Problem-solving in laboratory automation

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The presence of automation and robotics in the laboratory is becoming increasingly common. The use of these new tools is not, however, without its problems. For example, the first-time user is faced with the problem of how best to introduce automation. Even the experienced user may face recurrent, nagging problems in the use of automation. This paper discusses a range of problems that may be experienced by users and managers of automation, from the neophyte to the expert, and offers suggestions for practical solutions.

The application of automation and, in particular, robotics to laboratory operations offers many benefits, including increased productivity, lower costs and higher reliability of experimental data[1]. In some types of research, such as empirical drug discovery (e.g. high-throughput screening), automation can be indispensable[2]. Many other research disciplines, such as combinatorial chemistry[3,4], molecular biology[5] and clinical diagnostics[6], are also embracing the use of automation. However, besides the benefits that automation brings to the laboratory, it also brings a unique set of problems. These can be daunting to the bench scientist or laboratory manager unfamiliar with the use of automation, and trying for even the experienced user. This paper will discuss some of the more common problems and attempt to offer practical solutions.

Arguably the most problematic aspect of automating laboratory procedures is the initial introduction of automated instrumentation to the task. Some of the most important decisions must, unfortunately, be made early in this process, and incorrect choices can lead to persistent problems in the laboratory and beyond. Three important decisions that must almost always be made are:

- what to automate
- how fully to automate it, and
- what type(s) of instruments to employ.

Which tasks to automate

In considering the first decision, which tasks to automate, one should keep in mind that almost any laboratory procedure can be automated if there is sufficient motivation, time, talent and money. For some tasks, the requirements for these commodities may be very high, but even then it may be prudent to proceed with automating if the benefits of automation are sufficiently great. It is crucial, therefore, to be able to estimate how difficult a task will be to automate. There are some general predictors of difficulty in automation that can help in making a reasonable estimate. One 'warning sign' is the degree to which discretion must be exercised in the execution of a task. The current state of robotic programming does not allow for much flexibility in the performance of tasks. If there are variables associated with the task (e.g. pipetting depth or speed, amount of mixing required, optimal duration of the assay), then automating the task will be difficult. Another 'red flag' to easy automation is lack of robustness in an operation. A robot will not have the 'touch' of a good laboratory scientist. If, therefore, small changes in assay parameters (e.g. volumes, temperature, etc.) will greatly affect the results, the difficulty of attempting automation is increased and the chance of

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ultimate success small. If the task will not tolerate a small loss in precision or accuracy, it might also prove challenging to automate since there may also be a decrease in the precision or accuracy of measurements from the automated assay. This decrease is not due to the automated equipment (e.g. pipetters being less accurate than the manual variety). Instead it is due to mistakes occurring during the performance of the task, which a scientist would correct but which an instrument might not. In the case of pipetting, this might be improperly filled tips or carried drops. A complicated procedure is also generally more difficult to automate. If, for example, substantial manipulation is required to perform the task (e.g. removal of filters from filter-bottom plates or bagging of samples), automation may be unusually difficult.

If it appears that a task will be difficult to automate and one still wishes to proceed, certain pilot studies can be done to establish the probability of success. In the most trivial case, and assuming suitable equipment is available on-site or can be supplied on a trial basis by a vendor, a direct test of automation of the assay can be undertaken. If empirical testing is not an option, another way of establishing whether a task can be automated is to try performing the assay in the same way that a robot would. This can be accomplished by having the task done by someone unfamiliar with it, guided only by a written protocol. Manipulations made by this person should involve the thumb and forefinger of one hand only, whenever possible, to approximate the capability of a robotic hand. While this test of ease of automation is simplistic, it can be effective in identifying potential trouble spots. Finally, one may rely on past experience to judge how difficult a task will be to automate. If such experience is not available locally, it can be obtained through automation consultants such as Consultants for Automation and Robotics in Drug Discovery (CARDD; e-mail: Discovery4@aol.com), or through organizations with automation expertise such as the Society for Biomolecular Screening (SBS, 36 Tamarack Ave, Suite 348, Danbury, CT 06811, USA).

