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Process Development Automation: An Evolutionary Approach

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Abstract:

As it matures in the research laboratory as a tool for the combinatorial chemist, automation is now moving into the development area. However, the classical combinatorial robot is not appropriate for all development activities, as it is primarily a serial device and lacks on-line analysis—often a key requirement for high-speed development. Automation equipment is becoming commercially available to cover all three development stages—route scouting, process optimisation, and final process definition—but it is often highly specific, expensive, complex and may not offer a complete solution. In contrast, standard laboratory equipment already contains some automated capabilities but is normally unused in our automation strategies. This presentation will discuss issues related to a stepwise and unified approach to automation across all three stages, using existing standard laboratory equipment. Examples from diverse areas including calorimetry, DoE, crystallisation studies, and plant simulation will be discussed along with equipment and computer issues. Inexpensive commercial software is now available to control these systems, or software can be developed using modern visual development environments. This is not rocket science—you have the technology!

Introduction

The combinatorial chemist has had access to automation tools for some time now and in many companies its use has led to a significant increase in the number of compounds entering screening.

The development chemist is beginning to see this increase push into early development stages with more potential candidate compounds requiring earlier work. This, plus the growing pressure to shorten development cycles and control costs, leads to a fundamental problem: *we are asking development chemists to do more work, faster and with little or no additional resource.* The bottleneck is moving into Process Development![1]

Classically, a typical development chemist will carry out on average perhaps one experiment per day, at a current cost of £300−400—almost £1 per minute. Much of that time is spent setting up and then watching the experimental parameters and making notes, etc., operations ideally suited to automation. If we can use automation to increase productivity, either by running multiple parallel reactions or extending the working day (or both), we can significantly increase experimental throughput and simultaneously allow the chemist more time to plan, analyse, and utilise his chemical knowledge.

However, this direct approach has a number of drawbacks:

- **Cost.** Parallel and unattended working requires expensive equipment.
- **Complexity.** Automated systems are all different and often appear (and are) complex to set up and run.
- **Flexibility.** Current automation systems each handle only a small subset of normal process development activities. No "general purpose" automation systems exist.
- **Waste.** Automation equipment is bought specifically: You can seldom utilise existing laboratory equipment.
- "**Customer resistance**". Chemists must quickly adapt to new technologies, new practices, and skills.

This paper will address these issues and discuss an alternative approach to automation covering all areas that can be adopted in a stepwise manner.

Automation in Process Development

A recent review[1] presents a good overview of the issues surrounding automation in process development, and the model presented reflects the real activities within many departments. Most development work falls into one of three distinct areas:

- Route Scouting
- Process Optimisation
- Process Definition/Validation

These three areas all need a different approach to chemistry and radically different equipment and methodologies. Also, the time constraints involved vary significantly.

(a) Route Scouting. A large number of small-volume (1−10 mL) reactions are examined, looking at different reactions, reagents, and conditions, often in relatively simple equipment ("test tubes"). Sometimes only a yes/no or better/worse type of answer is required. Often design of experiments (DoE) and statistical methods will be utilised to indicate potentially the best reaction or best starting point for further, more detailed examination. This stage occurs early in a project and often has the most severe time constraints—a feasible, cost-effective route must be rapidly identified to make initial samples for trial purposes. Although not optimised, the route must clearly have potential to reach the required project targets on cost, purity, operability, etc.

Typically, this stage will be carried out in test tubes using Zymark[2] robots, ReactArray-[3], Bohdan-[4] or Argonaut-type[5] systems where 10−20 or more reactions can be examined under similar conditions in parallel. By and large, these are simply reactions, often only mix, stir, and heat.

(1) Weinmann, H. *Org. Process Res. Dev.* **1999**, *3*, 304.

(2) Zymark Corporation: http://www.zymark.com.
(3) ReactArray, formerly SK233: http://www.reactarray.com.
(4) Now part of Mettler Toledo: http://www.mt.com.
(5) Argonaut Technologies: http://www.argotech.com.

10.1021/op0100145 CCC: $20.00
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(b) Process Optimisation. Fewer reactions on a larger scale (10−100 mL), often carried out in "standard" reactors, will be used to optimise the best candidates from the route-scouting stage. Better monitoring of operating parameters is required, and more sophisticated types of control may be used—programmed addition of reagents, pH control, temperature profiling, etc. Again, DoE and statistical methods will often be used along with on-line monitoring of reaction progress by HPLC, FTIR, etc. Examination of processing problems—filtration, extraction, and workup will also be examined at this stage with additional equipment.

Typical systems would be the HEL Auto-MATE,[6] Mettler Toledo MutiMax,[4] etc.

(c) Process Definition and Validation. This is best performed using single reactions at 1 L or larger scale, controlled and datalogged in great detail in equipment with characteristics as close as possible to those of the proposed plant. Calorimetric, mass balance, and other physical data used as engineering design parameters will also normally be measured at this scale. A secondary use of this scale of equipment is automated repreparation or "kilo lab" work.

The equipment for this area is well defined—Mettler Toledo RC1[4] and LabMax, HEL Auto-Lab, and systems from Camile,[7] Systag,[8] etc.

In general, there is a diversity of commercial equipment available for route scouting and validation work, with parallel optimisation a little less well developed at this time, and this area is often covered in nonideal systems.

A key aspect of route scouting and particularly optimisation is on-line automated analysis—normally high throughput HPLC but often FTIR or Raman. Again, automated HPLC equipment is well established in analytical laboratories, but connection to automated equipment is largely restricted to the route-scouting areas (e.g., ReactArray and Argonaut systems) at this time.

Therefore, to cover the whole spectrum of process development activities, we need three distinct systems at £50K to +£150K each—probably from three separate manufacturers—plus a large investment in training, support, and so on.

This is a significant investment of resources, particularly for a small department, and unfortunately, an incremental approach is not possible if coverage of all areas is required using commercial systems. Is there an alternative way forwards? The answer to this is yes.

