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CONTROL STRATEGY FOR A

FLEXIBLE ANALYTICAL CHEMISTRY

ROBOTICS SYSTEM

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ABSTRACT

This thesis is the result of work carried out during more than two years on a Teaching Company Scheme. Liaison took place between Rhone-Poulenc Agriculture Limited (the industrial partner), hereafter referred to as RPAL or the company, and Middlesex University (the academic partner). The aim of the Scheme was to realise the design, development, commissioning, testing and validation of an intelligent robotic system for sample analysis of trace pesticides and metabolites in order to enable quicker product development. Due to the complexity of the project and the range of technical expertise and skills needed for its implementation, three associates participated in the Programme. I joined as the second associate. With my degree in Industrial Engineering, I have been in overall charge of developing the computational aspects of the system, from control overview to implementation and validation.

Two distinct types of studies will be carried out with the robot based system:

- Routine extraction of pesticide from soil or plant material, which is compound as well as analyst dependant.
- Method development studies, to optimise those routine extraction processes.

Traditional strategies of control were not applicable for such system because we were dealing with the automation of a non repetitive process involving non-deterministic operations (evaporation, filtration, etc.). The resulting control system should provide a high degree of flexibility to allow workcell reconfiguration without involving any reprogramming. Modularity is also a must if expansion and upgrading to new technologies and equipment is to involve relatively little cost and effort. In addition, all generated data has to be stored and reported following Good Laboratory Practice (GLP) standards.

As the system is both large and flexible in operation, it has proven a real challenge to develop. Software had to be written that can - among its many tasks - allow unrestricted analyst choice, optimise system performance, detect, prioritise and act upon error signals, dynamically schedule robot and instrument operation in real time, trace samples as they pass through the system and generate results as reports stored in databases.

The system is now virtually complete, and is presently undergoing the last stages of the validation. Due to the success of this scheme, further co-operative ventures are being planned between Rhone-Poulenc and Middlesex University in both the UK and France.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

TCS	Teaching Company Scheme
TCA	Teaching Company Associate
TCD	Teaching Company Directorate
TCP	Teaching Company Programme
RP	Rhône-Poulenc
RPAL	Rhône-Poulenc Agriculture Ltd
ORS	Ongar Research Station
GLP	Good Laboratory Practise
GALP	Good Automated Laboratory Practise
ES	Environmental Sciences
SPE	Solid Phase Extraction
GPC	Gas Permeation Chromatography
GC	Gas Chromatography
LSC	Liquid Scintillation Counter
HPLC	High Permeation Liquid Chromatography
TLC	Thin Layer Chromatography
AI	Artificial Intelligence
VB	Visual Basic

1. INTRODUCTION

The Analytical Chemistry department, today Environmental Sciences, of Rhone-Poulenc Agriculture Ltd (RPAL) required a robotic system for sample analysis of trace pesticides and metabolites in order to enable quicker product development. Since such system was not commercially available, it was developed in collaboration with Middlesex University under a Teaching Company Scheme.

1.1. The Company

1.1.1. Rhône-Poulenc SA

The company that was to become Rhône-Poulenc began life in the 1830's amidst the humble surroundings of a silk-dyeing workshop in Lyon, France. The company's involvement in plant protection began several years later with the manufacture of products to control powdery mildew on grape vines, and after several mergers, the company became known as S.C.U.R (Société Chimique des Usines du Rhône).

Meanwhile, in Paris, pharmacist Etienne Poulenc and his brothers formed 'Les Etablissements Poulenc Frères' in 1900, and in the early 1900's French and British chemical activities came together when the Poulenc-Frères sub-contracted May & Baker to supply carbonate and other lithium salts.

Over time, S.C.U.R. merged with several other companies, including in the late 1920's the Poulenc-Frères, and eventually, in 1961, the mergers produced the holding company known as Rhône-Poulenc S.A.

Active in 160 countries, Rhône-Poulenc is now a global company which ranks in the top seven pharmaceutical and chemical Groups worldwide, with leading positions in each of its core businesses. Worldwide sales top £10 billion.

"The Group's strategy, at the dawn of the third millennium, focuses on achieving growth through innovation and globalisation, with particular emphasis on creating value, professionalism and customer service."

After several re-organisations through the years, the Rhone-Poulenc Group was structured in three main sectors in 1998: Pharma, Plant & Animal Health, and Rhodia (grouping all the businesses in the Chemical sector).
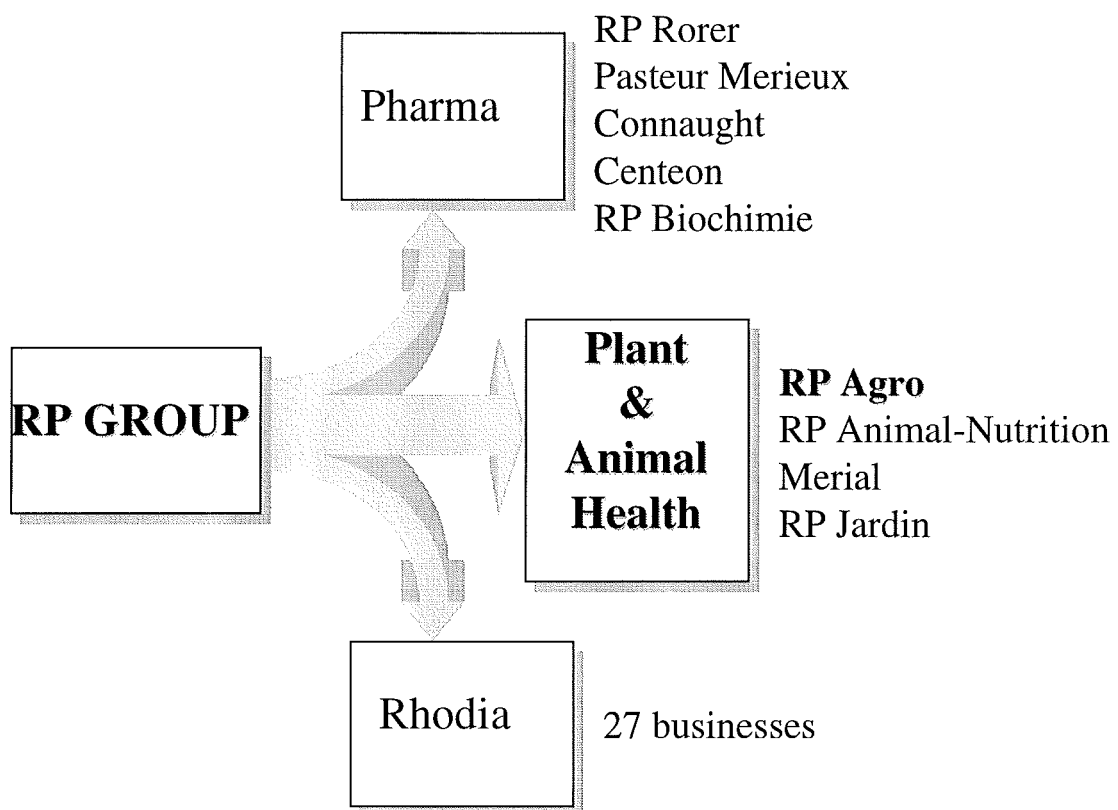
Figure 1 - RP Structure

In the UK, RP Group employs over 4000 people who work at more than 20 locations on products for both home and world markets. RP manufactures at 13 of these sites and also has

two world class Research & Development facilities at the leading edge of pharmaceutical and agricultural research. The agricultural one, based in Ongar, Essex, is key to Rhône-Poulenc's continued record of innovation.

1.1.2. Rhône-Poulenc Agriculture Ltd (RPAL)

The crop protection business of Rhône-Poulenc Agriculture Ltd in the UK draws upon and contributes to the strength of the Rhône-Poulenc Group, providing solutions to farmers the world over. The Company is able to use its wealth of experience to support the continuous programme of innovation that has established its envious reputation.

A world leader in plant health, Rhône-Poulenc Agriculture Ltd not only researches and develops successful new products, but is also aware of its continued responsibilities to the environment and the maintenance of wildlife populations.

All compounds that pass through the Company's laboratories undergo extensive research to make sure that they are safe in every possible way. It is the Company's duty to the environment to make sure that adverse effects are minimised and to avoid upsetting the balance of nature. Environmental studies are carried out on products to trace what happens in soil, water, flora and fauna.

In the world of agriculture, many crops are able to benefit from the protection of herbicides, fungicides and insecticides. Rhône-Poulenc Agriculture Ltd produces a wide range of crop protection products, carefully developed to meet the exacting needs of the farmer. Plants can become damaged, weak or stifled through a whole host of external forces whether it be attack by pests, fungal infection or being in competition for nutrients in the soil from weeds. By developing these products, Rhône-Poulenc Agriculture Ltd can help farmers to grow healthy crops and protect them from pest or fungal damage.

Many of Rhône-Poulenc Agriculture's products are brand leaders such as TEMIK®, Diflufenican®, and ROVRAL®, helping to make the Company a leading force in world and European markets. All of the Company's products

undergo many years of experimental tests prior to release into the public domain. The essential research and development and active ingredient manufacture is co-ordinated between three main centres in the UK, USA and France.

Crop protection has developed over the years into an exacting science. Experience has enabled application techniques to be finely tuned so that minimal amounts of product be applied at exactly the correct dosage rates. Developments have also made it possible to build plant resistance, so that they can be treated with products that previously would have killed them.

Rhône-Poulenc Agriculture Ltd's business is the care, protection and improvement of plants, enabling them to be healthier, stronger and produce greater yields. The world's population is increasing at a rapid rate and the company believes that chemical solutions to biological problems will help to meet the growing demands placed on food producers across the globe. Although the business plays a very significant part in improving crop yields, the company does not dismiss other approaches to growth and actively encourages the development of best practices in traditional farming methods.

The vision of RP Agro is to be one of the major world leaders in crop protection by being the supplier of the most innovative solutions:

- bringing value to the farmers
- increasing the quality and quantity of crop commodities
- respecting people and the environment

whilst conducting business within the Rhône-Poulenc Group's management principles and values.

1.2.   The Analytical Chemistry Automation Project

Rhone-Poulenc Agriculture Ltd. has a first-class research centre at Ongar, Essex, employing 165 scientific and technical staff, with a budget in 1997 of £11 million. Ongar has a successful record of product invention and consolidated its position in the Group when it became RP's worldwide centre for herbicide discovery in 1988. ORS, through its Environmental Sciences Domain, also encompasses the Group's centre of expertise for the study of the environmental fate of herbicides and fungicides.

Crop protection products need to be registered before they can be manufactured and marketed. The registration process requires the environmental fate of the active compound to be studied extensively, to ensure that only environmentally 'friendly' compounds are taken into the market place. This generally involves the use of radio-labelled molecules to aid following the degradation path. The analysis of the sample involves labour intensive techniques and complex quantification methods.

Equally critical to core registration is the development of methods of analysis. Methods need to be optimised to reduce costs and improve efficiency. The rapid development of a new compound requires a rapidly generated method. However, all work undertaken for registration of compounds must comply with International Standards, including GLP (Good Laboratory Practice). These regulatory requirements mean that only robust and validated methods can be used for analysis of plant and soil matrices.

In 1992, a project was set-up to look at the way work was conducted in the Environmental Sciences Department (then Analytical Chemistry) and assess how efficiency could be improved. The ES domain consisted of around 45 people, many of whom were specialist experts in their scientific discipline. However, the nature of the work is such, that highly qualified staff spent a high percentage of their time performing repetitive and tedious tasks. It was recognised that resources needed to be more efficiently used. Reducing the

time analysts spend on those labour intensive tasks, would give a chance to be more creative and innovative in problem solving and focus in data interpretation.
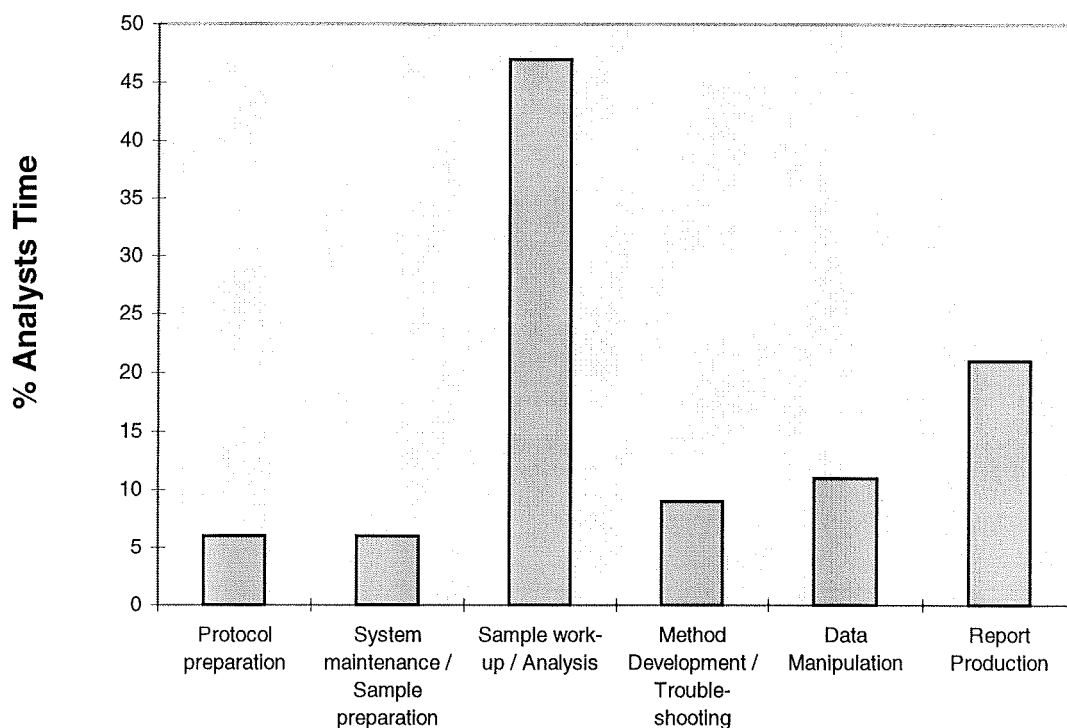
Figure 2 - Time allocation for analyst tasks

The project team identified that sample work-up and analysis, method development and data manipulation took more than 50% of analysts time (Manley, 1995). For some years, RPAL has considered the introduction of automated equipment as an essential step in its development plan. Laboratory automation has many potential benefits such as:

- freeing chemists for more challenging work
- improve productivity, thus reducing the product's time to market
- reduce costs

- improve precision and accuracy

- improve safety by minimising analyst contact with chemicals

However, the automation of the sample analysis process was an ambitious plan due to the complexity of the process, the size of such system and the degree of flexibility inherent to the variety of tasks the system should perform to substitute manpower.

There was not a commercially available system meeting all these specifications. As RPAL did not have the necessary engineering and computing expertise to design and implement such system, several automation companies were approached. The feasibility of the concept, cost and time scales for development were discussed. Although several companies were prepared to provide turn-key solutions, the risks and the costs were considered to be too high. This is the reason why Rhône-Poulenc Agriculture Ltd contacted Middlesex University. The University could provide the expertise and the technical support and RP the funding. In addition, the University was able to obtain external funding under the Teaching Company Scheme (TCS).

1.3. The Teaching Company Scheme

The mission of the Teaching Company Scheme (TCS) is to strengthen the competitiveness and wealth creation of the UK by the stimulation of innovation in industry through partnerships between academia and business.

TCS is supported and financed by a number of government agencies, known as sponsors. For this thesis, the programme was jointly funded by the DTI and RPAL.

The Teaching Company Directorate (TCD) comprises a number of regional Teaching Company Consultants who are responsible for giving general

support and advice to the programme participants. The programme participants are: The Teaching Company Associate (TCA), The Company and the University. The Teaching Company Consultant was Mr Brain Nuttall.

The emphasis on industry was appealing to RPAL with the anticipation of the automation knowledge they lacked and needed.

The Associate spends approximately 80% of his time with the industrial partner and 20% with the university making use of laboratory, workshop and library facilities.

Each programme has a written proposal called the Teaching Company Programme (TCP) covering the details of the work to be carried out, the personnel involved and the timescales for the completion of each stage for each Associate.

Due to the complexity of the project and the range of technical expertise and skills needed for its implementation, three associates participated in this Programme over 3 years. Two Associates in the first year, three in the second year and one in the last year.

The specific objectives for this programme were:
* to undertake the design, development and building of all mechanical elements for a robot system
* to undertake the design, development and integration of all electrical and electronic components of the robot system
* to undertake the design, development and integration of all software and computer algorithms to control and interface the robotic system.
* to provide all documentation and training for the system.

Every three months, a Local Management Committee (LMC) meeting is held between the industrial partner, the academic partner, the Associate and the

Teaching Company Consultant to assess the work which is being carried out and to make sure that there is still sense and direction to what is being done. This meeting allows to discuss any change in the programme objectives, resources and training needed by the Associate to complete the TCP.

1.4. The thesis

The main body of the thesis is organised in six chapters, followed by discussions, recommendations and further work and finalised with conclusions.

As in any other automation projects, the starting point is the study of the manual process. The obvious aims are the understanding of the process being automated as well as the familiarisation with the techniques and equipment involved.

However, the identification of real user requirements is equally important. "Wishes" should be separated from "needs", to promote a smooth transfer from manual to automated and deliver a system that meets all essential requirements. This is covered in Chapter 3, together with a description of all the elements included in the system: glassware, racks, manipulator, laboratory instruments as well as their distribution in the workspace.

Flexible automation workcells generally consist of a group of workstations, some from of material handling system, storage buffers and control hardware and software. The RPAL robotic system for sample analysis is not an exception.

The choice of controlling hardware and software and the overall control strategy required to achieve a system which is modular in principle and flexible in operation is discussed in Chapter 4. Chapter 5 describes in detail the software modules developed to convert the control strategy into a control system.

Issues related to the overall system operation, as for example safety, operating procedures, training and validation, are studied in Chapter 6.

An automation project of such a magnitude should not be over once the system has been implemented, validated and ready for operation. A "living" system, where growth, upgrades and further enhancements are considered and conveniently planned, adds real value to the investments made. In addition, the experience achieved during its development and posterior use should lead to the identification of those aspects that would have been done differently if commencing now. This will have a positive impact in future automation projects and, at a more personal level, in our professional development. All this is reviewed in Chapter 7.