How fully to automate

The second question, how fully to automate a task, may occur in two different contexts. First, after it has been decided that a task is amenable to total automation as discussed above, one should still ask whether it is beneficial to automate all of the steps involved in the task. The underlying question is whether the time and expense spent in automating a given step in a procedure is justified by the savings that will result from its automation. This point can be illustrated with an example. Suppose that a given microtiter-plate-based assay involves a number of steps, each of which can be accomplished at standard automated stations between which the plates are passed by a robotic arm. Automation of the final step, however, requires the purchase of a specially designed quantification instrument (e.g. a luminometer or scintillation counter) that is able to interface with the robotic arm. This instrument is expensive and is not accessible to other (e.g. manual) users because of its special design. Given these conditions, it may be more efficient simply to have the robotic arm place the plates into a rack before this final step and then have a scientist load them into an available manual instrument. The question of gain in efficiency through automation should be asked of each step in every procedure that one intends to automate, just as it was asked of the procedure as a whole.

Alternatively, if it is decided that a task is too difficult to automate completely, automating parts of it may still be sensible. Thus, if an assay has both rote and variable steps, it may be advantageous to automate the rote steps while leaving the performance of the variable steps to the scientist. The same applies if some of the steps require unusual manipulations. By constructing a flow chart of the task showing both the automated and the manual steps, the benefits of partial automation can be determined. For example, if with partial automation a scientist is required to attend to an instrument every five minutes (e.g. to move microtiter plates) and is thereby precluded from accomplishing other work, this partial automation may not be efficient. On the other hand, if the instrument accomplishes a step during its five-minute cycle that would require 15 minutes to do manually, then partial automation may be effective.

What type of automation to use

The final question in the introduction of automation into the laboratory is what type(s) of instrument to employ. Over the past five years the number of suppliers of automated laboratory equipment, including robots, has increased dramatically. Although this wealth of suppliers is positive in terms of offering variety and encouraging suppliers to continually improve their instruments because of competition, it makes the choice of the 'correct' instrument more difficult. In choosing an automated pipetting station, for example, there are over a dozen alternatives, many of which have similar characteristics (e.g. *x*-*y*-*z* arm, multipipetting capability, menu-driven software, etc.). With this number of alternatives, a side-by-side comparison becomes impractical. Similarly, the number of choices of robotic arms is increasing. To complicate matters further, a number of 'unitized' automation systems are also now being offered[6,7]. These systems are composed of automated stations already integrated with a robotic arm (e.g. a 'pick and place' robot to move samples between stations) and supplied with proprietary software. These can be contrasted with 'component' systems in which each automated instrument, as well as the robotic arm, might be purchased from a different supplier and then integrated into a single system[8].

There are a number of practical steps that can be taken to help choose the best automation solution. When deciding which system is best, both hardware and software should be considered. First, one should make sure that any system under consideration can actually accomplish the required operation. This means seeing the actual task performed successfully on the actual instrument. The supplier should be able to arrange to have a 'demo' instrument brought in for you to use, or for you to visit the site of an operational instrument. Never assume that an instrument can perform a desired operation just because other people have done 'similar tasks' or because the documentation indicates that it should be possible.

Second, the question of user friendliness must be addressed. Any automated instrument will require some user intervention. This may consist of changing the programming to accommodate modifications of the task, routinely adjusting the programming to correct for 'drift' or wearing-in of the instrument, fixing instrument crashes or, ultimately, programming the instrument for new tasks. It is naive to expect that all of these functions will be carried out entirely by others (e.g. contractors) and will not require any attention of the operator.

User friendliness can be established in a number of ways. The opinions of other users or consultants should always be sought first. Information from the instrument supplier, particularly a demonstration of the use of the equipment, is also helpful. The best method is to gain practical experience with the instrument before purchasing it. Most suppliers of instrumentation offer training for new users. When a decision has been reached on the purchase of an instrument, it may be wise to undertake the training before the actual purchase. In this way, the question of user friendliness can be answered directly. If the instrument's user interface is unsatisfactory, the only loss is a modest amount of time and money. A much greater penalty is incurred if the discovery that the instrument is difficult to work with is made after the purchase.

