid robot automated process would use a 384-well microtitre plate (equivalent to an Eppendorf tube), de-peeler (e.g. brooks x-peel – equivalent to opening the eppendorf), a plate sealer (e.g. Agilent plate loc – equivalent to closing the eppendorf) and manipulation using a liquid handling robot (e.g. cybio felix – equivalent to the pipette). Both methods produce the same result but redefining the process using microplates, rather than recreating how things could be done by hand, enables multiple experiments to be carried out (384/1536) in parallel.

Laboratory automation has matured over the past 30 years to solve specific problems, including high-throughput screening for drugs through to the synthesis of genetic pathways and construction of genomes for synthetic biology. Such automation systems carry out experiments in efficient ways that do not mimic human movements. Creating an anthropomorphic robot to automate
laboratory techniques seems to provide a solution to a problem that has already mainly been solved by liquid handling automation platforms that provide robust assays and measurement systems worldwide. What we need now is to alter our perception of automation by providing accessible, open source and inexpensive hardware solutions to routine ‘wetlab’ protocols and assay measurements. We think it is more feasible to begin the detailed open sharing of protocol methods, rather than the downloading and execution of ‘cloud sourced protocols’ as suggested by Yachie et al, as different workcell integrations and differing liquid handling capabilities may mean that alternate approaches have to be explored. However, by using a precise ontology to describe standardized protocols for routine and where appropriate complex measurements, the results of developments can be interpreted and shared leading to the creation of community standards and norms for molecular, cellular and synthetic biology. Ultimately such processes could be carried out remotely in ‘cloud-based’ labs where experimental designs can be sent to distributed foundries and the resulting data returned to the researcher, but care has to be taken to learn from existing automation approaches - avoid trying to recreate a manual method while understanding differing workcell capabilities. Such models are beginning to be developed with start-up companies like Emerald Cloud, Synthace and Transcriptic leading such developments. We envisage a future where there is a mix of routine and low cost automation workcells in individual research labs or clusters of co-located labs and ‘cloud-based’ distributed Foundries where more complex experimental workflows can be executed across the cloud. This mixed ‘economy’ will accelerate the development and sharing of standardized protocols and metrology standards and move molecular, cellular and synthetic biology into a fully quantitative and reproducible era.

References

1. Yachie et al. Robotic Crowd Biology with LabDroids NBT (reference to be finalized)