2.   THE MANUAL PROCESS

As it has been stated before, extensive trials are conducted in new or existing pesticides to verify the ability of the compounds to degrade in a reasonable timescale and without producing harmful metabolites. Experiments usually require using compounds radio-labelled with Carbon-14, to aid following the degradation path.

Samples are prepared either by grinding (soil), or homogenising and adding water to expand the cell structure (plants). A suitable solvent, or mix of solvents, is added to the prepared sample, which is then macerated, stirred or shaken to dissolve the compounds of interest. The extraction process may be repeated several times, perhaps using different solvents. The sample is filtered, or centrifuged, and decanted after each extraction to remove the soil material. Next, the resulting solution is evaporated and another solvent dose is added to clean up the sample by removing some of the co-extractives which were soluble in the original solvent. This process can be repeated and other techniques can be applied, such as solid phase extraction (SPE), until a sufficiently clean sample is achieved.

After each step in the process, aliquots are taken to be analysed in a Liquid Scintillation Counter (LSC) and thus, calculate the compound recovery at every stage.

Finally, aliquots of the sufficiently cleaned sample are analysed using chromatography, either High Performance Liquid Chromatography (HPLC) or Gas Chromatography (GC). The metabolites can then be identified using mass spectrometry.
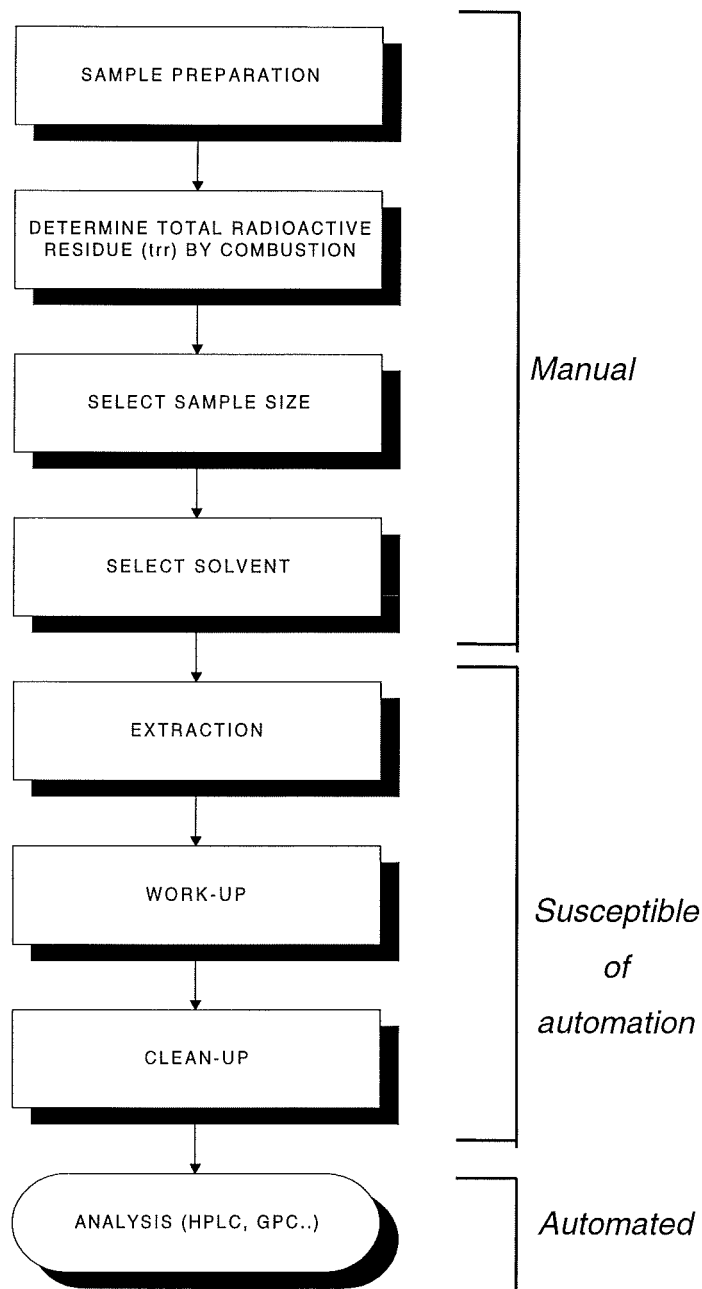
Figure 3 - General description of manual process

2.1. Sample preparation

The pesticide and metabolites, radio-labelled with Carbon-14 to aid following the degradation path, will initially be contained in soil or plant material, referred to as the matrix. The preparation of the sample prior to extraction depends on the form of the matrix. Soil samples do not usually require extensive preparation, although sometimes the soil must be dried in air

and/or prepared by grinding. Plants, however, must be cut and homogenised to produce a uniform sample. Some straw or other dry sample matrices are occasionally soaked overnight in water to expand the cell structure. If extraction cannot begin immediately, the samples are frozen to halt the metabolism, and removed from the freezer about half an hour before the extraction.

2.2. Determination of Total Activity in sample

Once a sample is homogenised, three aliquots are taken to determine the total level of radioactivity. This is referred to as the total radioactive residue (TRR). A cellulose thimble is used to hold 0.2 gr. of sample and the exact weight is recorded. The sample is then covered with cellulose powder to aid combustion and is placed in an oxidiser to be combusted. The Carbon Dioxide given off during the combustion is absorbed by a special material ('Carbosorb'). As the Carbon Dioxide collected contains the radio-labelled Carbon-14, the total activity of the sample, measured in disintegration per minute and per gram, can be calculated using a Liquid Scintillation Counter (LSC).

2.3. Liquid Scintillation Counter (LSC)

Liquid Scintillation Counting is the most sensitive and widely used technique for the quantification and detection of radioactivity. This analytical technique is defined by the incorporation of the radiolabelled analyte into uniform distribution with a liquid chemical medium (cocktail) capable of converting the kinetic energy of nuclear emissions into emitted photons. Photomultiplier tubes (PMT) in the LSC collect the light produced within the scintillation vial and convert it into electrical pulses. Registering each pulse during the time of the measurement provides an indication of the number of scintillation events occurred during that time (counts per minute or CPM).

However, virtually anything added to a counting vial (color, solvents, filters, etc.) can reduce the efficiency of the scintillation process by reducing the number of photons that reach the photomultiplier tubes. As a result, the energy spectrum detected from the radionuclide appears to shift toward lower energies. This effect is referred to as quenching. To correct for quench, it is essential to monitor the counting efficiency in each sample by comparisons with standards. The detected counts can then be converted to absolute units of desintegrations per minute (DPM).

$$\text{Counting efficiency (\%)} = 100 * \frac{CPM}{DPM}$$

Aliquots are taken for liquid scintillation counting after each extraction to calculate the extraction efficiency. In general, three aliquots are taken and the results averaged. If there is significant variation in the three results, the sample is mixed and a further set of aliquots is taken. The size of the aliquots varies between 50 μl and 1 ml, depending on the anticipated activity. An aliquot is taken with a calibrated pipette and using disposable tips to avoid cross contamination between samples. This is then transferred to a 10ml LSC vial. Liquid scintillation cocktail is added and the vial is capped and shaken by hand. Usually, a standard counting protocol is used in the LSC, the counting time being 10 minutes. The results (CPM, DPM, standard deviation, flags, etc.) are printed by the machine at the end of the batch.

The efficiency or percentage of recovery, is calculated according to the equation:

$$\text{recovery (\%)} = 100 * \frac{DPM * \text{volume of extract}}{TRR * \text{sample weight} * \text{volume of aliquot}}$$

The calculated efficiency of the extraction helps to decide the next step in the process, as shown in flowcharts describing the extraction process. Samples

are also counted after filtering, transfers, or any other stage where there is a possibility of losing some of the radioactive material.

2.4. Sample Size Selection

The size of the sample is often specified in the study protocol. It requires sufficient radioactivity. The minimum is 5000 disintegration per minute (DPM), depending on the number of metabolites present.

2.5. Solvent Selection

The first solvent used in the extraction process depends on different factors including:

- Analyst previous experience
- Polarity, solubility and stability of compound and metabolites
- Water solubility
- Boiling point
- Compatibility with next stage in method (e.g. HPLC)

However, the required data is not always available. Generally the solvent is selected on the basis of previous results, although those methods have not usually been optimised. The following solvents are commonly employed:

Acetonitrile & water
Acetonitrile
Methanol
Methanol & water
Acetone
Ethyl acetate
Acidified mixtures
Dicloromethane

The solvent used for subsequent extractions depends to some extent on the results of the preceding one and on predicted results based on previous experience.

Different analysts have different ideas about how to choose solvents and when to switch to a new solvent or a harsher technique. In general, extraction strategies that have worked in the past, are used again, even though they have not always been optimised by method development studies (Muecke, 1983). Radio labelled compounds are very expensive, and once a particular method has been shown to work, it is generally used and specified in advance in the study protocol.

2.6.   Extraction

The aim of the extraction process is to solubilise the residue in a suitable solvent and separate it from the bulk of the non-extractable material. The technique used is different depending on the matrix.

Depending on the efficiency of the process, several extractions could be required. That efficiency is calculated by counting 2 or 3 aliquots with the Liquid Scintillation Counter. The percentage of compound recovery is the key to decide the next step in the process.

The following flowcharts summarise the most commonly applied strategies for the extraction process in soil and plant material.
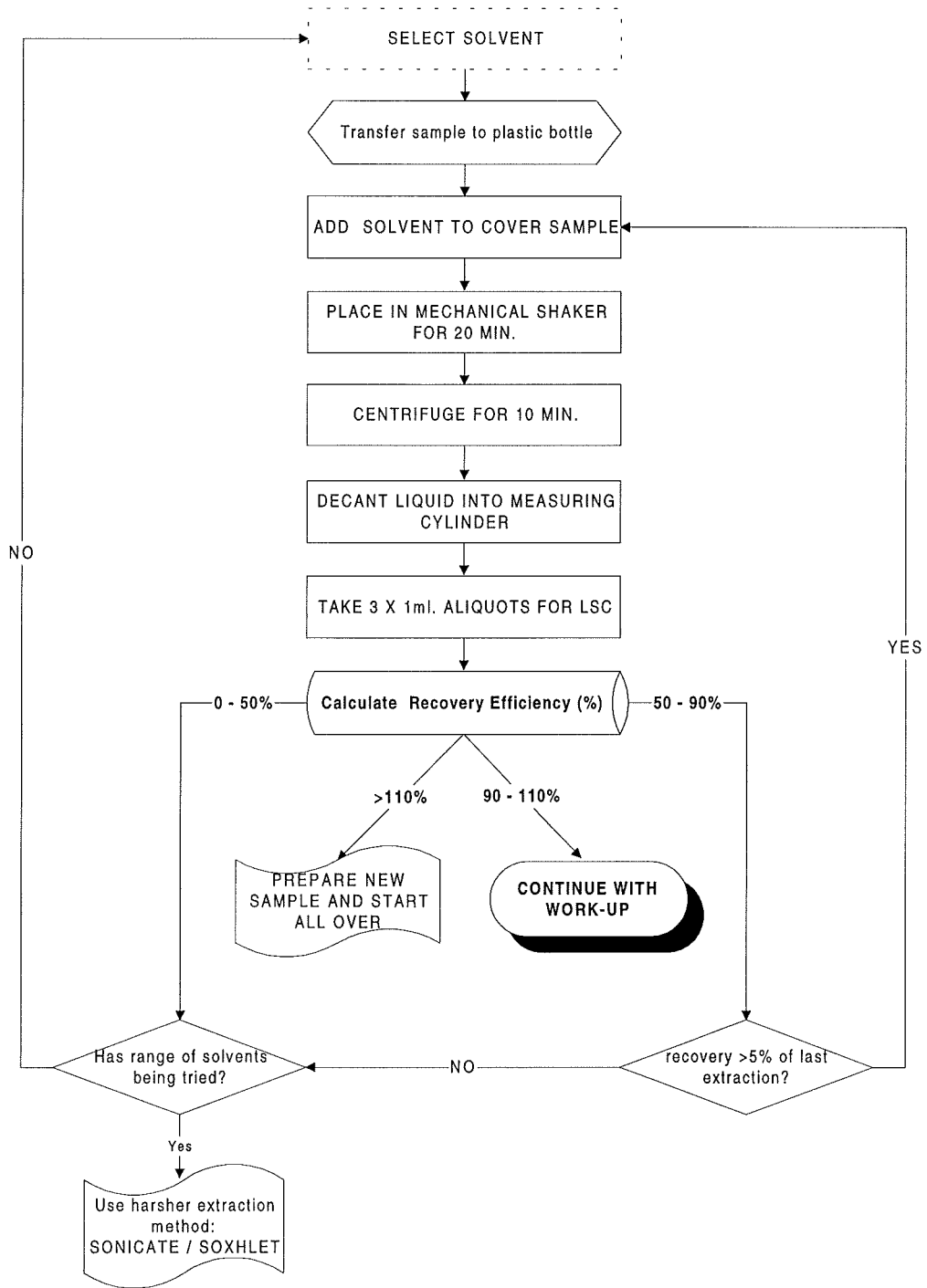
Figure 4 - Current Method for Soil Extraction
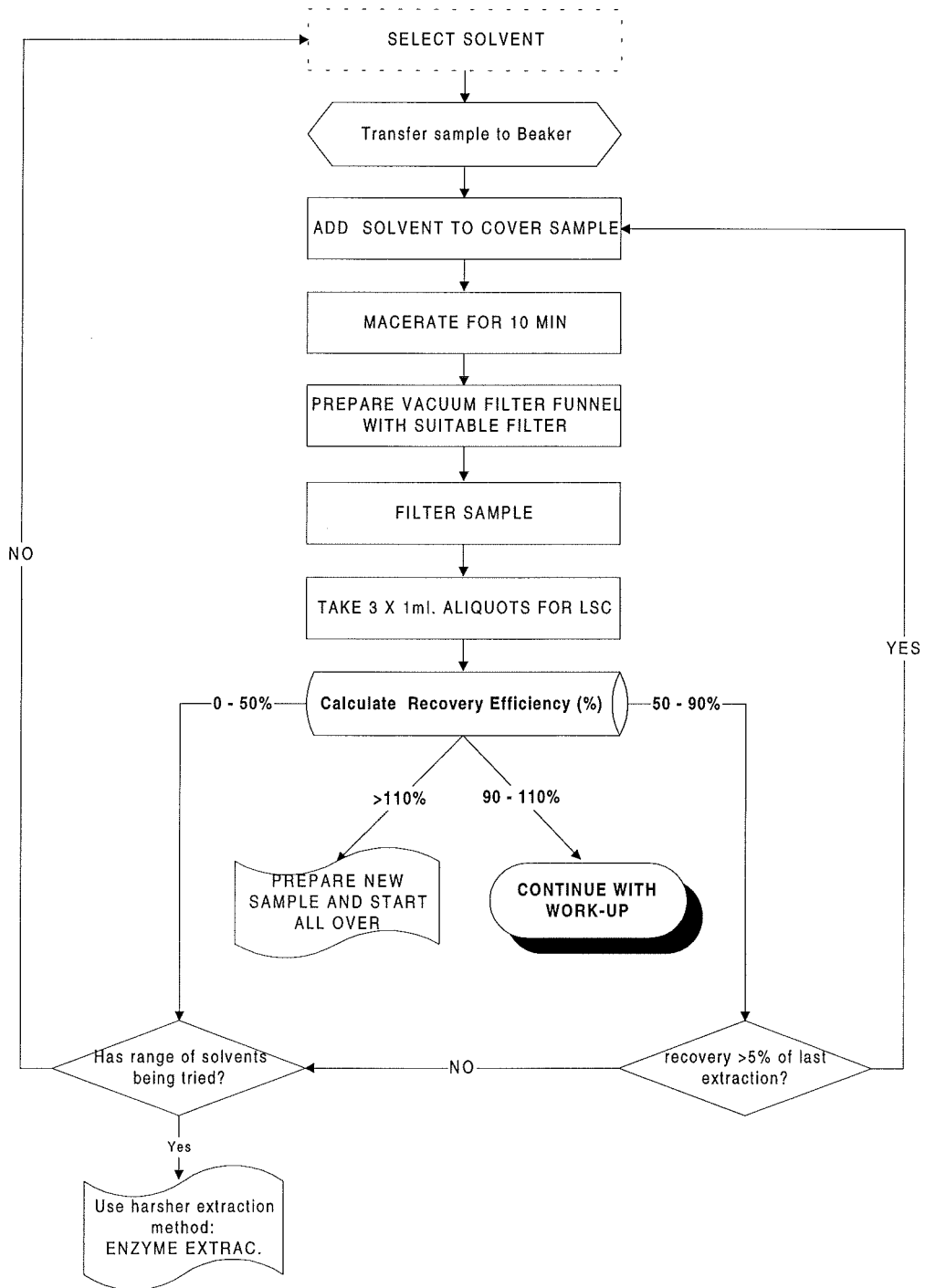
Figure 5 - Current Method for Plant Extraction

2.7. Sample Work-up

In general, extractions with the same solvent are combined, although for method development work they would be kept separate in order to determine the most efficient strategy.

If there is enough activity in the sample, aliquots are taken for analysis. The size of the aliquot depends on several factors, as the activity of the sample and the number of expected metabolites, but should contain at least 10000 DPM per 0.2 ml. Generally, 1/10 to 1/5 of the sample is used for analysis. The remaining volume of sample is kept until the process is finished, in case there is a problem and the analysis must be repeated.

If there is not enough activity in the combined extracts the sample is concentrated by evaporating at room temperature or slightly higher. Evaporation may also be used to remove an organic solvent or to completely dry the sample in order to change the solvent to one more suited to the next stage in the process. Two different techniques are commonly used: TurboVap and rotary evaporation.

2.8. Sample Clean-up

After centrifuging/filtering and concentration, the samples are rarely in a state ready for analysis and will require clean-up step. Combination of different techniques and variables must sometimes be used, depending on how pure the sample needs to be for the next stage in the process.