A third criterion for selecting the best instrument is adaptability to other tasks that it may be required to perform. Seldom do laboratory operations have a sufficiently long life that an automated instrument will be used for only one task. In an industrial setting, projects start and end, often abruptly.

Furthermore, once an automated instrument, particularly a robot, is on site, other applications for it are usually found. These additional or alternative uses need to be anticipated before the purchase. For example, after it has been established that a system can successfully accomplish its primary task, demonstrations of other capabilities of the system should be requested, particularly those relevant to other tasks being carried out in the department, even if there is no immediate need for their automation. The availability of both unitized and component systems as alternatives for automation was mentioned earlier. Often, anticipating alternative uses of an instrument is the deciding factor between these two types of system.

Unitized versus component automation systems

Unitized systems, as the name implies, are provided as fully integrated instruments with most or all components produced by a single supplier. They often include storage racks, a liquid handling station, an incubator, various types of plate readers, a robotic arm (often on a track system), and menu-driven software. The requirement for the successful use of one of these instruments is that the task can be accomplished with the stations available from the supplier, and using the existing preprogrammed steps. A major advantage of unitized systems is that they are fast to set up and offer friendly user interfacing. Some of these systems can be installed and functioning the day after they are received. Their major drawback is that they are not as adaptable to new tasks; especially tasks not anticipated by the designer. Although non-standard stations or programming steps can be added to a unitized system[1], it is certainly more difficult, and the result less satisfying, than adding functions to a system built up from components. Unitized systems are also generally more expensive than component systems because of the investment that the supplier has made in integrating the parts.

Assembling a system from components may involve obtaining a robotic arm from one supplier, a pipetting station from another, an incubator from a third, and then integrating them, or having them integrated, into a single system. This type of system can have several advantages over the unitized system. First, since it does not need to come from a single vendor, the best instrument can be chosen for each component of the system. For example, the best manufacturer of robotic arms may not produce the finest pipetting stations. In a unitized system one might have to settle for a suboptimal pipetter in order to get the best robotic arm, but with the component system the best of both platforms can be had. Second, a component system is more easily expandable. New stations can be added at will without having to depend on a third party to build them, integrate them into the system, or write the appropriate programming for their use. Finally, the component system is as flexible as the operator is clever, although this advantage is also the main drawback to this type of system. The operator must be capable of programming the system and of integrating the different parts or, at least, of overseeing these processes. This generally means that these systems require more time and labor to be installed and reach functional status. Generally, the suppliers of the individual components can aid in this process. For example, suppliers of pipetting stations often have experience in interfacing them with a number of robotic arms.

A growing trend is the availability of systems that might be considered hybrids between a component system and a unitized system. Such a quasicomponent system might consist of a robotic arm from one manufacturer combined with automated instruments made by a number of other suppliers but modified to interface with the robot, and tied together by a proprietary software package written by the actual vendor of the system. These systems can become almost as flexible as the true component system as the vendors integrate more and more instruments and robotic arms using their proprietary software. These systems require more user intervention and time spent in setting them up and learning how to operate them than the unitized systems, but not as much as the component systems. Likewise, they are intermediate in flexibility between the other types of system. An advantage of this type of system over the other two is that experts have selected the components from among the best available and already integrated them in an efficient manner. There is, of course, a price to be paid for the use of their expertise.

Unitized systems are generally preferable if the tasks to be performed are long-lived, if future tasks are likely to be of a similar nature, if the procedures do not involve unusually complicated steps, if rapid set up is required, or if one does not wish to become too involved in the automation process.

Component systems are usually better for short-lived, diverse, or complicated tasks, due to their greater flexibility. They will also generally be less expensive. More time and effort will be involved in the installation of component systems, and in using them. There is generally a return on this commitment, however, in enhanced appreciation of the capabilities, and limitations, of automation. For tasks that are intermediate in either lifetime or complexity, a quasicomponent system may be best. Even for diverse and complex tasks, a quasicomponent system may be superior for less experienced users of automation.