It is possible to develop systems based on existing laboratory equipment and practices, using in-house or commercial software, which will cover all three phases of development work. This approach has a number of advantages:

- tailor-made solutions with local design input to suit specific situations
- reuse of existing laboratory equipment
- gradual build up of capabilities—lower initial resource requirement
- minimisation of "technology shock"

In-house development of these systems, however, requires skills and capabilities that are historically not found in chemical laboratories but often do exist within other areas of most companies.

To explore this approach, it is useful to consider what automation means and is at a more fundamental level and to consider exactly what tools and skills we need to achieve this end.

What Is Automation?

Automated systems are always impressive when observed in action, but their apparent complexity belies relatively straightforward processes. If we step back and consider what the system is doing, it becomes clear that the basic operations are actually quite simple. The system's power lies in its ability to repeat these simple procedures rapidly, reliably, and tirelessly.

As we shall see below, the fundamental operation of all automated systems is to look at measured input values (temperature or time etc.) and convert it in some defined way into output signals (heat on, sample now etc.) On top of this, provision must exist for interaction with the user to control the operations via a display, keyboard, mouse, datalog, etc.

This latter aspect—the "user interface"—is all that the user will normally see. This is why all systems seem so different even though they all essentially function in the same way.

This arrangement is true, irrespective of the design of equipment or scale and is essentially the same for all three types of system—route scouting, optimisation, and validation.

What Can Be Automated?

Commercial equipment will often be supplied with a specific selection of pumps, balances, pH meters, etc. as an integral part of the automation system.

Existing standard laboratory equipment contains far more potential to be automated than is generally realised. Almost all electrical devices can produce a usable signal of some form, and most can be controlled—even if only by switching them on and off. The level of sophistication varies considerably from devices that will respond to a variety of complex digital signals (circulators, autosamplers, and HPLCs, etc). through devices that produce or respond to a simple voltage signal (thermometers, pH meters, pumps) to on/off switches and on/off control (heating mantles and valves).

What Other Equipment Do We Need?

The simple answer to this is:

- a PC with appropriate additional hardware
- suitable application software

All recent desktop or laptop PCs are capable of supporting the additional hardware required to run an automation system. In comparison to some modern PC-based applications, process control does not need a particularly highly specified machine.

(6) Hazard Evaluation Laboratory Ltd.: http://www.helgroup.co.uk.
(7) Now part of Argonaut: http://www.camile.com.
(8) Systag: http://www.systag.ch.

Control and datalogging applications software is available from a variety of manufacturers[9] that will measure and control laboratory devices, although configuration can be challenging as these programmes are usually very general purpose, requiring considerable initial setup work. There are very few "software only" solutions purposefully designed for control and datalogging of reactions available at present, though this will become a growth area.[6,8]

A more "chemist-friendly" system can be developed using a modern rapid application development (RAD) environment such as Delphi or C++ Builder[10] or even Visual Basic. This can result in a powerful and highly flexible system that exposes the average user to the bare minimum of complexity. However, this approach requires substantial effort and programming skills.

In practice, all of these approaches require a more detailed look at how a basic control system works. Just what is involved in converting a real world input measurement into a real world control signal?

Basic Control Systems

A basic control system contains three types of primary elements or objects:

- inputs from the real world
- control loops that use the inputs to produce...
- ...outputs to the real world.

In addition, it must fulfill a number of other secondary functions such as displaying data and datalogging and must provide some means of configuring, modifying, and controlling the overall system behaviour.

Practically, inputs may be primary that is, directly taken from some external device, or derived, produced from some mathematical combination of other primary (or derived) inputs. Control loops are the heart of the system and are the objects responsible for all control actions. Outputs are the ultimate result of the control loop action on an input but may also be fed back as an input themselves.

(a) Inputs and Outputs—The System Interface. The system interface—the hardware connection between the computer and the real world—is responsible for converting all input signals into numbers usable by the controlling programme and outputs back to real world values. Typically, the interface will take the form of one or more cards that are inserted into spare slots in a PC (devices that connect via the USB, serial, or parallel ports are also available and are particularly useful for laptops). Although this was a tricky procedure in the past, new operating systems and technologies now make this much simpler—your PC will normally recognise the new card immediately and install and configure all of the necessary software automatically. A wide range of hardware is available from many manufacturers, covering all of the different input types with differing speeds, resolutions, etc.[11]

Normally, the hardware manufacturer will provide software drivers that will give access to all the necessary functionality for a particular type of input or output device. Increasingly, hardware suppliers and third parties are providing "components"[12] that are easily and directly usable from a variety of programming environments as well as from high level applications (e.g., Excel) where they can typically be "dropped" into a document as functioning embedded objects with little or no requirement to directly handle computer code.

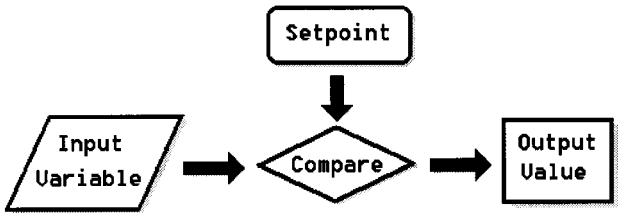

Figure 1.

Although there are many possible external devices, almost all input or output signals fall into one of three types:

- voltages, e.g.: pH meters, thermocouples, resistance thermometers, pumps, etc
- currents, e.g.: thermistors and 4−20 ma current sources
- digital, e.g.: serial, IEEE488, HPIB etc. devices, switches, relays, etc.

The hardware and its associated software are responsible for converting (reading, linearisation, scaling, etc.) these disparate input types into numbers (in engineering units—pH units or °C, etc.) and output numbers into the different outputs signals, and will normally do this with no user intervention once correctly installed.

From the point of view of the controlling programme, there is no difference between any of the different types of input or output, they are all treated simply as numbers. There is clearly no effect of scale, although types of available equipment do vary with scale.

(b) Control Systems—Primary Function. As discussed, there is only one basic action any control system needs to carry out, and that is to produce an output signal related in a defined way to a measured input variable. Typically, the system attempts to make the input signal match a particular value—the setpoint—by adjusting the output signal (see Figure 1).