Liquid-liquid extraction and solid-phase extraction are two of the most common techniques used to separate the compound of interest from soluble co-extractives.
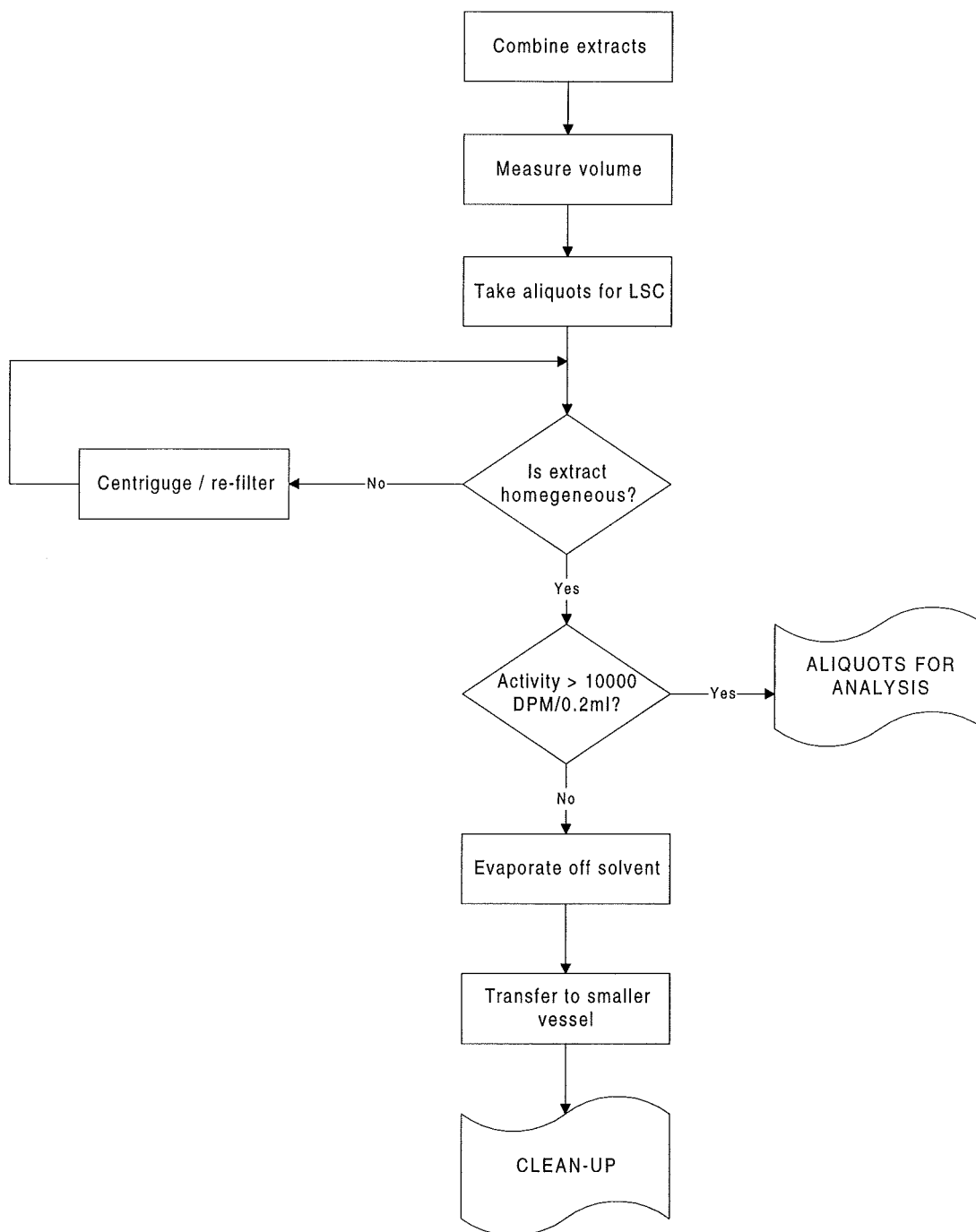
Figure 6. Description of sample Work-up

In liquid-liquid partition, an immiscible solvent is added. The solubility of the sample compounds and the co-extractives should be different in the two solvents, and so, the solvent in which the pesticide is most soluble will contain a lower concentration of co-extractives. The immiscible layers are separated by pipetting off the top layer and an aliquot from each layer is taken for counting in the LSC. Further separations are carried out as necessary to purify the sample. This technique is labour extensive and usually requires a lot of solvent. It is used for grains and sugars.

Solid phase extraction (SPE) is a technique to separate out analytes by passing the liquid sample through a permeable solid phase, which selectively absorbs molecules depending on their chemical properties. The SPE process is carried out using disposable extraction columns (DEC). Different DCE cartridges sizes are available with varying characteristics. Before the sample is poured into the cartridge, the cartridge must be conditioned by pouring clean solvent onto the packing material. Further fractions may be collected by passing additional solvents through the solid. An aliquot from each fraction is taken for LSC. Fractions containing no radioactivity can be discarded, and the other fractions will contain a purer sample. This technique is used with mainly aqueous sample and non-polar soluble compound.

When the existing solvent is not suitable for the next stage in the process, i.e. HPLC, GC, SPE, it has to be changed. A known volume of new solvent is added to the sample and mixed using ultrasonic bath or whirlimix.

Clean-up techniques are summarised in the next flowchart.
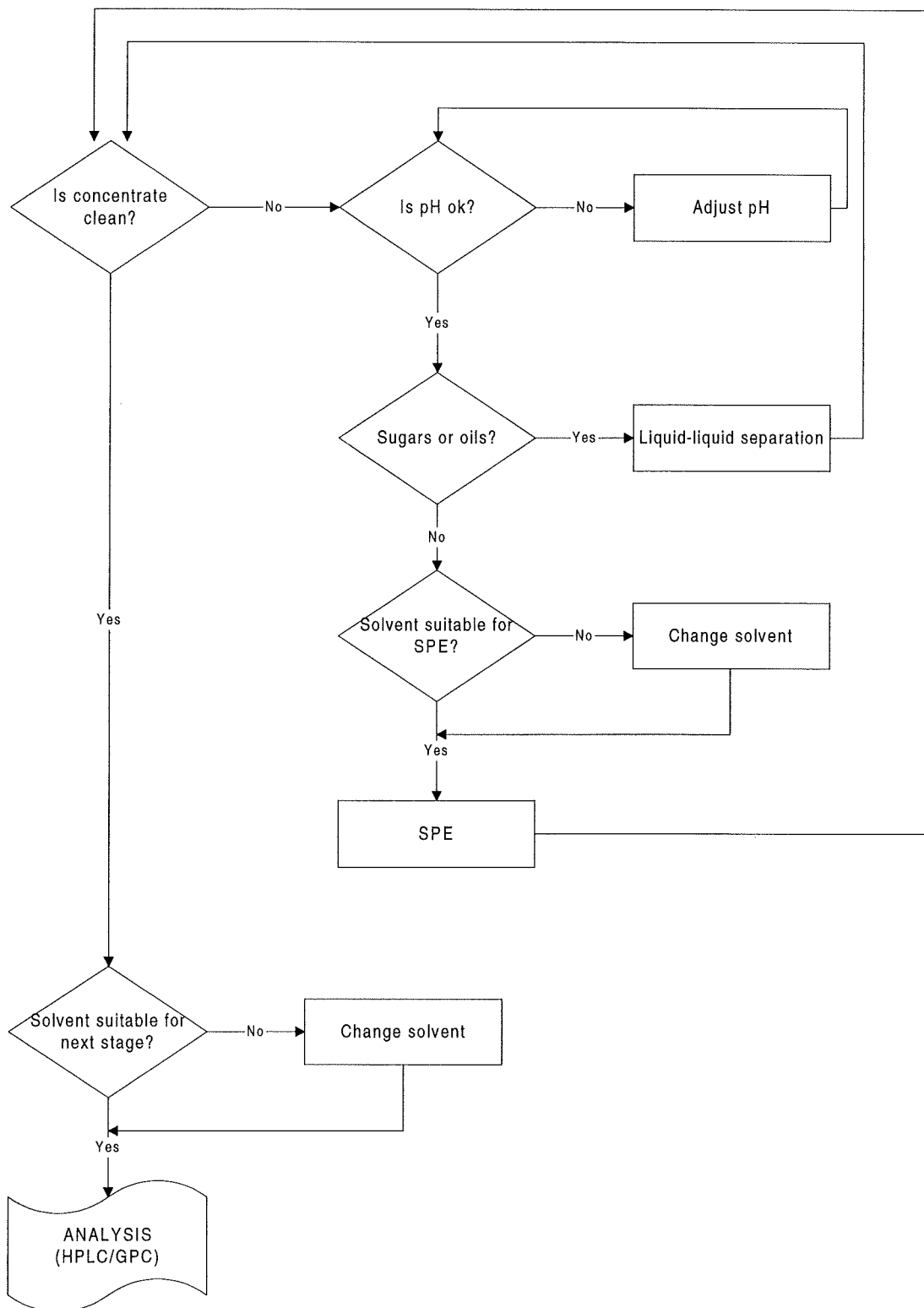
Figure 7. Description of sample Clean-up

2.9. Sample analysis

Once a reasonably pure sample has been achieved, it can be analysed by chromatography or mass spectrometry. The most commonly used technique is high performance liquid chromatography (HPLC), which is used for larger and more polar molecules. The sample is held in solution in a compatible solvent, and contained in a 1 ml. vial. Once the vial is placed in the input rack and the sample details entered in the controlling PC, the rest of the process is automatic. The sample is injected into the HPLC column, where molecules are separated by size, polarity and shape, so that they may be characterised as they pass the detector.

An alternative detection method for smaller and less polar molecules is gas chromatography (GC). Here, the sample is carried on a gaseous phase, but the general principal is the same as for HPLC.

Other techniques employed are gel permeation chromatography (GPC) and thin layer chromatography (TLC). For more in depth work, for example with a new compound where the metabolites are not known, mass spectrometry and nuclear magnetic resonance (NMR) are used.

3. AUTOMATED PROCESS

3.1. Identification of steps to be automated

All the steps involved in the process can be organised in five groups: Sample preparation and solvent selection, extraction, work-up, clean-up and final analysis.

Samples will have to be prepared by hand, as there are a very large number of matrices from which the pesticide must be extracted. In addition, the determination of the sample size and the mix of solvents to use in the extraction process depends not only in the compound being analysed and the protocol of study but also in every analyst previous experience.

As for the most common chromatography techniques used for detection and subsequent identification of metabolites by mass spectrometry, intelligent semi-autonomous HPLC and GC modules are already used as stand alone units in the laboratory.

The intermediate steps in the process, extraction, work-up and clean-up, are the ones susceptible of being automated. It has been estimated that 45% of analysts time is used for those tedious and repetitive tasks. The potential benefits of their automation are:

- Free chemists for more challenging work.
- Improved productivity, thus reducing the product time to market.
- Improved safety, by minimising the analyst contact with chemicals.

3.2. Functions for the automated system

Two distinct types of studies will be carried out with the robot based system:

- Method development, to improve the efficiency of the process to extract the pesticide. An optimised method could result in significant savings in time and quantities of chemical used.

- Routine extraction of pesticide, from soil or plant material. The system aims to process 70% of the samples entering the ES department. "Difficult" samples will be analysed manually in the laboratory and only the most routinely work will be automated. Techniques that are inefficient and time consuming in terms of manpower when carried out manually are also an inefficient use of system resources if automated directly.

3.3. Novelties and objectives

The first conclusion after revising the manual process is that, at present, each scientist performing the analysis have their own preferred methods, and there is little consensus as to the best procedure for extracting and cleaning up the samples, solvents to use, times for centrifuging, etc. The decision making process is protocol or compound dependent as well as analyst dependent. A large number of operational parameters would have to be determined by the chemist at the start of each run, and it is likely that no two runs will ever be identical. This makes the process very difficult to automate since there is not a standard procedure repeated over the time.

Partial automation of discrete operations is commonly used in laboratory environments (solid phase extraction, autosamplers, etc.) In some cases robots have been used to link these small automated cells. Until recently, robot based systems have required too much programming effort, been too inflexible in operation, and too expensive to use (Isenhour, 1989). Although there are numerous references to the use of robotic systems for sample analysis between 1985 and 1997 (Manley, 1999), only the most repetitive analysis has been automated, as for example water analysis (Lee, 1991; Cockburn-Price, 1995), routine pesticide residue or soil analysis (Laws, 1988; Koskinen, 1991).

However, recent technological advances have led automation outside the traditional manufacturing environment into industries where there is little or no repetition of tasks. Laboratory automation affects not only small or rigid processes, but more complex ones (Ahmed, 1994; Donzel, 1993). The RPAL Analytical Chemistry Automated system is one example.

The proposed system will be used for method development studies and it should process 70% of the samples entering the ES department. This made the standardisation of the process not to be an option, since it would limit the scope of application for the system and it would not justify the capital and resource investment required for its implementation. The system should be flexible enough to allow parallel processing of samples which follow different recipes, without any need for reprogramming or modification of the system. This is a big improvement if compared with similar systems (Laws, 1987). In addition, as technology is rapidly changing and so are methodologies of analysis, the system should be designed using a modular approach to allow for future expansion and modification (Buhlman, 1992).

Another special condition is that most of the work undertaken by the ES department is done under Good Laboratory Practice (GLP) regulations. The proposed system and the generated data had to be validated to accomplish GLP requirements. Safety and industry standards would need to be also considered. To summarise, the requirements for the automated system are:

- Being able to perform all the analytical chemistry techniques required for extraction, work-up and subsequent clean-up of samples.
- Flexibility to allow full system reconfiguration between runs without involving any re-programming.
- Easy of use to facilitate the migration from manual to automated processing of samples and promote the use of the system.

- Modularity to allow future expansion, upgrading of laboratory equipment and integration of new techniques.

- GLP compliance of methodologies and generated data which is required for registration and acceptance of any new compound by the regulatory bodies.

The project presents the novelty of addressing the automation of a non repetitive laboratory process involving non deterministic operations, as evaporation or filtration. In addition, parallel processing of samples following different recipes is a must since the overall time has to be optimised to improve productivity.

Glassware   ⟶

Solvents   ⟶   **SYSTEM**   ⟶ Report

Method   ⟶   ⟶ Final products

Figure 8. Aimed system

3.4. Elements in the Automated System

3.4.1. Introduction

To be able to automate the manual process, modifications were required in the way that some processes were performed. It was felt that as long as the chemistry of the process was unaffected and the modified processes validated, the changes were deemed to be acceptable.

This resulted in a list of key workstations that should be integrated in the robotic cell to be able to replicate the manual process performed in the laboratory (See Table 1).

In addition to laboratory instruments, a range of containers for samples and intermediate products had to be selected. Those vessels would sit in racks and would be transferred from one station to the next by a robotic arm.

Technique	Instrument
Extraction (Soil)	Stirrer
Extraction (Plant)	Macerator
Measurements	Balance
Aliquoting	Pipette
Quantification	LSC
Mixing	Vortex mixer
Concentration	Evaporator
Transfer to smaller vessel	Transfer station in ultrasonic bath
Heat	Heating Block
Solvent addition	Solvent dispenser
Liquid-liquid separation: Add solvent/ mix contents/ separate layers/ remove top layer	*Solvent dispenser/ Vortex Mixer/* *Pipette/* Centrifuge
Solid Phase Extraction	SPE station
Analysis	GPC

Table 1. List of station required for the automated system

A research among laboratory equipment suppliers lead to split all those elements between commercially available, those requiring some degree of customisation and custom built ones. However, none of the stations could be integrated directly without some modifications.

Off the shelf (minimal customisation): Balance, Liquid Scintillation Counter, Pipette, Solvent Dispenser, GPC, SPE, Robotic arm, Centrifuge.

Customised (extensive customisation): Vortex Mixer, Stirrer, Macerator, Heating Block.

Purposed built (total customisation): Evaporation, Ultrasonic bath /transfer station, Racks, Robot gripper, Centrifuge balancing station.

3.4.2. Glassware

Due to the wide range of techniques and instruments to be integrated in the robotics cell, different types of vessels must be used. The selection was based, when possible, in standard laboratory glassware, to facilitate the procurement and reduce operational costs. Vessels must be carefully chosen to allow maximum flexibility of extract manipulation with the minimum number of vessels.

The extraction vessel is the initial tube and contains the sample. Up to 100 g. of material can be extracted in this vessel. It consists of a modified Schott Buchner filter funnel. The lower part is a polypropylene base funnel that holds a slotted polypropylene disc sandwiched between two solvent resistant seals. On top of the slotted disc is placed a suitable glass-filter disc that is held in place with a stainless steel mesh. The funnel is screwed into a Pyrex glass filter head.

The filtrate is collected in the collection vessel. The tube selected, a 50 x 150 mm collection vessel, has enough capacity to hold the filtrate, plus some extra capacity to avoid spillage during its transfers from one station to the next (215 ml). During extraction process both the extraction and collection vessels are held vertically one on top of the other to allow the pass of solvent through the sinter.
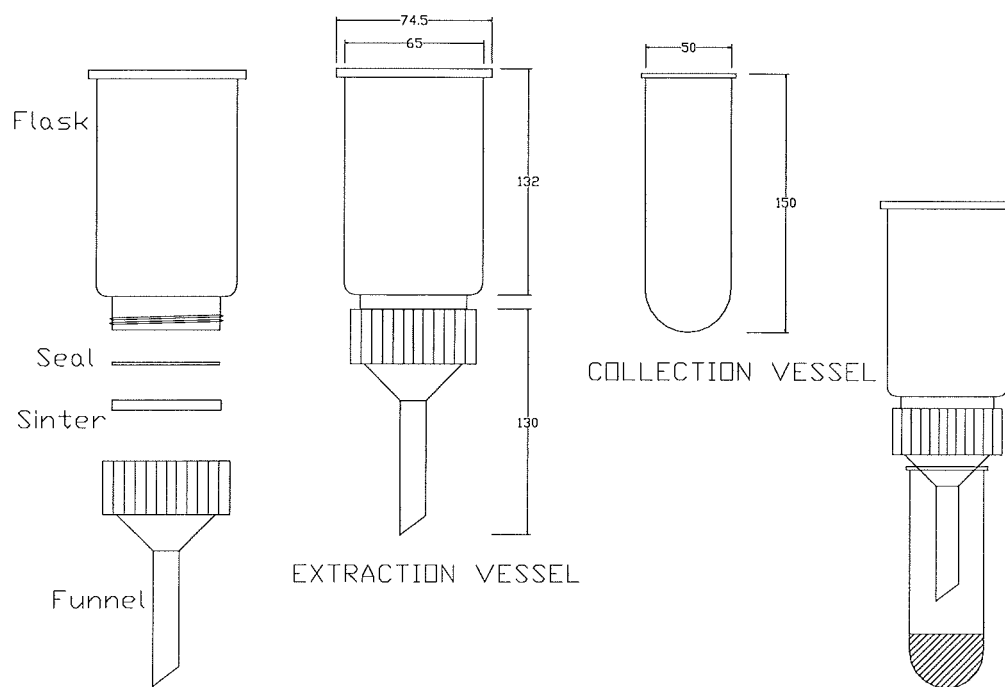
Figure 9. Extraction Vessel and collection vessels

Other two intermediate vessels are used in the system for the bulk of the sample work-up. Volume ratios between consecutive vessels are approximately five to one, allowing manipulation of volumes between 8 to 200 ml at two thirds of full mark. These two standard test tubes are 24 x 150 mm and16 x 100 mm.