Software considerations

In addition to the user friendliness and flexibility of the hardware, the software should also be assessed for these same qualities. Most software is now written in high-level languages that only require one to 'click' buttons or enter values in order to develop automated routines. This makes learning the use of automation easier. The drawback is that only the steps programmed onto the buttons or into command lines can be executed by the user. Other systems are programmed in a computer language or similar looking type of code. These systems require more time to learn but offer more flexibility in how the instrument may be used. The decision as to which type of language is best depends upon the complexity of the tasks being programmed as well as upon the experience of the user. For simpler tasks and/or less experienced users, the high-level languages may be better. Advanced programming features such as scheduling and multitasking should also be considered. Scheduling programs allow for the most efficient use of the robotic system. In a microtiter-plate-based procedure, for example, the steps required to process a single plate, as well as the number of plates to be processed, are entered into the program. The program then determines the most efficient method of processing the plates. This will often involve staggering the starting and finishing times of the plates. In addition to a gain in efficiency, scheduling can also improve the results from the procedure by eliminating the long delays that can occur when operations are performed in a batch mode. Multitasking programs allow a number of procedures to be run on an automated instrument or system at the same time. Thus, if a robotic system is running a task that has a long pause (e.g. an incubation step) in it, another task can be undertaken during this free period. Since obtaining these features can entail additional expense, it should be considered that, although these programming features will be beneficial to any user, they will be of most use to those with more experience in automation, or with more complicated tasks to perform.

How to build the automation team

As with any laboratory function, automation needs oversight. The equipment will need to be installed, programmed, adjusted, maintained, serviced and upgraded. In addition, new automated equipment will probably need to be added over time, and this will have to be integrated with the existing system. There are a number of options for accomplishing these functions. The first is to rely on contractors. This approach may work better for unitized systems. Its advantages are that no expense is incurred unless one of these functions needs to be performed and there is no need of increased personnel within the group. The disadvantages are that contractors are expensive (high overheads), not always immediately available and relatively unfamiliar with the tasks being automated. This last disadvantage is of the greatest concern. Familiarity with the task is, as we have seen, necessary in selecting and applying automation. Likewise, familiarity with the task is helpful in keeping it functioning properly under automated conditions. For example, one task that was automated in my laboratory experienced intermittent failures. The service person for the automated pipetting station being used for this task checked it over thoroughly and found it to be performing properly. A scientist familiar with the procedure analyzed the failure from a biological perspective and was quickly able to diagnose the problem as a reagent being carried over by the tips used by the pipetter.

A second support option is to assemble an in-house automation group. Ideally these people should have a scientific background. The advantages to this approach are rapid response to automation needs and problems, some familiarity by members of the team with the tasks and procedures involved, and the ability to use the group as a core resource. The members of this group can concentrate on automation and thus gain the experience and training to become experts. In addition, the expense of maintaining the group can be divided with other departments that share the use of automation. The disadvantages to this option are the increased expense, because the automation team members are employees and, again, the unfamiliarity of the automation team with the tasks being automated. This latter problem is less severe than when using outside contractors because the team members will have more access to proprietary information and to the scientists performing the task, but it can still be substantial. There are numerous examples of non-functional equipment that was built or purchased by automation experts who had spoken with the appropriate scientists and thought that they understood the tasks for which the equipment would be employed. I can think of at least one such non-functional instrument that stood for many years as a monument to this type of error since it weighed several hundred pounds and could not be moved through a normal doorway. None of us would like our names inscribed on such a monument.

A third and, in my opinion, preferred method of building an automation team is through cross-training. In this case, some of the scientists who perform the task are also trained to be automation specialists (or vice versa). The disadvantages to this approach are that:

- extra training must be given to the scientists who will be involved in automation;
- these scientists, because of their other duties, may never become true automation experts;
- talents in science and in automation are not necessarily correlated.