Usually, the input will be some measure of the effect of varying the output; for example, if the input is reactor temperature, the output may be the power level to the jacket heater. This is known as *closed loop control*—the effect of changes in the output are fed back directly to the input.[13]

Considering the above, it is clear that an arbitrarily complex system can be set up using multiple simple control loops—one for each output that must be controlled—with the system merely continuously and sequentially recalculating and updating the output values at an appropriate interval. Considering the time constant[14] of even a small reactor, this

(9) LabVIEW from National Instruments: http://www.ni.com or DASY*Lab* from Datalog GmbH: http://www.dasytec.com.
(10) Borland Software Corporation: http://www.borland.com.
(11) Manufacturers include National Instruments, IOTech, ComputerBoards Inc, Keithley, and many others. See http://www.adeptscientific.co.uk.
(12) There are many sources of reusable components available in a variety of languages, e.g.: SoftWIRE component system for Visual Basic: http://www.computerboards.com.
(13) Open-loop control is the situation where the input and output are not physically connected, and changes in the output do not affect the input—indeed no input may exist.
(14) A measure of how fast the bulk properties of the reaction system can change.

would probably not need to be more often than once every second or two for each loop. *This is normally the primary task of a control system and must be organised to proceed continually—in the background—irrespective of what the user is doing at any time.*

The most important part of the control loop is the method used to relate the measured input via the setpoint to the applied output. There are a number of ways to do this, but the most common is by using a three-term, or PID, control algorithm.[15] Here, a deviation or error term (E) is obtained by comparison of the setpoint and measured input value. Using this term, the output is typically calculated using a formula something like:

$$OP = P[E + I\Sigma E + D\Delta E]$$

Here, E is the deviation or error term, P, I, and D are constants specific to the particular output which govern the controller action. $I\Sigma E$ is the sum of the error terms over time (integral term—used to remove offset from the setpoint), and $D\Delta E$ is a measure of how fast the error term is changing (derivative—used to prevent overshoot). Often in laboratory systems, I and D can be set to 0. The reader is directed towards a chemical engineering book for more details.[16]

Thus, given an appropriate control action for each output, the required behaviour (for closed loop control) depends only on the input value and the setpoint defined by the user. The setpoint could be fixed (e.g., 40 °C), variable (e.g., 40 °C for 30 min then 2 °C/minute to 120 °C), or dynamically calculated (e.g., current reactor temperature −5 °C).

The fact that all inputs are equivalent at this stage means there is no reason inputs, outputs, and control loops cannot be reconnected as required to achieve any type of system configuration and hence to control any type of equipment on any scale.

It will be appreciated that this approach is scale-independent—the same algorithms will control 10 mL or 10 mt^3—and thus can be applied to all three areas of process development automation. One needs merely to alter the magnitudes of P, I, and D to reflect the longer time constant for larger systems.

(c) Control Systems—Secondary Functions. Besides controlling the outputs from the system, the control system will normally also be responsible for:

- PC side-system configuration—input and output connections, setpoints, control parameters, starting and stopping control
- graphical display of input data—"real-time" charts
- data logging of input values, user comments, etc.
- alarm condition monitoring logging and actions
- system fault monitoring and recovery—safe behaviour

The importance and complexity of these will vary from system to system depending on the ultimate use, size, and complexity of the equipment, but the fundamentals are again scale- and system-independent.

The system should normally be configurable from within itself, and once configured for a particular job, this configuration should be storable for future reuse. Control over what device is connected to which physical connection and which input controls which output is needed to initially define the control system. All of this will normally be provided through some form of graphical user interface. Whilst the process is running, the user will still need access to certain aspects of the configuration routinely—setpoints, PID terms, log names and display configuration, etc. to control the system.

Some form of graphical display is normally provided, typically as numbers and a scrolling X versus time plot. Trend analysis is much easier when some historical data can be seen rather than just the current data. Subtle effects can often be seen on graphical displays that are easily missed when only logging data every 10 min. The ability to print this display or capture it as an image for use elsewhere is also common.

Data logging also needs to be controlled. What, where, and how frequently the data is logged again depends on the use to which the captured data will be put. Data can be logged periodically, after specific triggers, or after specified changes are exceeded. Data logging format needs to be considered for compatibility with any postprocessing packages—Excel, graphing, DoE, or statistical packages.

Alarm conditions—excess temperatures, pressures, coolant loss, etc.—must be trapped and appropriate action taken. This is especially important if the system is to run unattended. A safe shutdown method must be defined for each system configuration and must be rigorously checked. This is one of the few areas that are scale-dependent. A 10 °C deviation on a 10 mL scale may not be a problem, but on 10 mt^3 scale, it could be disastrous.

System fault diagnosis and remedial action are real issues. Common experience tells us that PC operating systems are far from 100% bug-free and your control application is likely to be no better. System watchdogs[17] can be set up to monitor functions at all levels, including failure of the PC itself, and to take appropriate action. Uninterruptible power supplies are available for PCs but are normally too small to run the whole system.

Although these functions are largely the ones the user is aware of, they are all secondary functions as they are clearly not a time-critical task. The only time-critical task is updating the main controlling loop(s).

A block diagram of the overall basic system is shown in Figure 2.

It is the objects in the large inner rectangle that form the primary control loops and must be repeatedly iterated left to right and top to bottom in order to maintain overall control. All other functions are of secondary importance to this.

A "Do-It-Yourself" System—Historical Development

A do-it-yourself (DIY) automation system working along these lines has evolved and has been developed in-house

(15) PID control is perhaps the most common and can be implemented in a variety of ways. Some modern commercial equipment now use fuzzy logic or neural network controllers.

(16) Perry, R. H. *Chemical Engineers Handbook*, 7th ed.; McGraw-Hill: New York, 1997.

(17) Hardware watchdogs are preferable to software ones, although, e.g., monitoring a serial connection for continued activity can be usefully done in software.

