Addressing the challenges of the reproducibility crisis with improved automation and protocol sharing

Nigel Skinner, Andrew Alliance

A few years ago, the US$1.6-million Reproducibility Project: Cancer Biology set out to repeat key experiments from 50 high-profile cancer papers, and so assess the extent to which published results can be replicated. The project ended up stopping at 18 papers.

The reasons were varied but, importantly, included concerns over the reproducibility of experimental methods, as well as the ability to reproduce an experimental protocol based upon what had been disseminated in a peer reviewed scholarly publication. This article will discuss solutions that address both of these important shortcomings, through recent developments in laboratory automation and software.

Many research workflows in the life sciences that are used to better understand disease biology, as well as identify new targets for drugs, are highly dependent on a precise and reproducible preparation of sample to be analysed. This often involves some combination of weighing, shaking, heating, cooling, separation, purification, and, of course, liquid handling, which still often involves the manual pipette.

Automation of Liquid Handling

Pipetting is a frequent practice in laboratories conducting a wider range of biological and chemical assays. Indeed, it is one of the workhorses of the lab and a core skill for many scientists. For example, in drug discovery, IC50 assays, commonly used to evaluate drug efficacy, and assay development procedures as well as standard-curve generation involve the serial dilution of compounds, proteins, or detection agents. These processes can be streamlined by utilising automated liquid handling equipment with serial dilution capabilities, addressing two common workflow challenges: error propagation across the columns or rows of a microtitre plate due to transfer inaccuracies that lead to less accurate and less precise dispensing; and the risk of error in the calculation of serial dilutions themselves.

This is all well and good but any automation solutions on the market have been developed for high throughput liquid handling, are specific to a limited range of applications, and are pried beyond the budget of many research laboratories who cannot justify investment in automation for lower throughput liquid handling despite unquestionable improvements in reproducibility of the liquid handling steps in their workflow. This is especially the case if the 'solution' cannot be readily adapted to different workflows unless the researcher is well versed in Python or C++, as well as being willing to invest the time in reprogramming their lab automation or hire a programmer, and that is assuming that it can even be reprogrammed, i.e. is an 'open' vs 'closed' lab automation solution. Moreover, unlike many 'ideal' lab bench set-ups in trade shows, reality is usually very different, with the modern lab being increasingly 'rented', space constrained and it has become more important than ever that an automation solution be readily adaptable to different researcher workflows rather than the other way around, most especially in the earlier stages of research. Fitting a rectangular 'box' into a space under a laminar flow hood is rather like trying to fit a 'square peg into a round hole'.

Do you feel in control of your lab automation.. or is it controlling you.. or is it parked in the corner of the lab doing nothing at all?

The answer to this question likely explains why many laboratories still rely on manual operations to perform tasks, especially when it comes to liquid handling. Fully automated workflows have been achieved in the field of clinical diagnostics, but the same can't be said for research, due to the flexibility and continuous workflow changes required.

Andrew Alliance has addressed this need in its recent launch of the award-winning Andrew+ robot that is capable not only of automating liquid handling but the manipulation of labware crucial to sample management inherent to many research workflows. The robot is managed by its state-of-the art browser-based software called OneLab which allows the researcher to not only retain control of their workflow but readily adapt the pipetting robot to a wide range of other workflows using Andrew Alliance Domino accessories, thus making optimal use of space, resources and funding. OneLab requires zero programming know-how. Pick up your tablet or laptop, drag and drop the labware you require, volumes to be aspirated/dispensed, calculate your serial dilution in a way that is both highly visual, easily shared with other researchers, and even fun.. and you are ready to go!

This is just part of the story.. two-way communication with Bluetooth pipettes means that each step in the execution of your protocol is recorded along with the calibration data of the pipette itself. This ensures full traceability as well as a high degree of quality control, especially important if you want to automate costly and complex liquid handling steps associated with qPCR or NGS. In a simple qPCR experiment, typical pipetting errors with a standard, routinely calibrated pipette, can result in DNA copy numbers varying by as much as 3%. Imagine the impact of that on the results of an important translation biology experiment, or in a regulated diagnostic laboratory!

The Andrew+ itself is based upon the multi-award winning, highly successful, Andrew Pipetting Robot, launched in 2013 and used in many laboratories around the world. It offers fully automated pipetting, as well as more complex manipulations, using a wide range of accessories and Andrew Alliance electronic pipettes. Significantly, compared to its predecessor, it hosts 8 and 12 channel pipettes enabling much larger volumes to be dispensed far more quickly. This is a significant advantage, for example in qPCR and NGS workflows. It is a complete 'redesign' with the '+' referring to the fact that it is a fully 'connected' device, able to communicate with both OneLab, by ethernet or Wi-Fi, from which is receives step by step guidance of each step of a given protocol; and with the electronic pipettes themselves, by Bluetooth. This communication is two-way, with instructions being passed from OneLab to Andrew+, which ensures the remote programming of the pipettes, and back from the pipettes to OneLab, meaning that each step if being fully recorded.

The electronic pipettes comprise a full range of single and multichannel versions, dispensing volumes ranging from 0.2 ml to 10 mL. They are manufactured by Sartorius in Kajaani, Finland, and based on its market leading high performance Picus design. These are branded Andrew Alliance as they have been co-developed with Andrew Alliance so that they can work with OneLab. The pipettes are automatically paired with OneLab via special adapter on the rack to which they are mounted, and this process does not require any user intervention at all.

Andrew+ has a highly flexible workspace. It is modular thanks to the use of Dominos. A simple experiment requires only 2 Dominos whereas Andrew+ could manage up to 11 Dominos for more complex experiments. The system has been designed to fit the majority of laboratory hoods. Andrew+ with 2 full rows of Dominos occupies a depth of ~60cm/24", which would be viable for even the most challenging of hoods.