Thus, care must be exercised in selecting members of such a group. The advantage to this approach is that, because of their familiarity with automation, scientists are quick to apply it to their procedures. Programming a pipetting station becomes as routine as using a manual pipetter. As an example of this, my group was charged with a large one-time task involving pipetting. Instead of performing it by hand, which would have been very time-consuming, they were able to quickly program an automated pipetting station to complete the task. This approach also leads, in many cases, to better ideas about how to automate a task since the scientists have a good acquaintance with both the task and the equipment available for automation.

Problems in the routine use of automation

Once the automated instruments have been installed in the laboratory and the automation team is in place, the real fun starts. As with any complicated and sophisticated undertaking, unexpected problems can occur. This can happen even when the automation has been carefully applied to a task

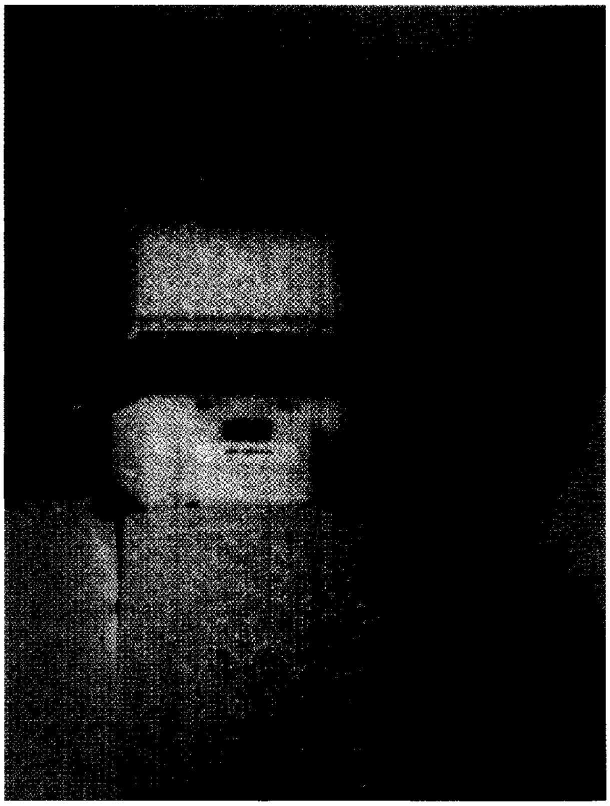

Figure 1. *A robotic arm (XP™ robot, Zymark Inc., Hopkinton, MA, USA) placing a microtiter plate onto an improvised filtration station (see text for details).*

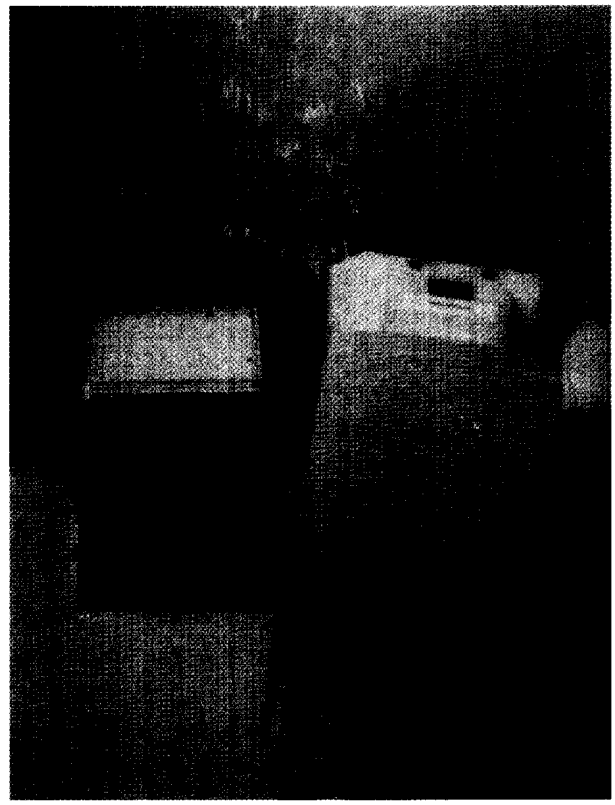

Figure 2. *The same station as in Figure 1, with the robotic arm shutting off the vacuum by changing the position of a three-way valve attached to a pipet.*