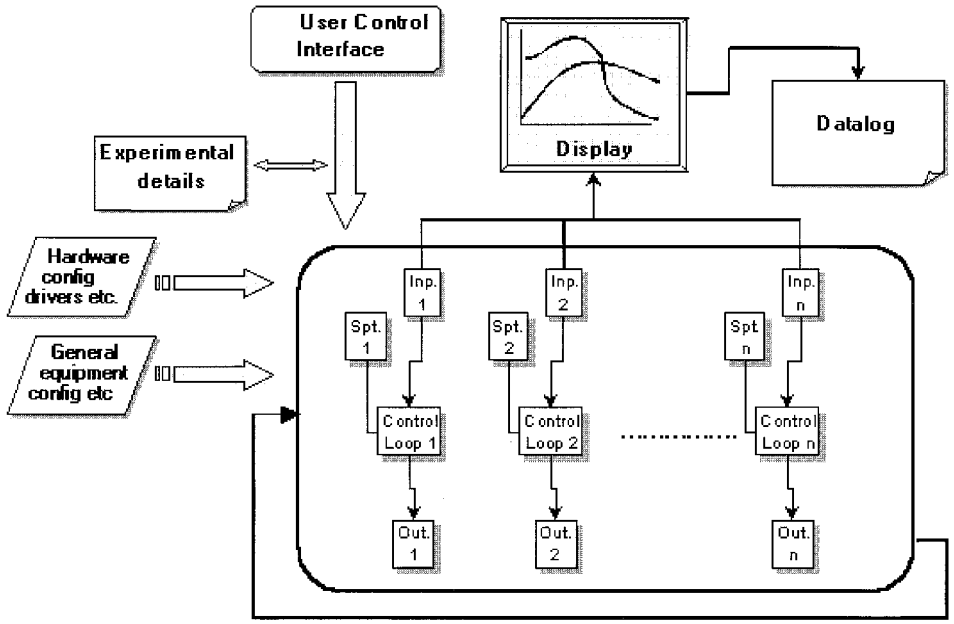

Figure 2.

within Aventis CropScience over the last 10 years. The computer-aided reactor system (CAR) can be used across all three phases of development activities and also to datalog and monitor a small pilot plant, presenting a single interface to chemist at all scales.

It controls a variety of external equipment including Gilson autosamplers and HPLC equipment, many types of heater/circulator, plus all normal laboratory equipment. It can provide round-the-clock capabilities of sophisticated multi-reaction control and datalogging on reactors from 10 mL to 10 L and datalogging at 2000 L.

The CAR system originated as a single automated laboratory reactor (ALR) which was used largely for DoE work. However, as the software developed, its more general applicability became apparent, particularly when the facility to manipulate inputs to form derived inputs was implemented. This resulted in much greater flexibility, and power has led to its use in many areas.

- ALRs—controlling multiple automated laboratory reactors, on many scales from 100 mL to 10 L for optimisation, validation, DoE, and "kilo-lab" work
- calorimetry—addition of an internal heater and controllable power supply gives calorimetric capabilities at many scales
- plant simulation—multiple independently controlled reactors, hold/feed vessels, and crystallisers can be used to simulate full-sized plant operation in the laboratory
- crystallisation studies—using optical sensors to detect the onset of crystallisation and control crystallisation processes
- optimisation, DoE, and kinetics—using an HPLC and autosampler directly from three small reactors, a fully automated parallel system has been produced
- route scouting—again, the autosampler system over a modified[18] Stem-type heating block allows 10 parallel reactions to study solvent/catalyst/base etc

(18) Glass Solutions: s.simcock@glass-solutions.co.uk.

Data logged from the system is generally handled in Excel, a suitable graphing or statistical package. Frequently, a graph of the temperature/weight/time data printed out and attached to a laboratory notebook is sufficient. Thus far, the volumes of data have been relatively low, but the increased use of the parallel systems for route scouting and optimisation will increase this and a more structured approach to data handling will need to be adopted.

Some examples of the use of the CAR system are given below.

(a) Power Compensation Calorimetry. The technique of power compensation calorimetry[19] lends itself well to implementation in a standard ALR with some modification. Addition of a standard heater/circulator, an internal PTFE-coated electrical heating coil, and a computer-controlled electronic DC power supply completes the system. The standard system software required no modification.

Power compensation calorimetry is essentially a simple process. In essence, reactions are carried out isothermally under constant cooling load in a jacketed reactor, the reaction temperature being maintained by the electrical supply to the internal heater. When an exothermic reaction takes place, less electrical power is required to maintain the constant reaction temperature. Integration of the changing power requirement, after correction for the changing heat transfer properties during the reaction (the "baseline"), gives the reaction exotherm directly. The automation system is responsible for all aspects of control of the experiment—temperature measurement and control by changing the heater power, integration of the heater power, plus possible control of one or more profiled additions of reagent into the reactor.

The example shown below (Figure 3) is a cycloaddition of a nitrile oxide and an alkene. A chlorooxime is added gradually (between 17:00 and 20:00 in Figure 3) to the alkene and base and stirred at controlled constant temperature, and

(19) *Ullmann's Encyclopaedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, 2001 electronic release; http://www.wiley-vch.de/vch/software/ullmann/.

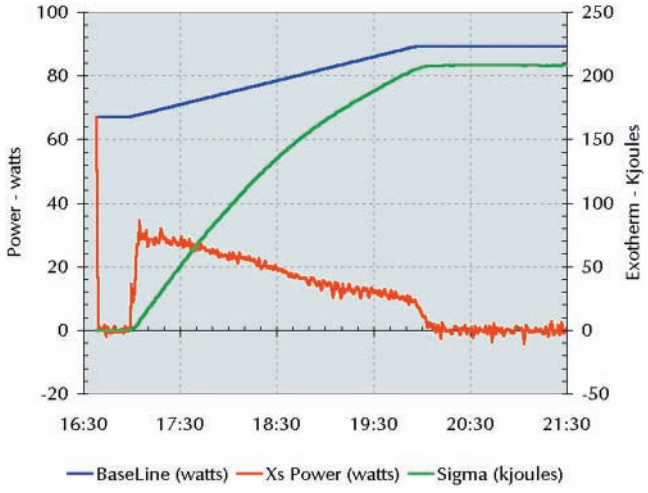

Figure 3. **Nitrile oxide/alkene cycloaddition: analysed by power compensation calorimetry using feed profile to modulate the baseline.**

the heater power profile and feed weight are datalogged. After complete reaction, the data is transferred to Excel where the baseline is reconstructed by interpolating the prereaction power value to the postreaction power value, (modulated by the feed weight to reflect changes in volume and hence heat transfer). Integration of the instantaneous power − baseline power gives the reaction exotherm.