The Liquid Scintillation Counter requires a special capped vial for its operation. To simplify operation and to avoid the integration of a cap / uncap station it was decided that the scintillant would be manually added before the process. Those LSC vials, with the cocktail inside, would then be placed in the rack. The robot should move those vials to a pipette workstation where the sample aliquots are added. This is possible because caps have holes centrally drilled. Solvent evaporation is avoided by using a sinter under the cap.
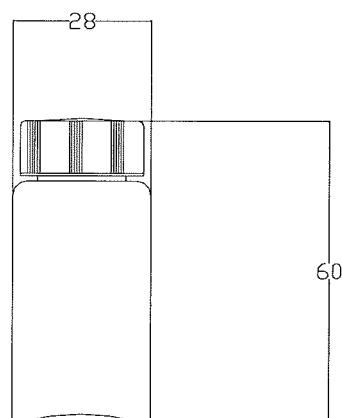
Figure 10. LSC vial

The final vessel is a standard 5 ml vial suitable for most automated chromatographic instruments (GC or HPLC).
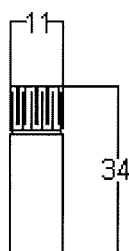
Figure 11. GC/HPLC vial

3.4.3. Manipulator

The purpose of the manipulator is to transfer sample containers between workstations, where the different operations are performed. Traditionally, fixed-base robotics arms have been used, with all the instruments located around it in a highly constricted work space. An example is the Zymark arm, which is a cylindrical robot with three degrees of freedom (DoF). Zymark based systems have been extensively used in the laboratory (Law 1987, 1988; Owens, 1989; Koskinen, 1991; Sheley, 1991; Clay, 1996; Lemme 1997).

However, the process being automated here requires a high number of instruments. Some of these intelligent modules are relatively large. If a fixed-based robot approach was going to be used, several inter-linked robotics cells should be integrated. This solution was not viable due to the high cost and the complexity of its control. To overcome the problem of mobility, a track mounted arm was the preferred option. The track also allows expandability, assuring modernisation and adaptation to new technologies and the possibility of solving bottlenecks by including additional units (Diaz, 1997)

Another limitation found in robots designed specifically for laboratory applications is the small pay-load. The system payload is set by the weight of the heaviest vessel with its contents and the calibration weights for the balance (500 gr). The four DoF Hewlett-Packard ORCA (Donzel, 1993) was unsuitable due to the lack of a waist, small pay-load (0.5 kg.), and limitations on track length (2 m.).

The chosen manipulator was the CRS A465 6DoF, with a similar kinetic arrangement as the KUKA 6/1 or PUMA 6-axis (Dugendre, 1998).

Figure 12. Kinematic representation of the CRS 6DoF robot

It has a high degree of accuracy (±0.05mm), high pay-load (3 kg.), 711 mm reach, customised track length (1m segments) and relatively low cost.

Although CRS robots are classified as small industrial robots, they have been successfully used in laboratory applications: water analysis in North West Water or those described by Cockburn-Price (1995) and Ogden (1996).

The CRS A465 is operated by a C-500 robot controller fitted with a RS232 interface, a System Input/Output (SYSIO) and a General purpose Input/Output (GPIO) module. The last two modules allow the robot to receive and generate signals directly from and to the PLC or other workstations without necessarily going through the serially linked computer.

The only modification required in the robot was the end effector. Variations in vessel size present no problem when chemists are handling samples manually, but in robotic procedures this is a difficult problem. Changeable grippers could be used (Ahmed and Sowma, 1994) but it is an extra operation requiring time and adding cost. To overcome the problem a single multipurpose hand needed to be designed.

The hand should allow a secure 4 point grip, preventing the vessels from swinging. The vessels should self locate in the gripper, allowing accurate placing of vessels in workstations and racks.

To pick up the largest vessel (65.5mm OD), the tips of the fingers would need to be at least 70mm apart. As the servo gripper supplied by CRS had a maximum opening distance of 50 mm, the tips would be at least 20 mm apart in the 'closed' position. This makes impossible the lifting of the smaller tubes (12 and 16 mm), so two pairs of fingers are required in the hand.

Front part of fingers   Rear pair of fingers

Extraction vessel   50 mm vessel   24 mm tube   16 mm tube   28 mm   12 mm
                                                                  vial   vial
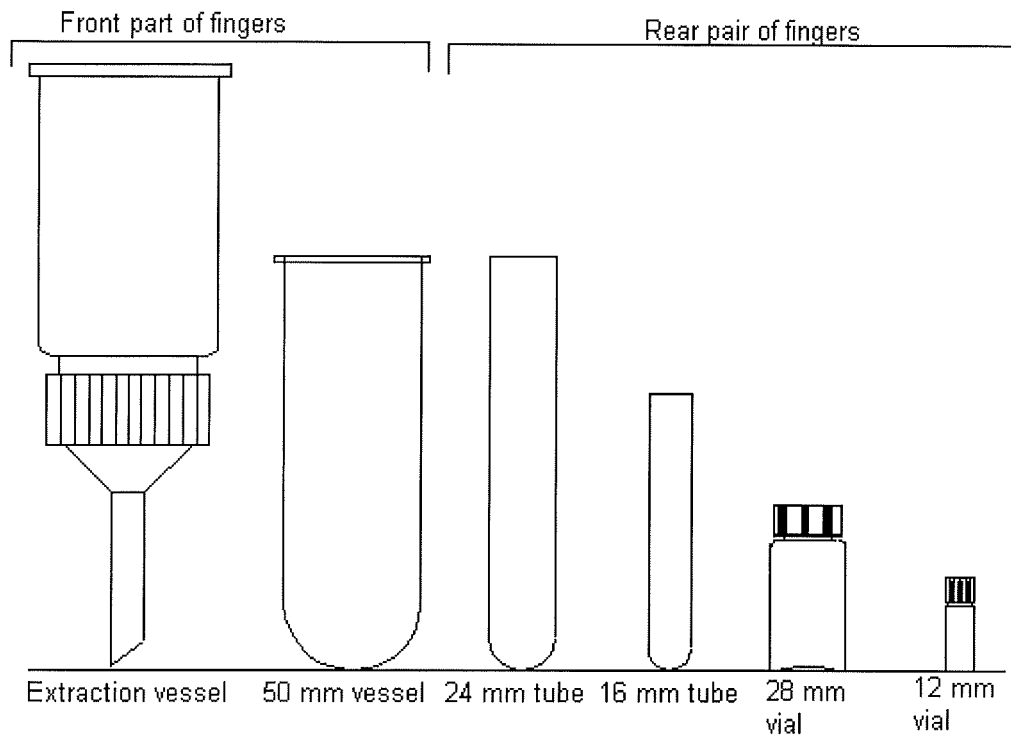
Figure 13. Distribution of vessels in gripper

Another factor taken into account during the gripper design stage was the limited access available in some workstations, as the centrifuge or the stirrer. The final prototype was machined in aluminium and orientated at an angle of 25º from the vertical in order to achieve the maximum vertical lift. Rubber pads were added to protect vessels from damage by the aluminium.

A force sensor is integrated into the servo gripper so that real-time feedback is obtained in the state of the fingers (opening distance, applied force).

Side View   Front View

Plan View
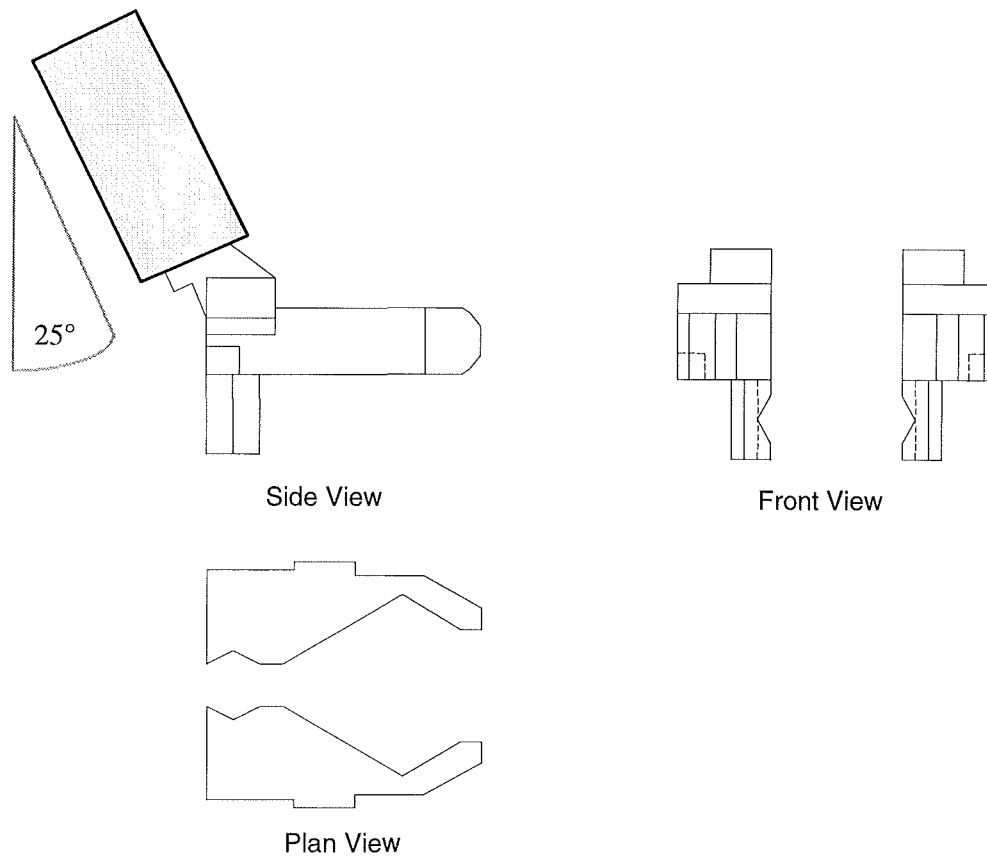
Figure 14. Drawing of gripper

3.4.4. Input and output racks

Racks are required to accommodate all the glassware used during system operation. Construction materials must be resistant to all the solvents employed. Their design is limited by the robot reach and gripper operability. In order to reduce the number of locations and to optimise the bench space, a unique rack will function as an input and output buffer for a certain vessel type. This means that the robot returns a processed container to the location from were it was taken.

The starting point for the automated process is the homogenised sample of soil or plant material, generally weighing between 25 and 100 grams. Samples have to be prepared by hand, as there are a very large number of matrices from which the pesticide must be extracted. The prepared sample

will then be placed by the analyst in the extraction vessel, which is allocated into an input rack. Some of the samples may need to be refrigerated or frozen to prevent further metabolism of the compound. Therefore, the input sample rack requires a chiller to maintain low temperatures. A terraced rack was built to optimise the amount of vessels that can be placed into the robot reachable workspace. It has capacity for 20 tubes distributed in 4 levels from which 12 are surrounded by a refrigerated coil. The same principle of terraced rack was applied to the collection vessel rack were 30 tubes can be stored in a 6 by 5 levels layout.

Buffers for general purpose 24 mm and 16 mm tubes as well as the LSC vials are flat racks containing 50, 108 and 176 tubes respectively arranged in a grid.

3.4.5. Balance

All the process checks and calculations will be performed by weight. This means that the balance is a key station in the system. Vessels will be weighed every time they are moved by the robot.

A customised rack must be fitted over the weighing pan to hold all the different system vessels during operation. The smallest vessel used weighs 2 gr. The extraction vessel, including the sample, does not exceed 450 gr. This bring us to a maximum required capacity of 500 g, including the weight of the rack (around 50 g). The Mettler-Toledo PB602 with a 0.01 g resolution was selected. Its RS232 interface allows the remote control of weighing operations.

3.4.6. Extraction

Extraction is usually the first step of any analytical process, and as a workstation was not available commercially it had to be designed. Some instruments were found in literature but were not suitable for high volume

use (Manley et al, 1999). Existing manual procedures were not suitable for automation. Physical agitation and filtering seemed to be the easiest method that could be automated. This idea lead to the design of a station in which the soil was physically stirred, or the plant macerated, using over head commercially available devices.

The soil extraction workstation is based on the Heidolph Model RZR 2102 stirrer. A frame was built to hold the stirrer and accommodate the containers: the extraction vessel, containing the sample, and the collection vessel, were the filtrate is collected. When both tubes are in place, they are raised to the stirring paddle by a lifting mechanism. Solvents are then added automatically and a slight positive pressure is applied to prevent dripping through the filter. The stirring process starts and, after a set time, the sample is filtered in situ, with the solvent being drawn through the filter by vacuum and collected in a collection vessel. The vacuum must be monitored to enable the detection of the end point or problems such as blockages.

The same principles are applied for the plant extraction workstation, but it is built around the PT6000 Polytron Homogenizer with the RP502 Electronic Programming Unit macerator.

From the communication point of view, the stirrer has an analogue interface for start/stop and speed control, while the macerator is fitted with an RS232 interface. All the in-house built components, as the lifting mechanism, the vacuum system, position switches, etc., will require I/O control.
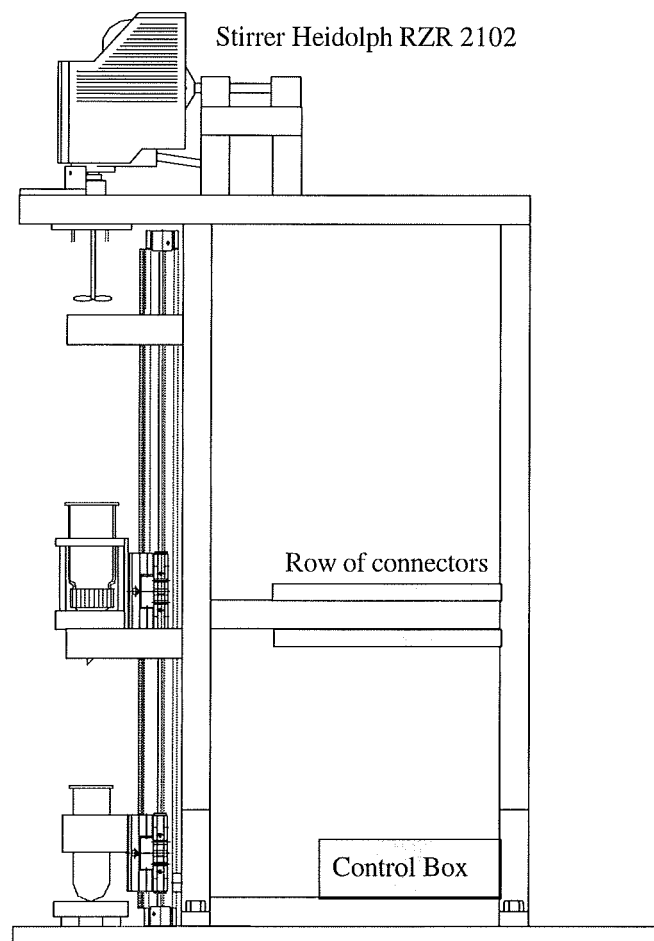
Figure 15. Schematic for soil extraction workstation

3.4.7. Solvent Dispenser

The Compudil D from Hook & Tucker, fitted with a 25 ml syringe, will be used for solvent dispensing in the collection vessel during sample work-up. Communication between the Compudil and the remote controller is via a sequence of ASCII characters through the RS232 interface.

3.4.8. Pipette

The pipette has to transfer aliquots from a vessel to one or several other containers. A Gilson 222XL liquid handler combined with a 402 syringe pump were chosen for the task. The 222 is a slave XYZ robot that can be

controlled by computer or the keypad through a RS232 connector. The 402 is a dual pump with two syringes of 5 ml and 0.1 ml capacity which works as a slave to the Gilson sampler. The XYZ arm moves a probe from location to location, while the pump is used to aspirate and dispense with and accuracy of ±2% of full stroke. A rack was designed to accommodate all the different system vessels.

3.4.9. LSC

The Liquid Scintillation Counter is dedicated to the detection and quantification of radioactivity. This analytical technique is defined by the incorporation of the radiolabeled analyte into uniform distribution with a liquid chemical medium (scintillant or cocktail) capable of converting the kinetic energy of nuclear emissions into emitted photons.

The cocktail is manually added into the LSC vials after which the vials are capped and placed into the input rack. During processing, the robot transfers the vials to the pipette, where the radiolabeled analyte is incorporated before they are counted in the LSC.

The Packard Tri-Carb 1000 is a one shot LSC that allows internal compensation for the effects of chemical or colour quenching. Its uni-directional RS232 interface allows the collection and storage of resulting data by a computer. However, no order or command can be sent through the serial link. To overcome the problem a relay was internally fitted to simulate the "start" keystroke of the front panel. In addition, a universal fixed counting protocol, entered and stored in the counter memory using the keypad, will be used at all times.

3.4.10.   Vortex Mixers

The station is based around three Heidolph laboratory vortex mixers (Model REAX 2000)., one for each of the three test tube sizes used in the system

(16, 24 and 50 mm tubes). The samples are mixed by rapidly rotating the base of the test tube whilst keeping the top still, thus forming a vortex inside the tube. Digital signalling is required for remote control of each mixing station.