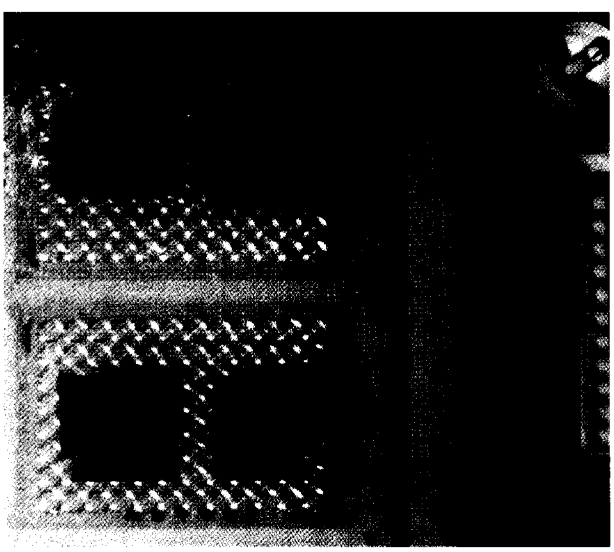

Figure 3. *A device for allowing a microtiter plate to be put into a horizontal rack in a vertical orientation.*

because running in pilot mode and running at full throughput place different constraints on the system. The three most common start-up problems are:

- discrepancies in results obtained with manual operation,
- 'crashes', and
- the 'you can't get there from here' dilemma.

These problems can also occur sporadically in automated tasks even after months of trouble-free operation.

Discrepancies in results between running the task in an automated format and performing it manually are often found after sufficient amounts of data have been collected. These are usually caused by seemingly insignificant differences between the two versions of the task. If this problem occurs, the most straightforward solution is to examine the effect of automation of each step on the final results of the procedure. For example, starting with the fully automated version of the task, a single step can be done manually and the effect on the results observed. This can be repeated for each step until that step is found which, when done manually, causes the results to agree with those of the completely manual procedure. The reason why automating this step changes the results of the task can then be determined. Variations on this theme can also be employed. Common causes of these types of discrepancies are variation in incubator temperatures or tolerances (if different incubators are used for the manual and automated procedures), different volumes being pipetted (never trust an instrument to pipet the amount it says it will), changes in the order or duration of certain steps in the procedure, and interactions of reagents with instrument components.

Crashes can be defined as unanticipated events that make it impossible for the instrument to complete its task successfully. These are the easiest problems to handle. Most crashes occur early in the implementation of automation and result from 'user error'. They can usually be avoided by automating a procedure in small stages, rather than in one fell swoop, and observing the effect of each increase in automation on the performance of the task. Later crashes can be caused by normal wear on the instrument. For example, rack positions on a pipetting station or robot movement coordinates may drift over time, eventually producing an instrument failure. This type of crash can be avoided by periodically checking the alignments of the instruments. Visitors to the laboratory can produce crashes by inadvertently altering the positions of automated stations (i.e. bumping into things). This type of crash can be prevented by checking equipment positioning after visits by tour groups, service people, etc.

Often crashes can be fixed through operator intervention. In programming a system, it is usually a good idea to insert commands that cause the system to check on the performance of a task and pause, but not terminate, if an error is detected. This gives the operator a chance to correct the problem and then continue the operation rather than having to restart the procedure. For example, when a robotic hand is required to pick up a plate, a checking step can be inserted to make sure that it has done so. If the operation has not been completed successfully, the robot can pause and wait for the operator to correct the situation. In some cases the robot might be programmed to re-try the task before pausing. Some platforms terminate their operation when an error is detected. Getting the procedure to continue after the problem has been corrected can be exceedingly difficult with these systems because it often involves altering the programming to initiate the task part of the way through. In order to minimize the effect of crashes that occur when an instrument is not being observed, such as outside normal working hours, a 'babysitting' system should be installed. These systems monitor the operation of the instrument and detect any pauses, usually as missed switch closures ('button pushes'). When a pause occurs, the babysitter alerts the person who is 'on call', often by phone or through a pager. More sophisticated systems are being designed with additional remote capabilities that may allow correction of some problems from off-site (Visualan, e-mail: bwatson@aimnet.com).