This equipment is easy to set up and use and, practically, handles about 90% of our calorimetric needs. Besides overall exotherms, instantaneous heat load figures and much kinetic data are also provided. The equipment has been checked by performing a variety of known "standard" reactions (e.g., the mineral acid-catalyzed esterification of acetic anhydride) and gives excellent results with good reproducibility. A sensitivity of <0.3 W in 2 L of water has been measured— equivalent to 1 mL of concentrated H_2SO_4 added to 2 L of water over 2 h. Total cost of additional equipment (heater and power supply) was less than £1000.

(b) Crystallisation Studies. Detection of the onset of crystallisation can be achieved in a number of ways. The simplest is to use a suitable optical sensor, and a simple photodiode (costing a few pounds) provides a device with a voltage output directly proportional to the incident light. By placing this sensor on one side of a jacketed reactor and a suitable light source on the other side, a noninvasive crystallisation probe is produced.

Configuring the CAR system with the diode as a measured input directly through a jacketed vessel and performing a normal linear cooling ramp on a typical organic compound will give a response typically as shown below in Figure 4.

This particular compound shows some propensity to supersaturate, and hence, the transparency of the medium decreases rapidly once crystallisation starts, which results in a very fine product (Figure 5), with poor filtration characteristics. A small exotherm is clearly visible in both the reactor temperature and jacket temperature once crystallisation starts.

If we look very carefully at the point of crystallisation (Figure 6), we see that the optical sensor is very much more

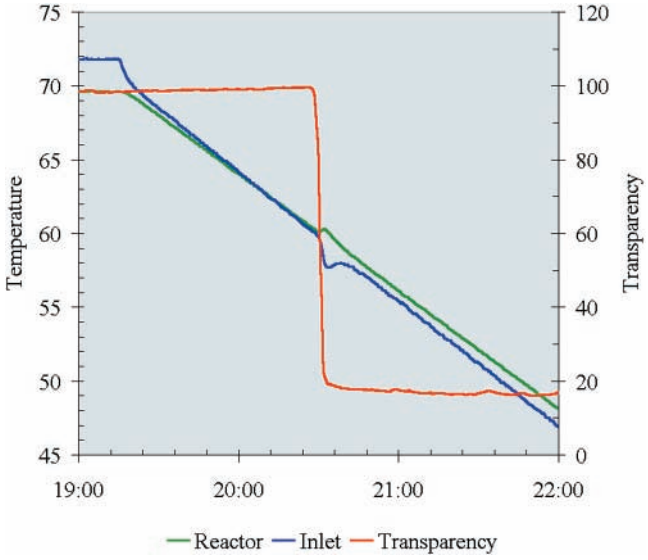

Figure 4.

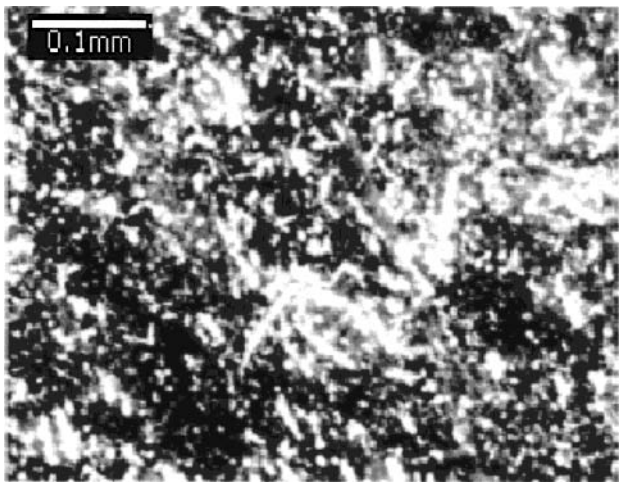

Figure 5.

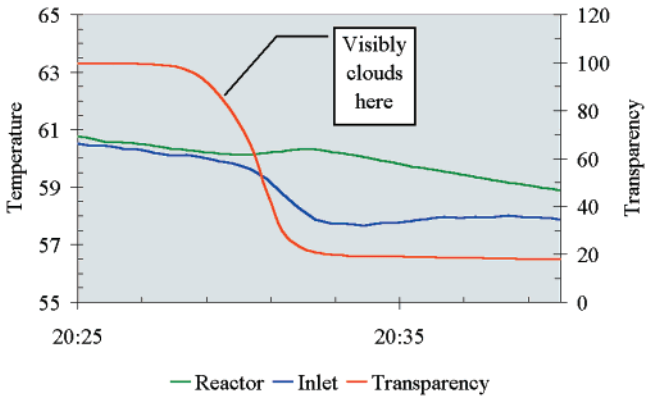

Figure 6.

sensitive to the onset than detection of the exotherm. In fact, it was more sensitive than the chemist's eye!

To increase the particle size of the product, typically you need to minimise the number of nuclei during the crystallisation and suppress secondary nucleation (always difficult with materials that supersaturate). This involves maintaining the system within the metastable region.[20] The envelope of this region can be automatically determined in this kind of

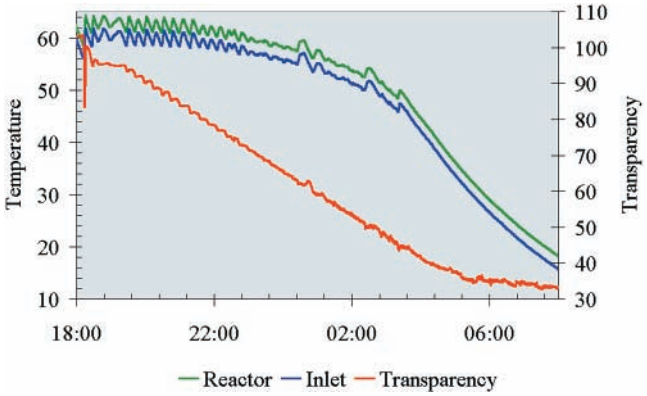

Figure 7.