A rigid frame, made of extruded aluminium modules, was built to support the various components of the workstation. The frame was designed to ensure that the robot gripper had access to the station and enough space to manipulate the vessels. When the robot places the test tube into the station a manifold is lowered onto the vessel. This holds the top of the vessel firmly in place during mixing. Force and actuator speed control is important to ensure correct mixing and to avoid breakage of vessels.
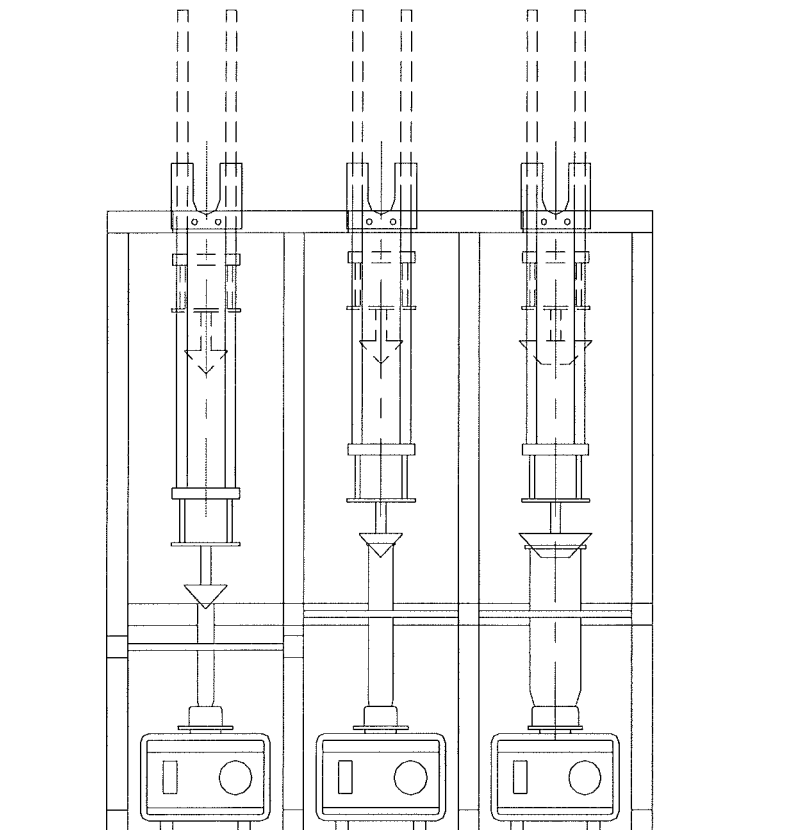
Figure 16. Vortex Mixer Layout

3.4.11. Evaporators

The evaporation workstation reduces the volume of sample by evaporating solvent. The end point of the evaporation should be set remotely, to allow the user to decide how much of the solvent to evaporate. A suitable off-the-shelf workstation is not available on the market, so the workstation needed to be custom designed. The closest commercially available device is the Zymark 'TurboVap', which is unsuitable because of the unreliability of the end point sensing.

A rigid frame, made of extruded aluminium modules, was built to support the various components of the workstation. The frame was designed to ensure that the robot gripper had access to the station and enough space to manipulate the vessels.

When the robot places the test tube into the station a manifold is lowered onto the vessel. Once the target temperature is reached, it is maintained by means of a temperature controller. The evaporation is carried out under a partial vacuum to improve the rate of evaporation. The vacuum draws air into the tube through a narrow nozzle which disturbs the surface of the liquid, increasing the surface area of the liquid and improving the evaporation rate. The end point is determined using optical level detection. Four levels, and consequently four volumes, can be pre-set by the user as the final volume.

Digital and analogue (temperature control) signalling is required for remote control of each evaporation station.
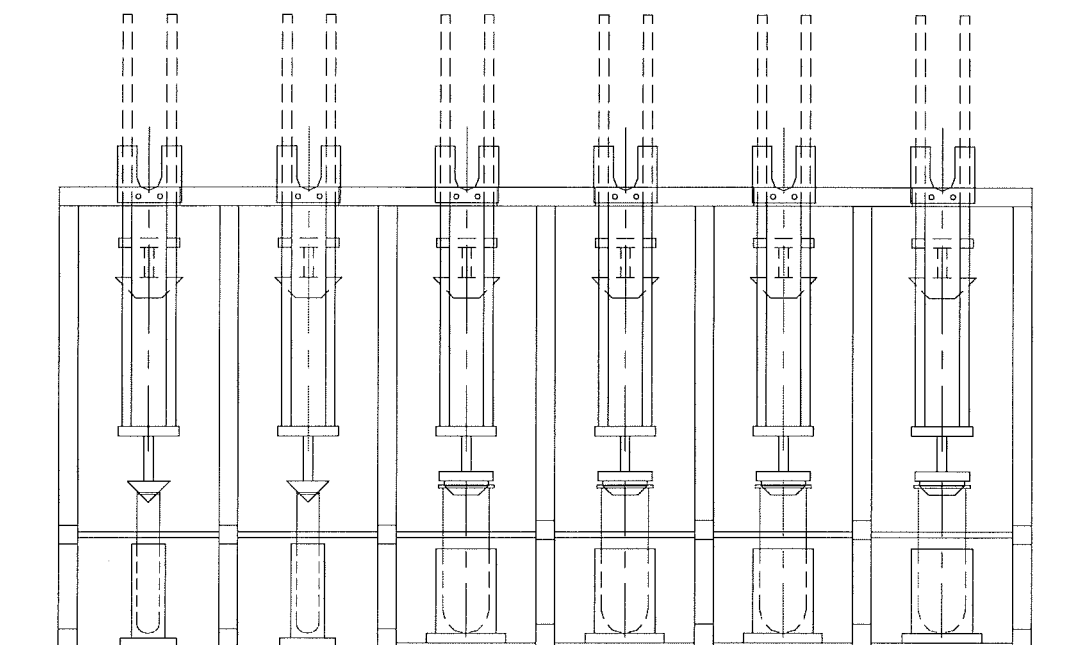
Figure 17. Evaporation Layout

3.4.12.   Centrifuge

The system centrifuge is a Sigma 6K10 fitted with a swing-out rotor for four buckets. The buckets provide accommodation for two collection vessels, four general purpose 24 mm tubes and four general purpose 16 mm tubes.
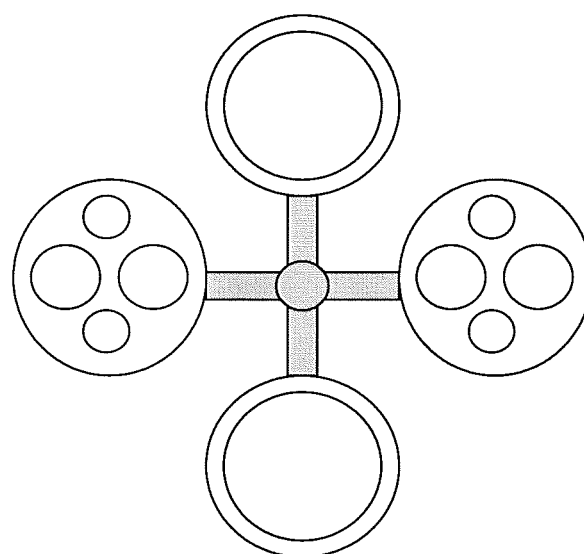
Figure 18. Centrifuge chamber schematic

The rotary centrifuge is equipped with brushless, silent asynchronous motors. It is built into a solid aluminium frame and cased with foamed synthetic parts. An upper lid offers access to the rotor chamber. If the lid is open the operation of the centrifuge is prevented. Motorised covers are automatically locked if the cover is closed.

Centrifuges are not frequently integrated into automated robotic cells due to two reasons:

- Fixed access locations: The robot is used to load and unload the centrifuge. To avoid crashes fixed pickup locations must be used at all times. VA Howe developed an indexing mechanism which operates during the stopping phase to drive the rotor to the same point where it started from.
- Rotor imbalances: In case of uneven loading of opposite buckets the drive is switched off during acceleration or during run. A balancing workstation was developed to balance the rotor when centrifuging just one collection vessel.

The centrifuge operation can be directly controlled by a Master PC via the bi-directional RS232 interface. The only extra feature required is an automatic lid closing. A relay box was added to interface the required external digital signals to the centrifuge front panel for keystroke simulation.

3.4.13.   Centrifuge balancing workstation

The aim of this workstation is to balance the rotor of the centrifuge when processing only one 50mm vessel. The weight tolerance between two opposite buckets is 10g, and that the tolerance between two consecutive buckets 100g.
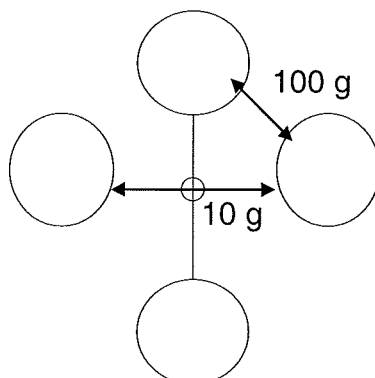
Figure 19. Rotor imbalance tolerance

The station is based in a Mettler-Toledo PE400 balance and a Gilson M312 peristaltic pump. When the robot moves a sample to the centrifuge, its weight is recorded and used as a reference value for the balancing station. The arm will then place an empty vessel over the PE400 balance and the solvent pump will dispense water until its weight matches the weight of the sample to be centrifuged (within 10gr). This compensation vessel will then be loaded into the opposite bucket.

The Mettler balance can be interfaced to a computer via a unidirectional RS232 interface. The continuous flow of data is interrupted manually by removing an internal pin. A reed relay is used to replace the manual process. As for the Gilson pump, its I/O interface module allows the remote control of the start/stop signals.

3.4.14.   Heating Blocks

These stations are based around two Liebish Thermochem heating blocks fitted with West 6100 temperature controllers. The purpose of this workstation is to heat or evaporate the contents of the vessels. The temperature for evaporation is usually less than the heating temperature. As

the time to cool down would be too long, two different heating units were integrated.

The heating unit will be used for three types of tubes (50mm, 24mm and 16mm) while the evaporation unit is used for 16mm tubes only. The latest will be covered by a manifold and positive pressure will be blown inside while the vapours are extracted.

The 6100 are equipped with a two-wire RS485 compatible serial communications facility, by which means communication may occur with a controlling computer. A RS232/RS485 converter was externally added to homogenise system communications.

3.4.15.   Ultrasonic Bath

The ultrasonic bath is a standard laboratory piece of equipment that has been equipped with a vessel drying system. Its main function is the mixing of tube contents.

A rigid frame, made of extruded aluminium modules, was built to support the various components of the workstation. The frame was designed to ensure that the robot gripper had access to the station and enough space to manipulate the vessels. When the robot places the test tube into the station a manifold is lowered onto the vessel. As this station is also used for sample transfer, stainless steel HPLC tubing slides through each nylon cap. The tubing is spring mounted to take into account the variation in size of the test tubes.

Digital signalling is required for remote control of the ultrasonic bath station.

3.4.16.   GPC & SPE

The Gilson GPC system and the Waters Millilab (SPE) were purchased by RPAL before the start of the project. Both are semi-autonomous workstations that can be programmed off-line through a keypad or a PC. However, some dynamic interaction is required if they are going to be part of the robotic cell.

Their operation will be started remotely by using a contact closure from the PLC. In a similar way, a stop signal will be flagged in the PLC when the process is finished.

3.5.   Simulation of process

Simulation is the process of imitating the behaviour of a real system by constructing and experimenting with a model which is a simplified representation of the system. Simulation is beneficial practise when a mathematical solution to a particular problem cannot be found to the complexity and variability of the real system being modelled. Experimenting with the real system is expensive, time consuming and impractical, so a visual interactive simulation (VIS) provides a convenient tool for testing different approaches (Smartt, 1997).

The purpose of the simulation in our laboratory environment is to produce an overall layout of the stations in the cell, identify and solve bottlenecks and define a scheduling strategy for the robot.

Three dimensional graphical simulation has been used to derive a workable and efficient layout. Solid modelling or wire frame models of a robot cell provide a great deal of detailed information, but they can make re-arrangement of the layout difficult and time consuming. If it is valid to simplify the workcell to a two dimensional representation, the flexibility of the resulting model allows a large number of possible layouts to be evaluated

(Smartt, 1996). A legitimate example of a two dimensional model is one based around a track mounted robot.

Lanner Group's (then AT&T Istel) "Witness" package was chosen because it provides facilities for graphically creating and running a simple two dimensional model with an appropriate level of detail. Simulation models can be created and edited in a Windows environment and the display animated at run-time, providing a graphical representation of the simulated system.

A 2D scale plan of the robot workspace was produced using AutoCAD (Autodesk Ltd) and the accessible area was divided into sixty equally sized addresses. A scale drawing of each workstation was then produced and added to the overall layout drawing. This indicates whether the layout can be physically realised.

Stations are initially modelled as independent "machine elements". These elements include information such as the estimated process time and variability. The robot track is modelled as a one dimensional array of sixty elements, each one referring to a physical address in the cell. At the beginning of each run, every station is allocated to a particular address in the cell.

The main problem was to determine which process to simulate since the proposed system should operate at a high level of flexibility and no process may ever be repeated. If the results of the simulation are to be valid, it is important that the simulated process is representative of the processes likely to be performed by the real workcell. Layouts were evaluated using a standard experiment which was considered to be representative by analysts at RPAL. This consisted of a batch of four samples, with each sample extracted three times.
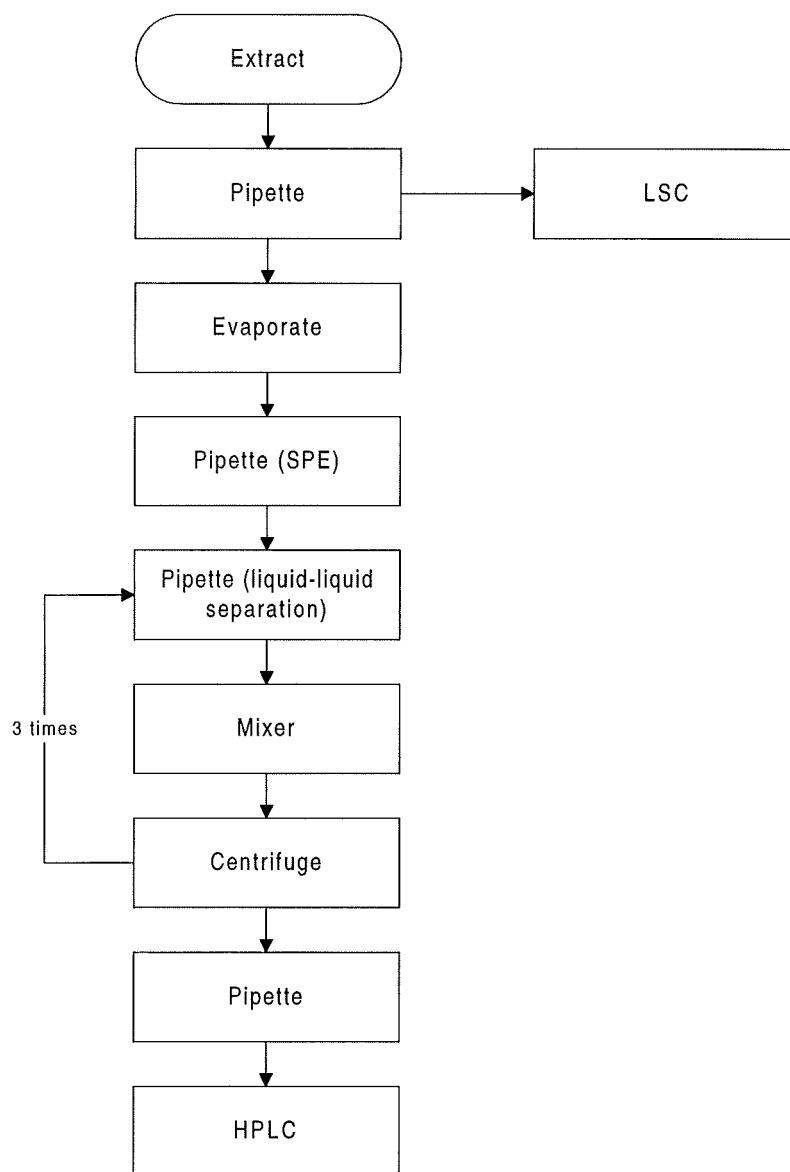
Figure 20. Experiment used for simulation

3.5.1. Simulation results and final layout

The different criteria used to evaluate the modelled layouts were:

1. Cycle time for the representative batch of samples
2. Total distance travelled by the robot
3. Time taken to answer the station calls by the robot
4. Percentage of busy and idle times for key workstations

Simulation probed that one of the busiest elements in the system was the robot. Optimisation of robot time increases the capacity and throughput of the system (Little, 1993). Measures had to be taken to reduce the robot workload and the effort was concentrated on reducing the transfer time between frequently used workstations by rearranging the layout of the workcell. These measures resulted in a 27% reduction in the predicted total process time.

The main bottleneck, when using the proposed analytical method, was the liquid-liquid separation loop. Pipette, solvent dispenser, vortex mixer and centrifuge should be placed as close together as possible to reduce the transfer time between them.

The evaporation is the longest step in the process and could become a limiting factor in the flow of samples. The problem was solved by multiplying the number of modules. Four stations for 50 mm vessels and two for 24 mm tubes were integrated in the robotic system.

Extraction and specially LSC were also identified as critical due to their high workload and long operating time. The expense of the equipment precludes the purchase of more than one instrument. High scheduling priority should be assigned to those workstations during operation.