The 'you can't get there from here' dilemma occurs when a particular piece of equipment needed to perform part of a task is not available. Even in the best case scenario, in which the equipment exists elsewhere, obtaining it involves delays and expense. In the worst case, the equipment might need to be designed and built at an even greater expenditure of time and money. For example, in an automated procedure being run in my laboratory, the insertion of a filtration step was needed. No device was available that could perform this step for the robotic platform being used. In another case, the orientation of plates on an automated pipetting station needed to be changed from horizontal to vertical. Although a device had been developed to perform this operation, there would be a long delay in obtaining it (it was not off-the-shelf) and it was relatively expensive.

When these types of problems occur there are at least four possible solutions. The first is to try to perform the task in another way. For example, it might have been possible to replace the above filtration step with centrifugation and washing steps, for which equipment was available. The second is to try to adapt available equipment to the task. For example, a robotic arm can be used as a mixer by programming a number of short, jerky movements. I don't recommend this approach. A third solution is to buy or have built the necessary equipment and absorb the delay and expense. This option may not be practical for smaller companies, which have smaller budgets and shorter time lines. A fourth possible solution, and the one that I recommend, is to improvise.

Devices were built in-house to solve the problems mentioned above, as well as others, and have been described in detail elsewhere[1]. They were constructed with the most basic of materials using a few simple tools. The filtration station, built from a dot blotter (Bio-Dot™, Bio-Rad, Hercules, CA, USA), empty pipet tip racks, hanger wire (for robot 'friendlies'), tubing, a three-way valve and a pipet, was assembled and operational in a few hours. A robotic arm places the plate onto the dot blotter using the hanger-wire friendlies as locators (Figure 1). The robot arm then rotates the three-way valve by pushing the attached pipet to direct the vacuum to the blotter. After filtration, the valve is returned to its original location to release the vacuum (Figure 2) and the plate is removed. The device for altering the orientation of plates on a pipetting platform was built from two microtiter plates and a pipet tip rack cover, and took only minutes to construct. These 'guides' are placed in the rack of the pipetting platform in the normal horizontal orientation, but when in place form a vertical rack (Figure 3). They can be installed and removed by a robotic arm just as ordinary microtiter plates would be.

There are several advantages in being able to build simple devices quickly and inexpensively to solve automation problems. The first is the obvious savings in time and money. A second is the greater flexibility that this allows: one can assemble a system to accommodate the optimal configuration of the task rather than trying to alter the task to fit the system. A third advantage is that one can try variations in a task that might not be undertaken if the delay and expense of purchasing special equipment was a factor. This is a great boon to optimization of the task.

There are also disadvantages to building one's own equipment. The first is that improvised equipment is often not as reliable as that designed and built by commercial suppliers. The second is that it requires a 'tinker' attitude that not everyone possesses. Help in this area can be obtained from consultants, organizations with expertise in automation, and companies (or groups within one's organization) with scientific engineering capability (e.g. Tomtec Inc., Orange, CT, USA). Finally, the resulting creations can be an eyesore when giving tours of one's state-of-the-art automation facility. The advantages to improvisation, in my opinion, greatly outweigh these disadvantages.

General comments

Automation in some form is likely to be involved in most aspects of laboratory work and, thereby, the life of most scientists at least until the next innovation comes along. Because of this, it is important for laboratory personnel to gain some measure of familiarity and comfort with its use. This paper has attempted to aid this cause by addressing some of the more common problems associated with the use of automation and offering suggestions for their solution. It is hoped that these ideas will embolden the automation neophyte and give heart to the experienced user.

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