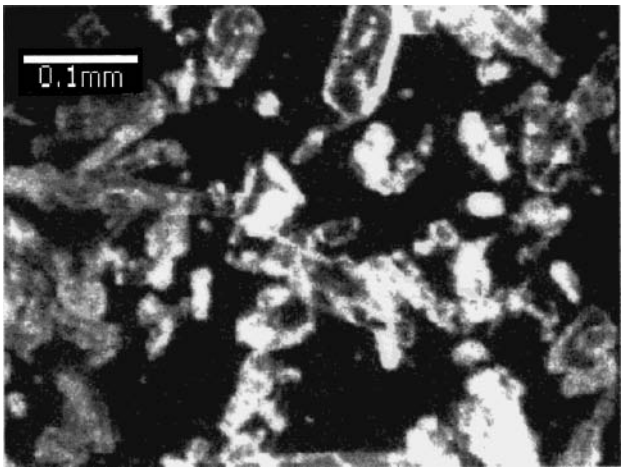

Figure 8.

system by repeatedly cycling the material in and out of solution with automatic dilution at each step.

However, one quick approach to increase particle size in the laboratory is to force the *transparency* down a linear ramp rather than the temperature. This is easily done in the CAR system by using the transparency as the input to control an internal electrical heater (quick response) and controlling the jacket temperature just 3 °C below the reactor temperature to prevent nucleation on the cold jacket walls. An example of the profiles from this is shown in Figure 7 with the product in Figure 8.

As can be seen, this method of control causes the reactor temperature to cycle over a few degrees initially, but a dramatic increase in crystal size has occurred with almost half the crystallisation (as measured by transparency) occurring within 3 or 4 °C of the onset of crystallisation.

With this particular compound, even larger crystals can be grown by controlling the crystallisation down a "saw-toothed" transparency ramp rather than a linear one, causing the smallest crystals to redissolve on periodically warming to increase the mediums' transparency.

There are many other uses for this particular probe. Photodiodes with a variety of spectral responses are available, but the most general-purpose photodiodes have a peak response between 600 and 900 nm, that is, in the red to infrared region. The infrared variety are much less disturbed by ambient light, although this is not normally a problem with these devices. It is quite practical to do this type of work on black solutions that are completely "visibly" opaque. The detector will also detect suspended phases, emulsions, and phase changes across interfaces during separations. A fibre optic version, used as an immersion probe, can be used in opaque vessels.

(c) Plant Simulation. Following successful laboratory development work, a set of revised processing conditions for an existing product were found that allows a 30% increase in concentration during the last stage. The new process involves significant recycling of various streams, including the final product filtrate (which contains a large amount of the desired product), and the final product has a particularly tight specification on a number of minor impurities.

Before extensive plant trials, a laboratory "recycle series" was undertaken in a suite of 2−5 L reactors, controlled by the CAR system, to check for any problems in the processing or product after a number of recycles. Plant materials, heating/cooling profiles, etc. were used, and the process was operated around the clock for a week, with full recycling and recovery of all streams, to obtain a robust mass balance.

An outline of the basic equipment is shown in Figure 9, and a vessel description is given in Table 1.

This particular exercise was carried out on an earlier version of the CAR system, and all of the above was controlled and scheduled from a single computer, leaving the chemists free to observe and sample and organise the logistics of the complex recycle system.

The final outcome was a full mass balance with complete temperature/time profile data for each part of the process, run over five complete cycles, which eventually contributed to an incident-free and successful plant implementation.

(d) DoE and Optimisation. The latest and most flexible version of the CAR system runs a set of three purpose-built jacketed reactors attached to a Gilson analytical autosampler and high throughput HPLC system (Figure 10).

Each reactor is equipped with a speed-controlled overhead stirrer, reflux condenser, thermopocket and sample port, and two nondedicated ports for additions, pH probe, etc. The reactor working volume is 50 to 150 mL. Each reactor has an independent heater/circulator to heat the jacket and a temperature range up to 200 °C. Any other normal laboratory equipment can also be utilised—balances, pumps, pH meters, etc.

The autosampler is programmed to directly sample each reactor on command from the control system. The system can slow or stop the agitation during sampling and alter the sampling height to sample different phases. Samples can be diluted (with or without internal standard) and then injected automatically onto the HPLC, set up with run times of typically less than 10 min. A standard analytical LIMS system allows easy visual examination of "stacked" chromatograms for qualitative assessment of reaction profiles or more sophisticated kinetic analyses may be performed.

Although not implemented yet, it is perfectly feasible to take the HPLC detector output signal back into the CAR system for reuse as an input signal to control the system,

(20) See e.g.: Mettler Toledo publication 00724550, *Optimisation of industrial crystallisation processes* at www.mt.com.