The final layout of the system is shown in the following figure
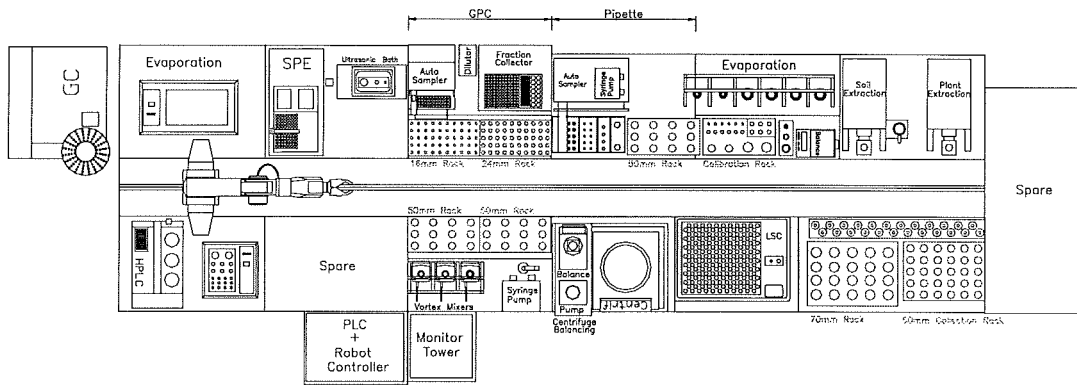
Figure 21. Layout of workstations along the track

4. SYSTEM CONTROL STRATEGY

Flexible automation workcells generally consist of a group of workstations, some form of material handling system, storage buffers and control hardware and software. The RPAL robotic system is not an exception. It consists of a robot mounted on a 6 metre linear track whose function is to transfer vessels between racks and instrument positioned along the track. The question arising is how to control all these resources to achieve an integrated unit. Controlling hardware and software as well as the overall control strategy have to be defined.

4.1. Controlling hardware

A high number of instruments from different vendors must be integrated in the system. As shown in Table2, some of them can be remotely controlled via an RS232 interface, other by digital and/or analogue signals and a last group requires a combination of both.

Workstation	RS232	I/O
Extraction (Soil)		v
Extraction (Plant)	v	v
Balance	v	
Evaporation (x6)		v
Pipette	v	
LSC	v	v
Vortex Mixer (x3)		v
Solvent Dispenser (Compudil)	v	v
Ultrasonic Bath		v
Centrifuge & Centrifuge balancing	v	v
SPE & GPC		v
Heating Block I (heating)	v	
Heating Block II (evaporation)	v	v

Table 2. Instruments and signals

RS232 instruments can be directly controlled by a computer, but some form of controller is required to integrate the rest of the stations.

4.1.1. I/O controller

Programmable logic controllers (PLC), data acquisition cards (DAQ) and micro-controllers were evaluated in terms of expandability, cost and implementation time.

Micro-controllers are an attractive alternative since they provide modularity and expandability. Each station would have its own controller, becoming a semi-autonomous instrument like any other intelligent serial device. However, this presented some disadvantages. Firstly, the highest implementation time due to the fact that some electronic circuitry would need to be developed. Secondly, a dramatic increase in the number of RS232 ports to be interfaced.

DAQ cards were dismissed because of the high number of I/O involved and their different nature (digital, analogue, timers, temperature controllers). Too many different cards would need to be integrated. All control tasks would be computer based which would have a significant impact in the CPU workload. To avoid a reduction in performance, a computer network of a considerable size would be required to control the system, with the subsequent increase in cost.

Micro-controllers are certainly a good option for stand-alone units or small systems. DAQ cards would be a good alternative if only digital technology was required. However, for an integrated system the size and complexity of ours, a PLC was considered the most time and cost effective option.

A PLC of adequate capacity would be able to perform all the low level control tasks without increasing computer demands or the number of RS232 links. Both factors are important if we consider the number of serial instruments

that need to be controlled via PC. In addition, it provides expandability without affecting system performance and without requiring significant modification of the existing system.

The Omron C200HS-CPU21-E PLC was selected because it has capacity to drive all the existing inputs and outputs (14 modules all together), has extra capacity for future expansion and includes an RS232 module for system interaction.

4.1.2. Robot controller

The CRS A465 robot is operated by a CRS C-500 controller fitted with a RS232 interface, a System Input/Output (SYSIO) module and a General purpose Input/Output (GPIO) module. The last two modules allow the robot to receive and generate signals directly from and to the PLC or other workstations without necessarily going through the serially linked master computer.

4.1.3. Distributed computer environment (DCE)

Computer power is required for process scheduling, supervisory control, management of serial communications and data storage. The centralisation of tasks in a unique master PC is not appropriate due to the high workload to be sustained. A lack of system resources would have knock-on effects on system speed and performance. Even worse, it could originate loss of data if the system is busy and not able to process a serial port interruption.

Distributed computing environments (DCE) comprised of networked workstations or personal computers or both, are rapidly becoming the standard configuration for manufacturing automation and process control systems, indicating a trend towards networked computer based controlling systems. (Usdata, 1993). In a system the size and complexity of ours it provides clear benefits in terms of:

Compatibility: multiple platforms and different vendors software standards can interoperate through a common network.

Expandability: new stations can be integrated by simply connecting a new computer to the network and developing the required software for that piece of equipment.

Modularity: the system can still operate if one of the modules fails. In addition, only specific software has to be modified when upgrading or adding a certain laboratory instrument.

Performance: the multiplied CPU capacity and the distribution of workload has a positive impact in the speed and capacity of the controlling system. Applications running concurrently in several computers provide a global multitasking environment.

Cost: available computers in RPAL can be used for the development period and being upgraded at a later date. This would enable a phased purchase strategy.

Upgrading: the fast improvement rate of PC technology ensures an efficient transition to future processor generations and networking technologies in a computer based control system.
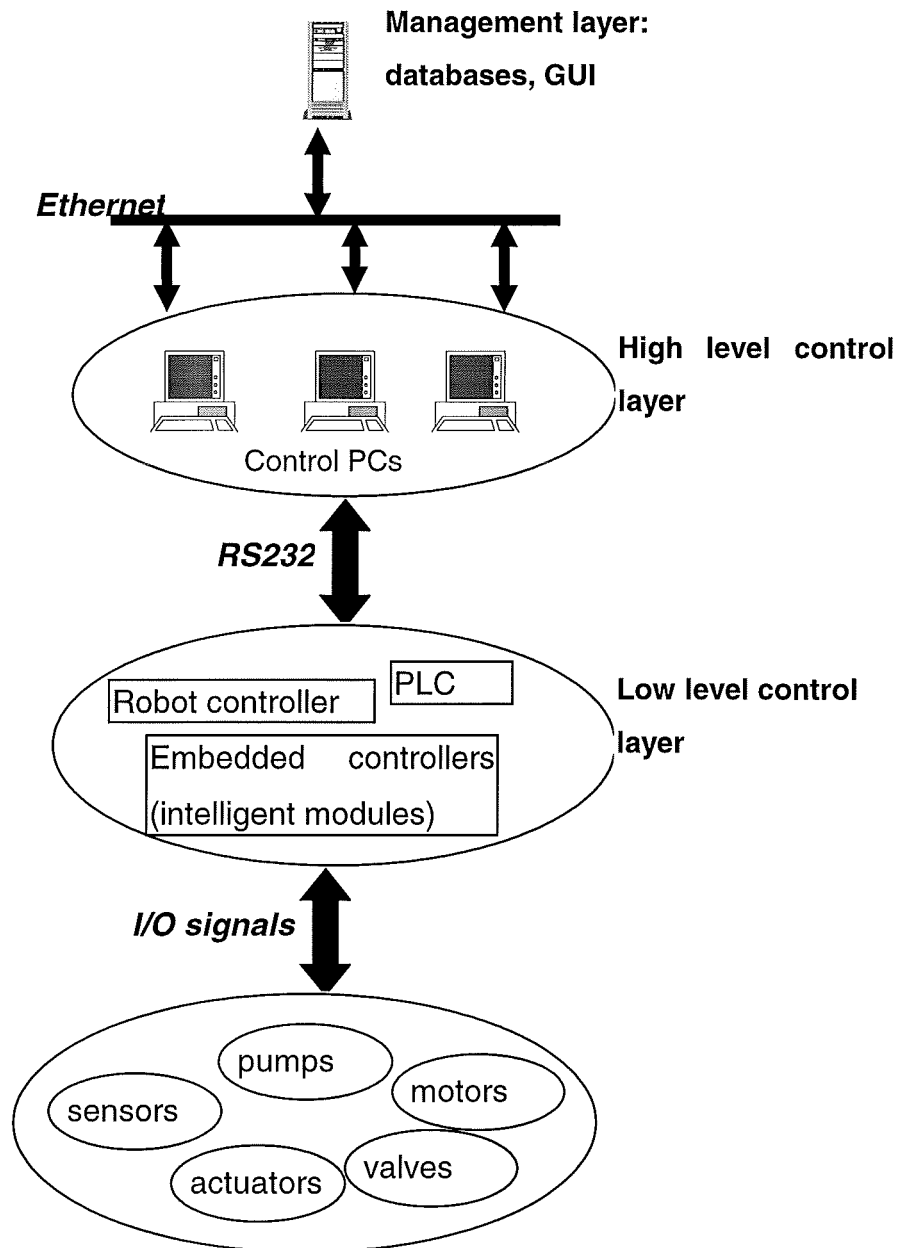
Figure 22. Control hierarchy with a DCE

The number of required computers as well as the distribution of serial links across the network need to be studied to finalise the definition of the control hardware architecture. The following devices have a RS232 interface and need to be classified in groups:

Robot controller	LSC
PLC	Macerator
Balance	Heating Block 1
Compudil (solvent dispenser)	Heating Block 2
Pipette	Centrifuge
	Centrifuge balancing

4.1.4. Final control hardware architecture

Scheduling will be the main function of the computer in charge of the robot. Most of the time, the robot simply acts as a manipulator, moving containers to the next. This is not applicable to the balance and the Compudil.

A weighing step is required between operations to ensure that there is no sample loss and to perform process checks and calculations. This means that the manipulator will have to place a container in the balance, wait until the weight is stored and continue to its final destination.
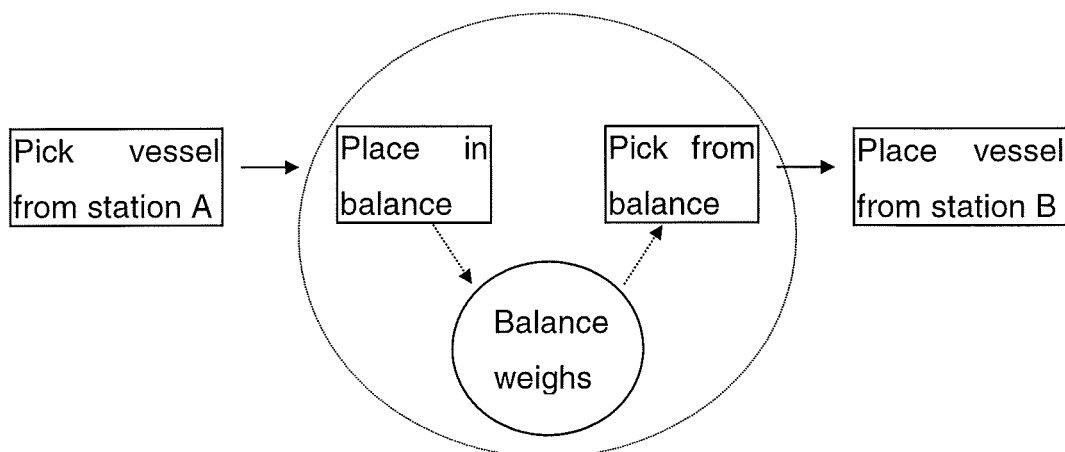
Figure 23. Pick and place sequence with weighing step

The Compudil requires robot aid to hold the vessel under the probe during solvent dispensing. Those robot pauses during station operation have no significant effect in the overall process time, due to the short time involved in both solvent dispensing and, specially, weighing. Robot controller, balance

and Compudil are connected to the same computer to facilitate their interaction.

Most of the units with triangular control (RS232 and I/O) require little PLC interaction. The I/O control relates to safety measures or start/stop features:

However, for the macerator, the centrifuge balancing and the heating block II (evaporation in 16mm tubes) the proportion of PLC control reaches the 50% or more. The macerator is built around the Polytron PT6000 which is fitted with an RS232 interface. However, the degree of customisation required to integrate the device into the system is extensive: vessel holders with limit switches to detect vessels, lifting mechanism with position switches and up/down control, solvent pump system, vacuum system, etc. The same could be applied to the Liebish 2004 heating block: level sensors for end point detection, manifold system, vacuum system, etc.

As for the centrifuge balancing station, when an empty vessel is placed over the PE400 balance, the solvent pump has to dispense water until the weight matches that of the sample to be centrifuged (within 10gr). A continuous flow of balance data is sent to a computer through an unidirectional RS232 interface, but no control over the initiation or termination of a transmission is allowed over the link. Data transmissions and solvent dispensing operations have to be started by the PLC. The computer can then read the weights and when the target value is reached, it notifies the PLC that both balance transmissions and solvent addition have to be terminated.

To facilitate their control, PLC, macerator, heating block II and centrifuge balancing station will be plugged in the same computer.

The LSC provides crucial information for the sample study and a loss of information would be disastrous. The Packard Tri-Carb 1000 is a one-shot liquid scintillation counter, fitted with a unidirectional RS232 interface. This

means that data can be collected but no command or order can be sent to the instrument. To overcome the problem, the start signal will be generated by the PLC and the same fixed protocol, stored in the LSC memory, will be always used for operation. The counter sends the resulting data to the computer without any warning. To elude any possibility of data loss, the controlling PC has to continually monitor the serial port once the counting process has been initiated.

Replicates for counting are normally taken every time there is a volume variation or a volume transfer. The consequent high workload and the long operation time (up to ten minutes per vial) mean that the LSC can only share controller with a "non demanding" instrument.

The Heating Block I has capacity to simultaneously heat several vessels, whenever the target temperature is the same. Temperature is controlled and monitored by an embedded controller. If the requirements do not change, the computer only task would be the monitoring of status.

LSC and Heating Block I are linked to the same PC. Pipette and centrifuge share another one.

All the computers are linked in a 10-base T Ethernet network. More computers can be easily integrated and laboratory instruments easily redistributed if required.
A link to the out world, the server, is required at the top level of the control hierarchy. Analysts must interact with the system to develop process recipes, to reconfigure the equipment and to access all generated data.
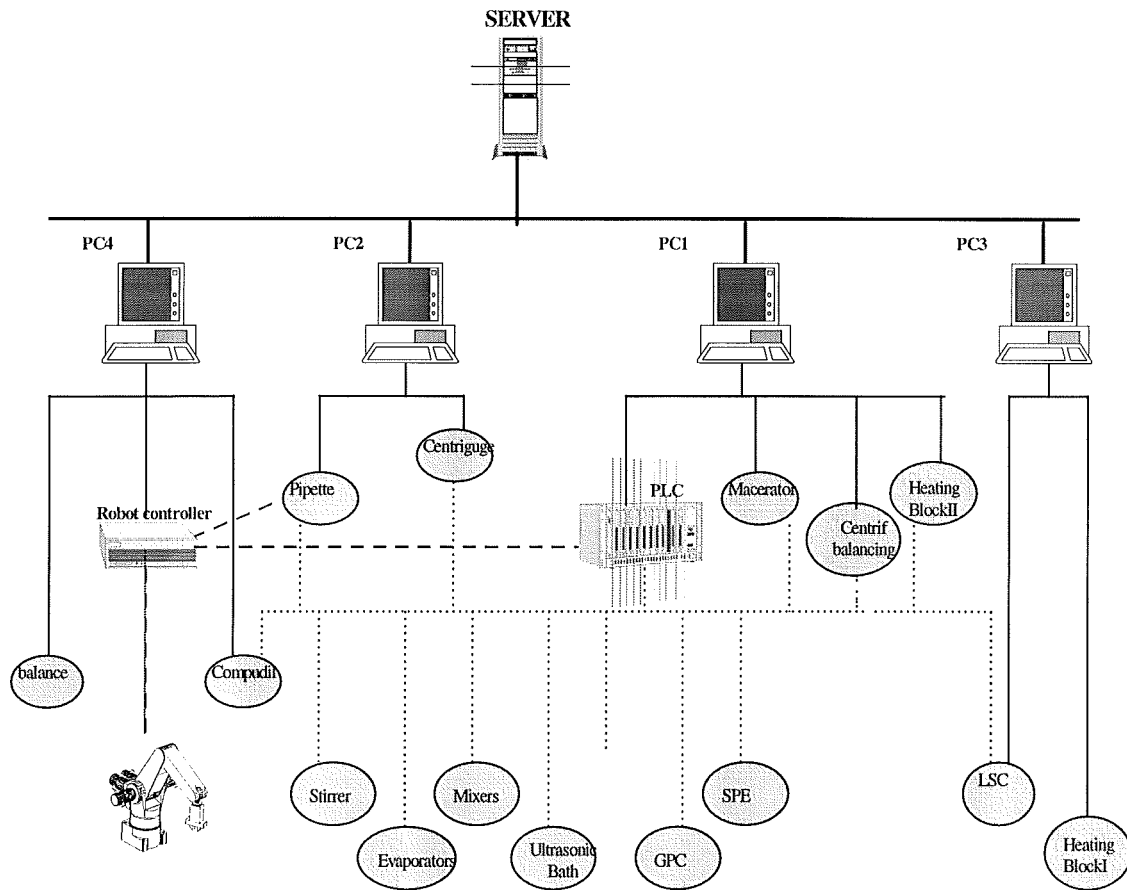
Figure 24. Controlling hardware layout

4.2. Controlling Software

4.2.1. Identification of control applications

Software applications residing in the controlling hardware are the real drive of the automated system. Developing the control modules of a sophisticated and flexible automated workcell can be a complex and difficult problem. As J. Tracy O'Rourke said "every system is governed by two kinds of software: the information system, which tells the machines what to build, and the control system, which tells the machines how to build. The question is, what information has to be know in real-time?" (Harvard Business Review, 1989).

Efficient use of our robotic system requires solving several highly complex scheduling problems. The system must be capable of carrying out multiple tasks simultaneously and should cope with processes that are non deterministic. In addition, it has to be capable of processing samples according to different recipes. To avoid downtime and protect the financial investment made, reconfiguration of the system must take place without involving any reprogramming, time or cost.

As a consequence is that static or off-line schedulers, traditionally used for the automation of repetitive or well defined processes, are of no use here. Those schedulers accept time constraint and resource information for the various operations and compute a template, which is the optimised plan for running the samples on the system. At run time, instruments and robot operate following the sequence and timing designated in that scheduling algorithm (Donzel, 1983). However, the time required for operations like evaporation or filtration, depends on too many parameters and cannot be easily estimated. In addition, most of those off-line schedulers are more efficient when orchestrating smaller rather than large unit operations.