The robot is designed for indoor use. It can be used in temperatures between 0°C to 30°C, with a maximum relative humidity of no more than 80%, and for an altitude of up to 2000 meters. It is safe to be used on an open bench thanks to force detection and the motors not needing to be powerful.

Simplifying the Creation and Sharing of Protocols

One big reason why the Reproducibility Project: Cancer Biology project was stopped after just 18 papers, was the difficulty of working out what exactly was done in the original experiments. Protocols - precise step-by-step recipes for repeating experiments - are missing from published research more often than not, and even the original researchers can have trouble pinpointing particulars years later.

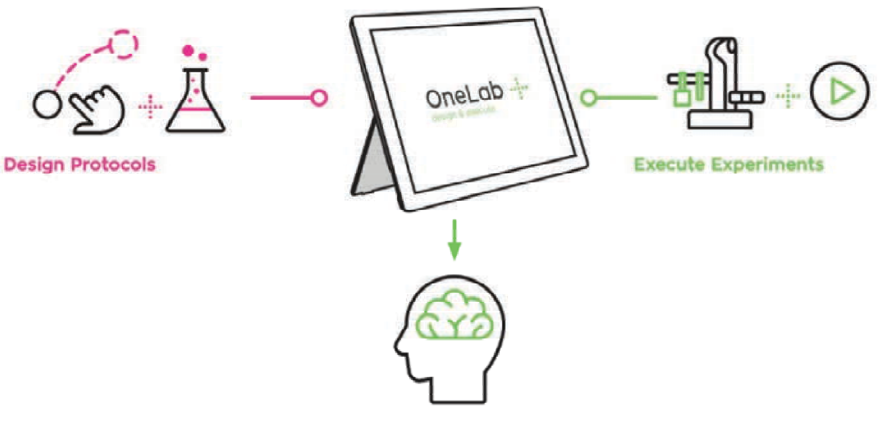
Of course, repeating the step-by-step execution of an experiment is never easy. Firstly, you need to extract the details from another researcher's published work, which hopefully shares everything you need to know in its 'methods and materials' section. Then you have to assume that any differences in labware used (e.g. purchasing a microtitre plate or pipette from one vendor vs another will not result in differences to experimental outcome). But, unfortunately, it still requires on a degree of 'interpretation' and the way in which a particular step is implemented by the researcher. Take the workhorse of the life science lab, the pipette: can we assume that every researcher uses a pipette in exactly the same way? The answer is, 'no', we absolutely cannot. What we can do, however, is to take advantage of mobile-friendly, web-based technology, in order to minimise the risk of such errors, and usher in an era of more-efficient, more-confident science.

My own obsession with sharing methods derives from an all-too-common frustration during my PhD. I spent 1 whole year (the first of 3) and all the (limited) funding associated with repeating a technique developed by a previous student, upon which an important part of my research was based. Imagine electrochemically immobilising an enzyme in an electroactive polymer subject to precise control of pH and enzyme activity whilst trying to ensure accurate and repetitive dispensing of the correct microliter volume of a reagent used for doping that same polymer. I'm sure you get the point. Not easy, especially when the required level of detail had not been fully committed to paper and the individual had moved to another country to pursue a Post-Doc!

The advancement of science critically depends upon the ability of the researcher to execute a specific protocol, in order to test a hypothesis, and other researchers to be able to repeat it and observe the same results. Errors in the execution of an experiment waste valuable time and resources. Worse still, they may go undetected by the peer review process, potentially wasting the time and funding of other research groups, and ultimately damage the reputation of the researcher.

In February 2019, Andrew Alliance launched a unique browser-based intelligent software environment enabling researchers to design, and share, their own protocols, through a highly intuitive graphical interface that can then be executed step-by-step, from any PC or tablet.

Imagine being able to set up each step of your serial dilution on an iPad, including all the required labware and reagents, and then execute your experiment either automatically on a pipetting robot, or semi-automatically, by remotely setting up the required volumes on an electronic pipette, rather than having to input them yourself – tiny buttons can be fiddly with gloved hands, and small displays awkward to read!



Of course, pipetting is just one, albeit highly important, step in a life science experiment workflow. There are others (grabbing, heating, shaking, weighing, and so on) which is why Andrew Alliance is working with partners to expand its offering of connected devices solutions, towards a more 'connected' laboratory.

Not only does this free up time for the researcher to focus on higher level tasks but it also provides full traceability, with OneLab acquiring data detailing the precise execution of each step of an experiment, beneficial for troubleshooting and ensuring a full audit trail for regulated laboratories.

Currently, life science laboratories need to manually program individual electronic pipettes, which can be time-consuming and susceptible to human error. Designed to enable seamless connectivity with electronic pipettes, OneLab is the first web-based application to facilitate efficient, centralised programming of connected pipettes and rapid sharing of protocols, enabling laboratories to boost productivity and performance!

In October 2019, an Online Protocol Library was added to the software such that users can now select pre-validated protocols, for example for qPCR, flow cytometry or CRISPR. New protocols are added to this on a monthly basis.

Each year at the Society of Laboratory Automation and Screening International Conference and Exhibition, the New Product Award is given to up to three companies showcasing new products that are commercially available within 90 days pre- and post-conference. Products are evaluated by a judging panel onsite at the companies' booths. Winning products are granted use of the New Product Award designation for a year. Andrew+ won the New Product Award in February 2019.

SLAS NPA DESIGNATION 2019
Andrew Alliance