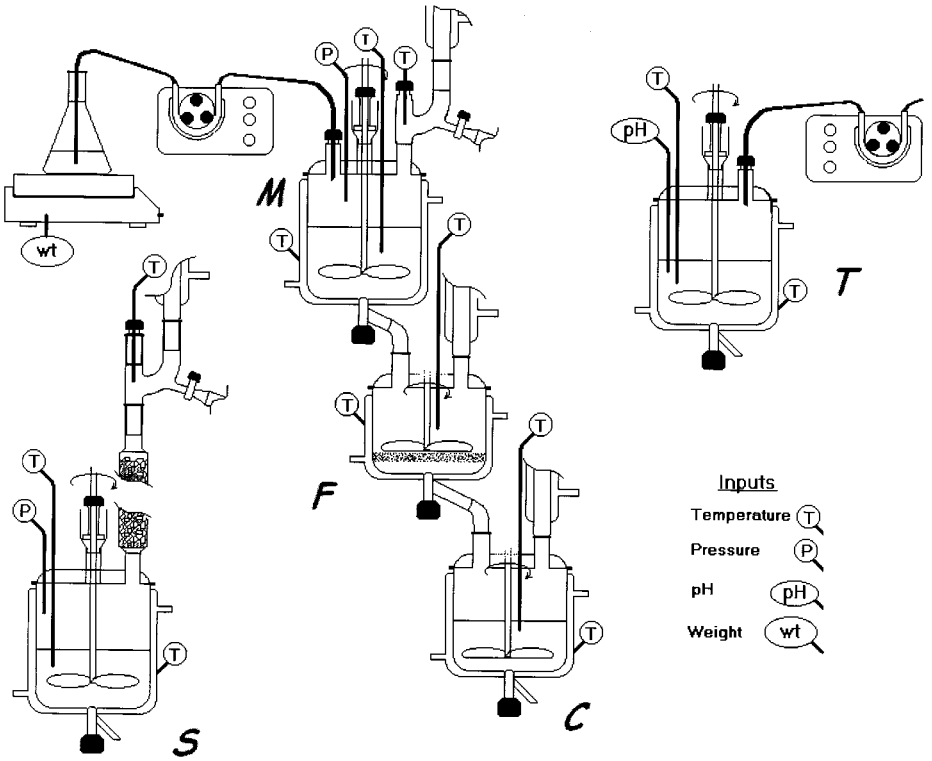

Figure 9.

Table 1.

vessel		description	
M	main reactor	2-L jacketed vessel	temperature-controlled and vacuum distillation system for solvent recovery
F	heated filter	sintered glass funnel	enclosed, jacketed, heated, and stirred for intermediate inorganics removal and washing
C	crystalliser	3-L jacketed vessel	temperature-controlled to allow profiled cooling/crystallisation between 100 and 40 °C
T	filtrate treatment vessel	5-L jacketed vessel	temperature-controlled, controlled caustic addition via pump/balance
S	solvent recovery still	3-L jacketed vessel	temperature-controlled, takeoff temperature/reflux ratio and vacuum

for example, to automatically cool back once an appropriate end-of-reaction condition is met.

The system has seen considerable use for DoE optimisation work on a variety of projects. Once a basic configuration has been established, the experimental variation can be implemented by adjusting the various setpoints for temperatures, feed weights, and times, and the system can be repeatedly rerun.

(e) Route Scouting. A similar system to the three-reactor optimisation system discussed above can be constructed around Gilson autosampler/HPLC and Stem or Variomag heating block with modified glassware.[18] This system is in development, but there are no practical obstacles—the system is technically simpler than the optimisation system above. The existing CAR system already contains all of the necessary functionality to control the common types of heater block.

In route scouting, high throughput HPLC comes into its own. It is a simple matter to see how a reaction has performed from its HPLC traces, and this can save substantial effort. With the ability to do more work in parallel, chemists now have more time to investigate reactions expected to have a lower chance of success. Those that do not work from the HPLC trace can be safely discarded without the need for time-consuming work ups.

At present, work is progressing on the route-scouting system, and here, for the first time, the volume of data generated may become a dominant issue.

CAR Safety Issues

As an issue, safety has not been mentioned thus far but must always be of primary importance.

CAR contains two levels of high and low limits on both primary and derived inputs—"warnings" (visual and audible) and "cut-outs", when a predefined "safe" state is entered. Other alarms can also be generated from some system elements—mathematical errors from derived inputs, errors from the hardware driver subsystems, and watchdogs from the serial subsystem, and these will generally result in a safe shut down if the relevant subsystem cannot be restarted