For all those reasons, our system must be dynamically scheduled at runtime according to an algorithm of rules and decision trees. In addition, a powerful graphical interface has to provide users the ability to configure the different laboratory instruments and to assemble them in any desired way. During recipe configuration it should ensure that that the designated equipment is capable of executing the required procedures.

The master recipe has to be somehow transformed into a working recipe understandable and accessible to the applications residing in the high level control computers. Those applications have to perform three tasks:

- Dynamic scheduling of robot and workstations, providing the synchronisation required for integrated execution.

- Supervisory control of the instruments attached to the PC.

- Management of serial communications with the instruments attached to the PC. Each serial instrument requires a software device driver that provides the external device-specific protocol communication functions.

Finally, any data generated during the process must be collected and stored in some sort of permanent support that allows the generation of reports at the end of the process.
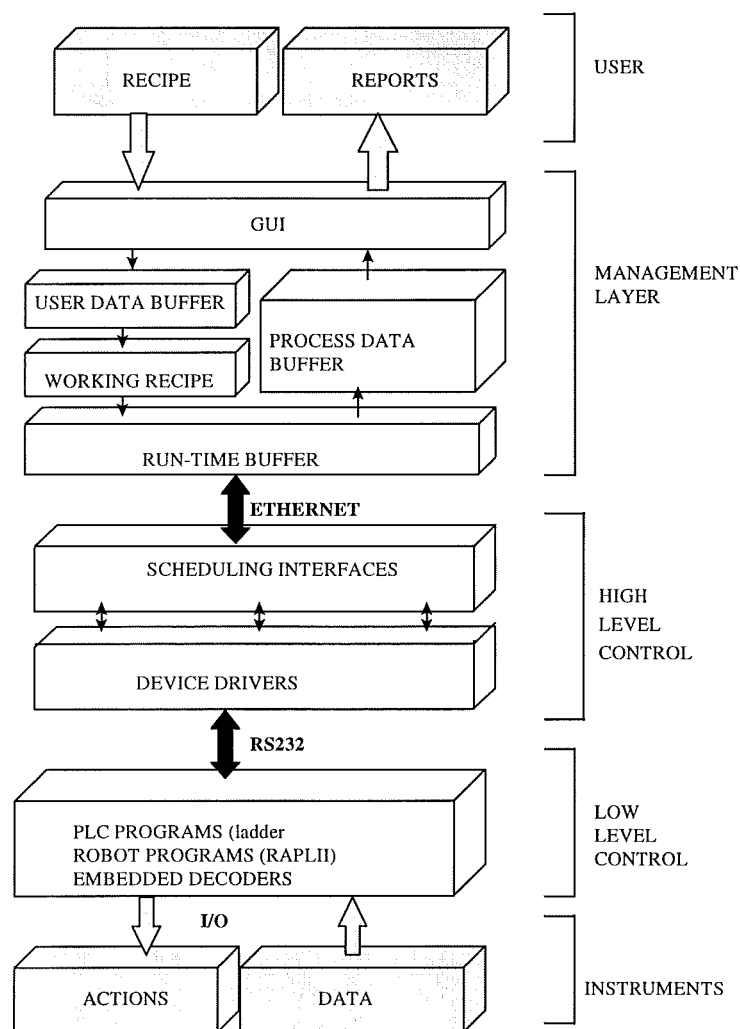
Figure 25. Software elements

PLC and robot controller are programmed using proprietary software provided by the manufacturers. Applications are written in ladder logic and RAPL II respectively.

However, the programming tools to develop all applications in the management and the high level control layers, as well as their interaction mechanisms, need to be determined.

4.2.2. Selection of programming environment

To smooth the learning curve, reduce implementation time and facilitate debugging and troubleshooting, the number of different programming tools used should be kept to a minimum.

Traditionally, "monolithic" codes consisting of a single program into which a batch procedure was hard coded was used in the automation of batch operations. If a change in procedure was required, the programme would have to be modified. Systems usually lacked flexibility and required considerable time and money for modification.

The introduction of modular programming brought two significant advantages: re-usable code and flexible batch procedures. However, the system was still dependant on an individual with an overall understanding of all the modules, their interactions and data structure.

Current developments in process control include object-oriented programming (OOP) which allows the building of software objects that map to real world and conceptual objects. Object-oriented programming provides a complete batch automation environment, with the seamless integration of a variety of hardware and software as opposed to proprietary control systems (Brown, 1995).

Despite the potential benefits of OOP (reusability, better debugging, robustness) I could only find few examples of its application to the laboratory environment at the time (Zhou 1992, 1993, 1994).

Object-oriented language is not the only requirement for our programming tool. A graphical environment is also needed for the development of the user interface application and the human-machine interfaces. The user interface has to provide the ability to configure the different laboratory instruments and graphically assemble them in any desired way. In addition, every computer must have an interactive graphical window from which the operator can monitor the status of the process at runtime.

Visual Basic (VB) and Delphi were the packages considered. Although VB seemed to be more extensively used (Cadavid, 1996; Echols, 1996; Ogden 1996) Delphi, new in the market, was the preferred option. It combines the graphic simplicity of Visual Basic with the power of a fully compiled object-oriented language. It also features two-way tools technology and scalable database technology. A well-structured exception handling makes for rapid debugging during development and robust error handling after release (PC user, 03/10/1995).

Delphi also incorporates the Borland Database Engine (BDE) providing direct access to data stored in dBASE, Paradox, Local InterBase Server and to other data formats via ODBC. Paradox 7 for Windows was the selected database for storage of information.

4.2.3. Interaction mechanisms: high level control

A modular approach to system control implies the incorporation of mechanisms for linking applications whether they run on the same computer or in different nodes.
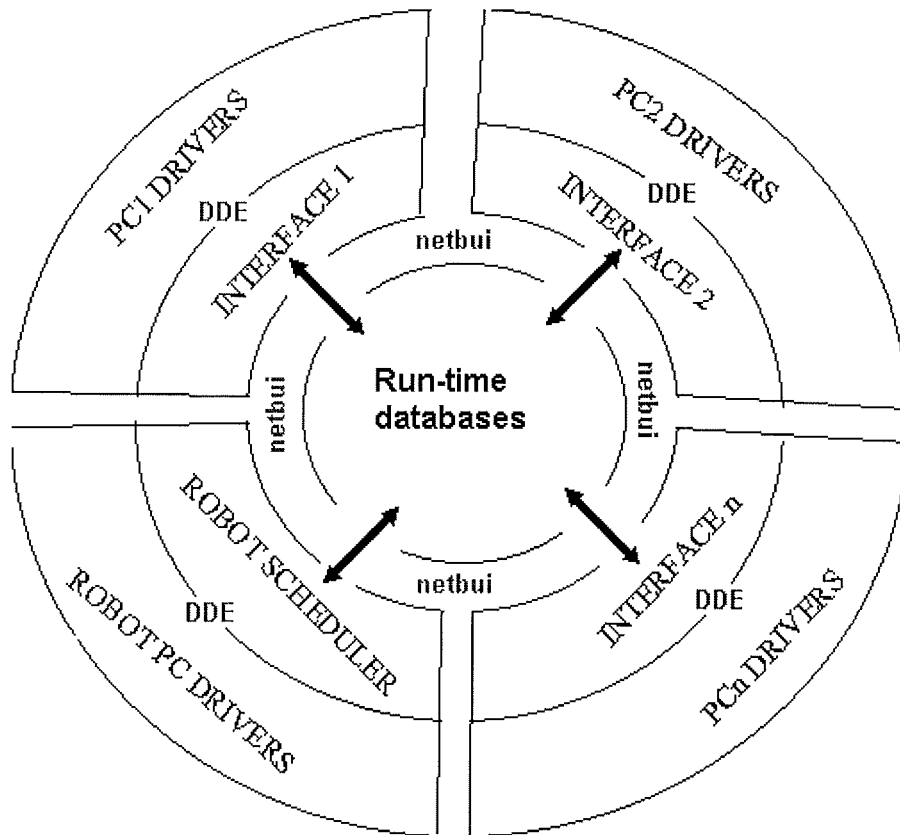
Figure 26. Interaction mechanisms during process control.

The scheduling interfaces, deployed in the high level control PCs, communicate through the server resident run-time databases rather than directly with each other. With this approach to inter-task communication, the applications are independent from each other. In addition, they are insulated from underlying technologies and standards, thus leaving future options for upgrading and expansion open.

Some form of inter-communication is also required between the scheduling interface and the device drivers co-existing in the same computer. Dynamic Data Exchange (DDE) is a message protocol in Windows that allows application programs to request and exchange data automatically. The data occurs via "conversations" consisting of a DDE server and a DDE client. A server is the supplier of the information for clients applications. The data

transfer can occur at timed intervals, on triggered conditions or on client request (Usdata, 1993).

4.2.4. Interaction mechanisms: management layer

The so call management level of the system control performs his tasks off-line, this is, before or after the process execution.
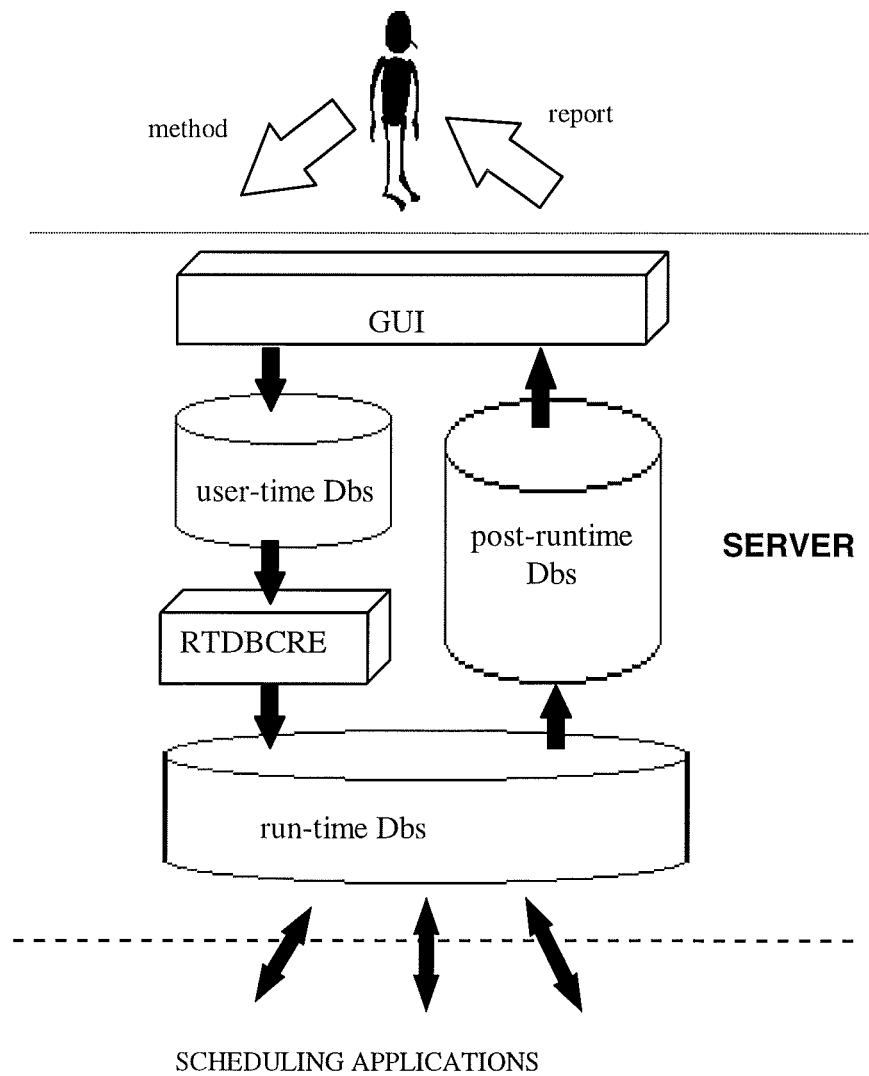
Figure 27. Module interactions in the management layer

As it has been stated before, analysts will create their sample analysis methods and set up instrument parameters by using the graphical user

interface. All this information will be permanently stored in the user-time set of databases. Before robot and workstations can execute that method, RTDBCRE.EXE has to convert that master recipe into a working recipe by creating the run-time database set. Those databases will be dynamically updated by the control system during operation. Once the analysis has been performed, all generated data will be transferred from the run-time set to the post-run databases for permanent storage. A reporting tool integrated in the GUI will provide access to the information by automatically producing a report.

Delphi based GUI and RTDBCRE applications access and update data contained in the different Paradox databases (user-time, run-time, post-runtime) through the Borland Database Engine (BDE). The BDE, included in Delphi, provides integrated database support by automatically handling all database connection mechanisms.

5.   CONTROL SYSTEM DESCRIPTION

5.1.   Database system

The database system is the key core of the robotic system control architecture. It is used for data storage as well as for runtime system inter-communications. It has been developed using Paradox 7 for Windows 3.11 (Borland International). They are organised in three subsets which reside in the server PC: User-time databases, Run-time databases and Post-run databases.
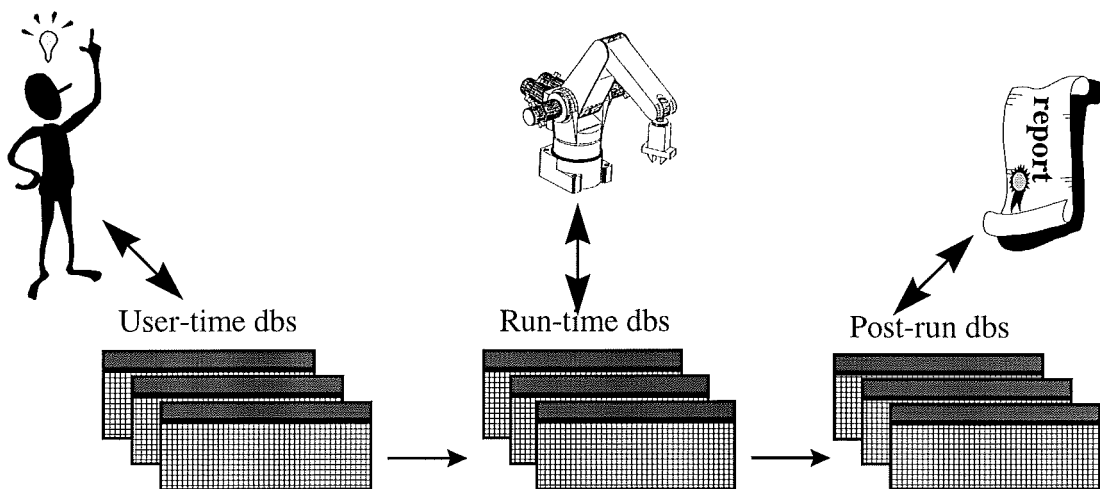
Figure 28. Database system schematic

5.1.1.   User-time databases

Their main function is to permanently store method information entered by analysts using the graphical user interface. Methods can then be, processed, reported or copied to allow modification. User-time databases can be grouped according to the type of information they store.

User related databases contain information about authorised users and their security information.

Instrument related databases store all the different combinations of parameters, each one identified by a "Configuration Number", that have been used by users so far. There is one database per laboratory instrument. This way, EVAP.DB stores different configurations for evaporators, PIPETTE.DB for the pipette, and so on.

LSC, GPC and SPE use fixed protocols for their operation and do not need to be configured. As a consequence, they do not have an associated database. Others, as the centrifuge balancing station, have unknown settings, since the target weight to balance will be specified at run time. The last special case is the balance, which does not require any special setting for its operation.

Method related databases store information about all the recipes entered by analysts with the GUI, including the equipment involved in every method, the way they are interconnected and how they appear graphically on screen.

Temporary databases are working databases used as data buffers by the GUI to temporarily store information about a method being developed. Once the analyst saves the method, the information is transferred to the Method related databases for permanent storage.

Database name	Storage of information about
STATIONS.DB	all the steps (equipment) used in the method being developed
FLOWS.DB	how those station are connected (sequence) in the method being developed
DESSTAT.D	graphical representation (screen co-ordinates, etc.) of the method being developed

Table 3. Temporary databases

5.1.2. Run-time databases

This set of temporary databases contains initially the working recipe which is accessible and understandable to all controlling computers. Information is dynamically updated at runtime by the different control applications. Two different types of data are stored: data generated by the instruments which is related to the analysis of the sample and data generated by the control system itself for scheduling purposes. Databases can be grouped following a similar criteria to the user time databases.

Instrument related databases contain the set of parameters each station has to use every time it operates. Each step in the process has a unique "Station ID" with an associated configuration. There is one database per station type. This way, RTEVAP.DB contains all the different operations to be performed by the evaporators, RTPIPET.DB operations to be performed by the pipette, and so on.

The data generated by the counter is collected in RTLSC.DB. It consists of counting time, counts per minute (CPM), standard deviation ($2\sigma\%$), quench parameter values (Spectral Index of the Sample or SIS and Transformed Spectral Index of the Internal Standard spectrum or TSIE), disintegrations per minute (DPM), % luminescence and % reference.

RTROBOT.DB, it is a fixed database storing all the system locations the robot has access to. This database is not created from user information or updated at runtime.

Method related databases contain information about the method, all the stations involved and their sequence in the process.

Database name	Existing information	Generated runtime data
RTGENERA.DB	method general information	start & end times
RTSTATI.DB	all steps (equipment) used in the method	operation start & end times
RTFLOWS.DB	robot pick & place operations	intermediate weights

Table 4. Method related databases (runtime)

RTFLOWS.DB describes how all the steps of the process are interconnected, that is, the sequence of operation for all the equipment.

Project ID	Flow ID	Sample No	Vessel ID	...	From (st ID)	From Type	To (st ID)	To Type	Weight (gr)	...
(......)										
test1	3	1	1		2	Extra	4	Pipet	149.76	
(......)										

Figure 29. Key fields of RTFLOWS.DB

Every flow represents a pick and place robot operation. In the example shown above, the robot picks the vessel from "Station ID" 2, which happens to be the stirrer, and will have to place it in the pipette because is the next step in sample process. The order in which flows are executed is decided at runtime by dynamic scheduling of the system.