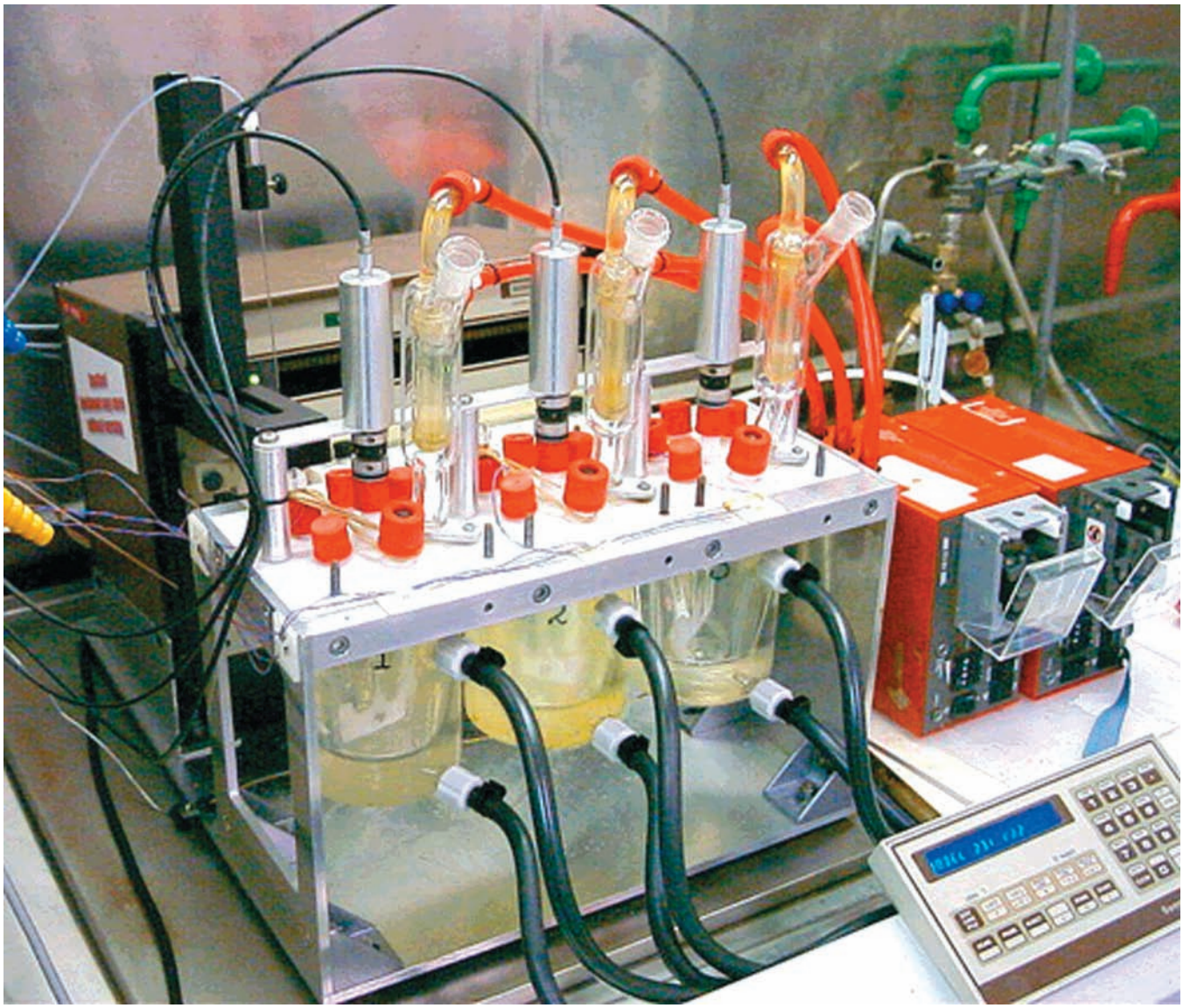

Figure 10.

automatically. All warnings and cut-out alarms are logged with a time stamp. Alarm states will "cascade" through derived inputs to any attached control loop. Each output and control loop has its own set of high and low limits and a safe state, and the complete system can be paused until an alarm clears, or it can be automatically shut down.

Not withstanding the above, by using normal PC and Windows operating systems, it is difficult—if not impossible—to produce a truly fault-tolerant system, and so the control system itself is not considered to be a primary safety element.

The primary safety features on all CAR-controlled systems are the external hard-wired trips—over temperature cut-outs, float switches, etc.—associated with the controlled devices. The normal procedure prior to unattended use is as follows:

- fully "HAZOP" (hazard and operability study) the process and equipment
- set up the CAR alarms, cut-outs, and setpoints appropriately for the experiment and check their function
- install and check the external hard-wired trips
- run repeatedly with a chemist in attendance to check functionality

Even with the above procedures in place, the system is never used unattended with certain types of materials or reactions, for example, pyrophors or toxic gases.

CAR Development Issues

Although originally planned as a simple ALR, developing and expanding CAR has produced much valuable experience and insight into the issues in DIY automation generally. There are many arguments for and against this approach, and most companies will need to make a judgment based on local situations before embarking on an in-house option.

Some advantages and disadvantages are outlined in Table 2. Since the core control functions were frozen some years ago, the CAR system has proved to be very stable and robust—often more so than the attached laboratory equipment, which is the most common source of any problems. Careful planning and configuration for fault tolerance can often overcome some mechanical failures; for example, make sure the autosampler continues to take and store samples even

Table 2.

advantages	disadvantages
tailor-made solutions (what you need may not be commercially available) − you can design exactly what you need	requires a local "specialist" with skills in programming, electronics, etc
flexible, scaleable	development costs
cheap to implement multiple copies	hidden development costs? need to generate support documentation − help files, manuals
stepwise approach is possible − you can fit development to resource	Need to source "unusual" components − glassware, mechanical, electronics...
common approach to automation throughout all three development phases	lack of external support
easier learning curve − local interface design input from chemists	lack of "user group" support
reusability of existing laboratory equipment	

if the HPLC fails, do not start programmed additions until the reactor is up to temperature, etc.

Future developments will be driven largely by the activities within process development, but the flexibility and scalability of the system gives a stable platform on which to base future systems.

One area of interest is the growth in sensor technology, and the generic approach taken by CAR to inputs from external devices means that new sensors can be easily utilised without software modification. Historically, we have often seen some unexpected responses from many different types of sensors when datalogged that would normally pass unnoticed. Sometimes, it may not be obvious what the sensor is measuring in a particular situation, but it is trying to tell you something! The optical probe mentioned above and redox probes are perhaps the most frequent examples of this.

Without a doubt, we have made process observations and gained knowledge using this system that would have been missed with only periodic manual chemist control.

Where Do You Start?

It is beyond the scope of this article to explain this process except by way of a few general points, many of which are common to development of all new computer-related systems or tasks, not just automation. Much of this applies to whichever approach is adopted—commercial software or in-house—although most are aimed mainly at in-house developed systems.

- Is there an acceptable commercial solution?—It will probably be cheaper if you only need one.
- Start small and expand—this is lower risk.
- Start with datalogging only—again, lower risk.
- Get some training. A number of hardware manufacturers and resellers run free seminars on data acquisition. See National Instruments[9] and Adept Scientific.[11]
- Involve your IT department, but keep control of the project—it will start to grow!
- Give careful consideration to the underlying data structure—keep it standard.
- Give consideration to what you will do with the data. Interfaces to other systems need to be considered.
- Use an object-oriented programming environment. This increases code reusability, development speed, and reliability and makes expansion much easier. By encapsulating specific functions and activities within objects, these can be modified or changed without major impact on the rest of the system.
- Don't reinvent the wheel! You seldom need to start completely from scratch. Use commercial components and libraries where possible and modify as required.
- If you have a good idea and you cannot do it yourself, try interesting an existing manufacturer. ReactArray is a good example of this.
- Canvas opinion from potential users—particularly for the interface design. Involved chemists are more likely to use the system.

Although a DIY approach appears daunting, it does offer flexibility and a number of other advantages. Even the totally in-house software approach is not as difficult as might be imagined if a stepwise approach is taken. The necessary tools and hardware are well established, and this area of automation is low-speed and has no unusual requirements. It can be implemented quite adequately with mid 1990s technology.

Conclusions

In Aventis CropScience process development, in-house design of a general purpose laboratory automation system has resulted in the successful development of a flexible tool that fulfils our present requirements. Development has been gradual over a number of years and has been driven by the need to tackle increasingly complex control problems, in particular, parallel working arising from the "combi-chem" approach to route scouting and DoE. This system is now be regarded as mature.

In a more general sense, in-house development is not the best solution in many cases, particularly if a commercial alternative is available, although it can still offer many advantages of flexibility, scalability, and a common tool for all jobs.

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