Scheduling databases are created exclusively for control application inter-communication. The scheduling process, explained in a simple manner, takes place as follows:

a) When an instrument finishes its operation, it "calls" the robot to remove the vessel(s) (RTCALLS.DB).

b) The robot finds out which is the destination station, that is, the one performing the next stage of the sample process (RTFLOWS.DB). As an example, let's say that it is evaporator1.

c) The robot will accept the call if evaporator 1 is idle (Evaporator1 "Status"=0 in RTPC1.DB).

d) Once the robot has placed the vessel in evaporator 1, it will set a flag indicating that evaporator1 that it can start its operation (Evaporator1 "Status"=1 in RTPC1.DB).

The scheduling process will be described in detail further in this chapter.

Database name	Function
RTPC1.DB	Status of all instruments controlled by PC1
RTPC2.DB	Status of all instruments controlled by PC2
RTPC3.DB	Status of all instruments controlled by PC3
RTCALLS.DB	Storage of instrument "calls" for the robot
SAMPSTIR.DB	Extra robot transfers required for stirrer operation
SAMPMACE.DB	Extra robot transfers required for macerator operation
RTERRLOG.DB	Records runtime errors

Table 5. Scheduling databases

The load and unload of the sample as well as the load and unload of the wash vessel in the stirrer and macerator are not explicitly stated in the user interface. This means that they are not collected in RTFLOWS.DB. Those operations are calculated prior to the run and stored in SAMPSTIR.DB and SAMPMACE.DB.

Calibration databases collect the results of the instrument calibration procedure performed before processing any batch of samples.

5.1.3. Post runtime databases

Once the batch of samples has been processed, all generated data is transferred from the runtime databases to a set of permanent databases. This set is exclusively related to that specific run as specified by GLP (Good Laboratory Practise) standards. The collected data will be used during report generation.

5.2. Graphical User Interface (GUI)

Modular automation involves the definition of the physical and procedural aspects of batch processes through a well-defined hierarchy. The power and flexibility of this approach stems from the ability to configure the components of this hierarchy and then to assemble them in any desired configuration (Brown, 1995).

The RPAL analytical chemistry robotic system involves both physical models (laboratory instruments) and procedural models (analytical methods for sample analysis) and the GUI provides the ability to configure them. The GUI brings the power of computer-aided design to the sample analysis recipe configuration. Interactive graphics makes the GUI easy to use and understand, requiring no computer knowledge to work with it.

Figure 30. Presentation screen in GUI

From the security point of view, only authorised users have access to the system which is also password protected. Two level of users are considered: Normal users and Super users. Super users have system administration powers to add new users and study numbers.
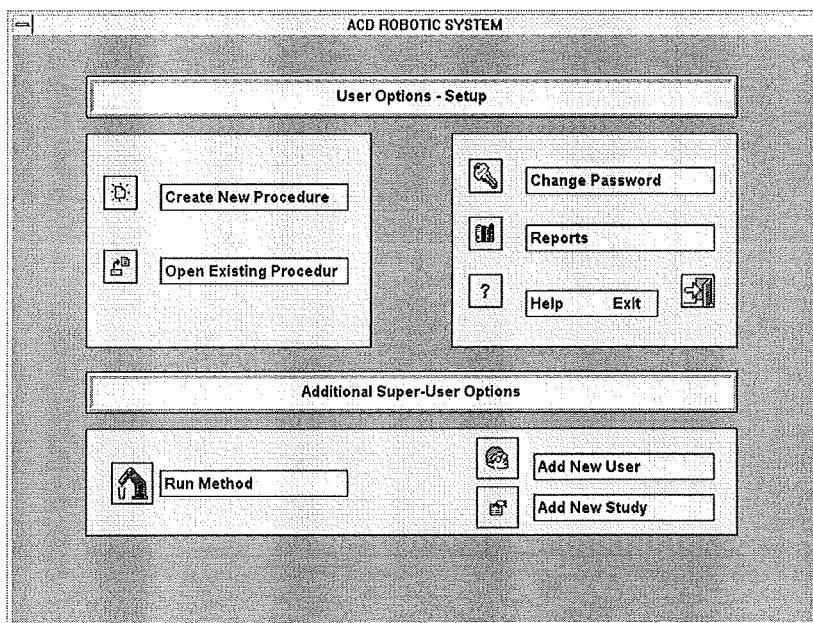
Figure 31. User Interface main screen

5.2.1. Creation of methods

A "stay on top" drawing palette contains objects that graphically represent the laboratory equipment included in the system. Equipment is placed on the design form with a simple drag and drop operation and it is assigned with a unique "Station ID". A configuration screen automatically pops up to allow the set up of operational parameters. The instrument, or better the object, is tagged with that "Configuration ID". The last step is to connect the blocks, representing instruments, to describe workflows or processes. Every connection, referred to as flow, represent robot pick and place operations.
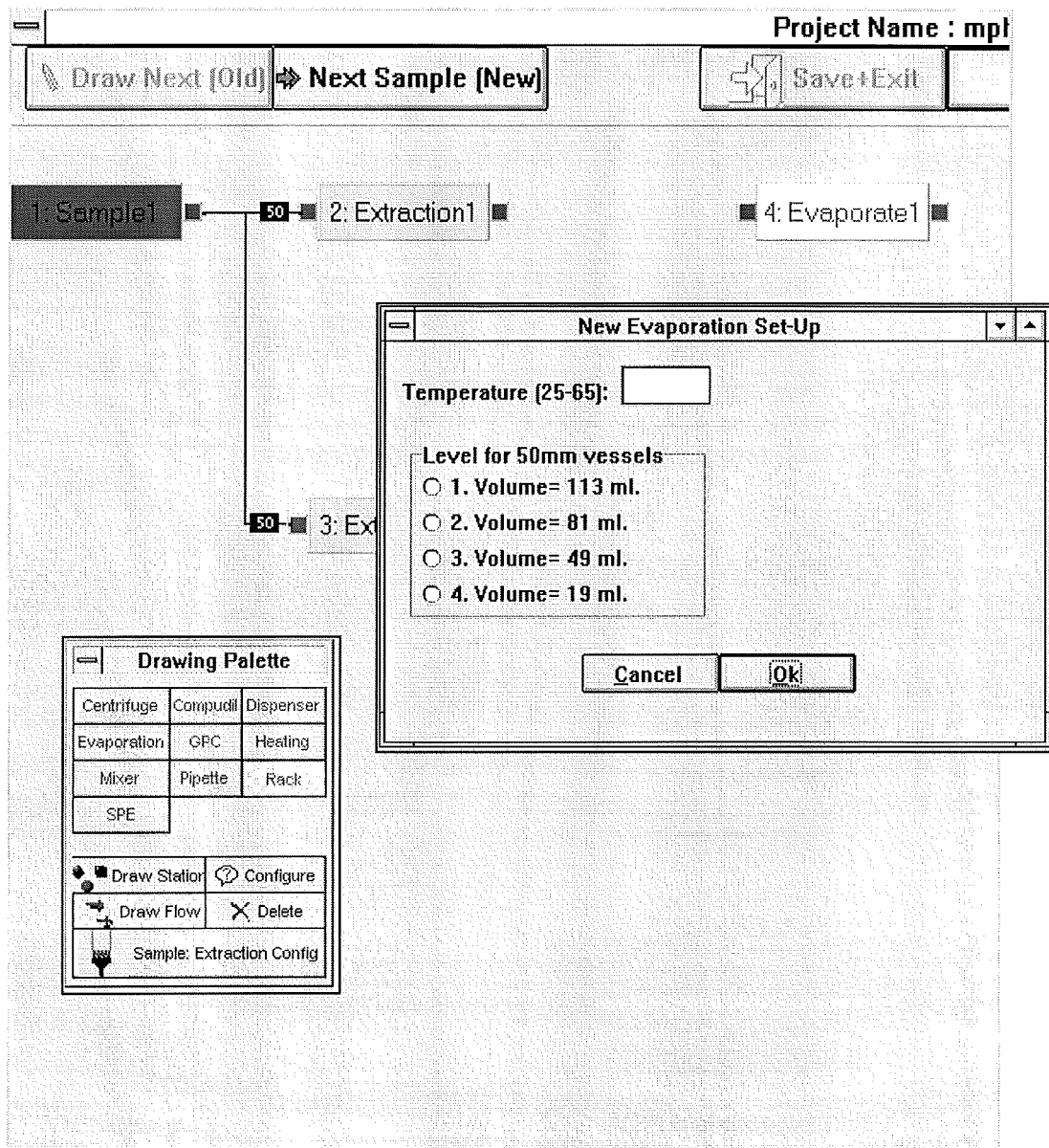
Figure 32. Design form with configuration screen

Methods designed are validated on-line, ensuring that the designated equipment is capable of executing the required procedure. Some of the safety checks performed are:

- Two consecutive stations are "vessel compatible". For example, it is unacceptable to transfer a collection vessel to the LSC because the latest can just accommodate LSC vials (∅28 mm).

- All parameters required for station operation must be configured.

- Theoretical volumes are tracked along the process to avoid overflows when adding solvent, under capacity when pipetting, etc.

- All vessels must come back to the rack at the end of the process. No container can be left in the stations.

The immediate feedback makes the design process easier and improves the robustness of the working recipes to be executed. Complex methods of analysis can be represented and managed easily and naturally.
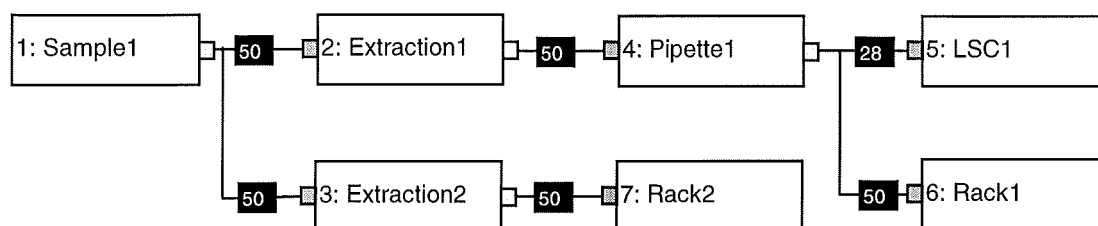
Figure 33. Example of method designed with the User Interface

When a method is saved, all this graphical information and the underlying configurations are permanently stored in a database format. Modification of a existing method is not allowed to ensure GLP compliance. If any change is introduced, the workflow has to be saved under a different name.

5.2.2. Reporting tool

When the processing of samples has finished, results must be reported back to the user. The reporting tool, integrated in the GUI, is a Delphi application that interacts with Paradox 7 to automatically create a report on a particular run of the method requested by the analyst. Three types of data can be printed out: The graphical representation of the method, the configuration of all the stations involved in the process, and the data generated during the analysis of the samples.
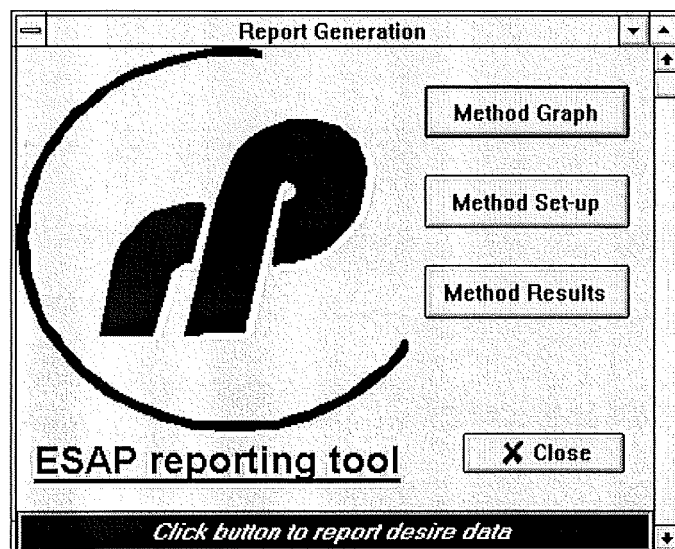
Figure 34. Reporting tool main screen

An example of report generated by the reporting tool integrated in the GUI can be found in Appendix C.

5.3.   Application for creation of runtime databases (RTDBCRE)

This application converts the master recipe, entered by the analyst with the GUI, into a executable recipe which is accessible and understandable to all control system applications. The conversion involves the selection of all data relevant to the method from the user-time databases and its transfer to the run-time databases. In addition, calculations have to be performed to determine extra pick and place robot operations deriving from the method to be run and the resources required to execute the method. Glassware is mapped to rack locations and graphically displayed on screen. The analyst just has to place the vessels in the specified locations and check that there is enough solvent for the whole run.

Three types of robot transfers are not explicitly indicated when the analyst designs a method with the user interface. The first one is the loading and unloading of samples in the stirrer or macerator. Once the sample has been extracted and the vessel returned to the output rack, the stirrer (or macerator) needs to be cleaned to avoid cross-contamination between

samples. A washing routine is always required and, therefore, the loading and unloading of the wash vessel in the station. The third type corresponds to the loading in the pipette of empty vessels where the pipetted aliquots will be collected.

```
                    ┌────────────────────┐
                    │ user enters method to run │
                    └────────────────────┘
                              │
                              ▼
                    ┌────────────────────┐
                    │ "Run number" calculation │
                    └────────────────────┘
                              │
                              ▼
                    ╭────────────────────╮
                    │      Display        │
                    ╰────────────────────╯
                              │
                              ▼
                    ┌────────────────────────┐
                    │ Extract data relevant data │
                    │ from user-time databases   │
                    └────────────────────────┘
          ┌───────────────────┼──────────────────────────┐
          ▼                    │                           ▼
Glassware  ┌──────────────────┐│              ┌──────────────────────┐
Rack locations │ Calculate resources │            │ Calculate extra robot │  Pipette
Solvents   └──────────────────┘│            │      operations       │  Extraction
          │                     │            └──────────────────────┘
          ▼                     │                           │
    ╭──────────────╮            │                           │
    │   Display     │           │                           │
    ╰──────────────╯            │                           │
          │                     ▼                           │
          └──────────►┌────────────────────┐◄──────────────┘
                      │ Transfer to run-time │
                      │     databases        │
                      └────────────────────┘
                              │
                              ▼
                    ╭────────────────────╮
                    │   SYSTEM READY      │
                    ╰────────────────────╯
```
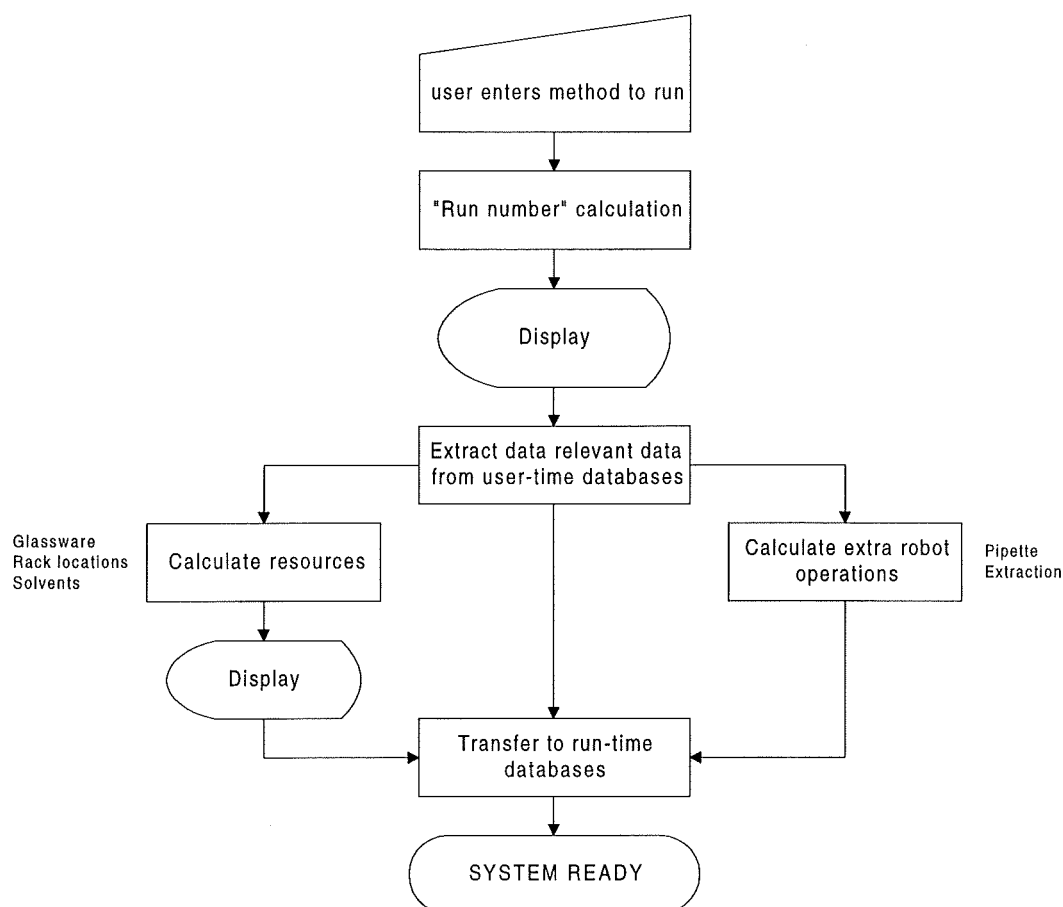
Figure 35. Algorithm for run-time database creation

5.4. Dynamic Scheduler

It is been explained why traditional static schedulers are of not use for our analytical chemistry robotic system. We are dealing with the automation of a non-repetitive process where non-deterministic operations take place (evaporation, filtration). In addition, parallel processing of samples is a must if the overall process time is going to be optimised. A dynamic scheduler had to be developed for real-time control and synchronisation of operations.

There are three key elements in this dynamic scheduler. The first one is the robot scheduler which sequences and controls all glassware transfers performed by the manipulator. The second one consists of co-ordination interfaces, residing in every PC controlling laboratory equipment. The last element is the set of runtime databases, used by the other elements for real time inter-communication.

When an instrument finishes its operation the master interface in charge of its supervision sets a call for the robot. The robot scheduler selects the next pick and place operation from all those calls, based on a set of priority rules. When the sample has been transferred to the next station and the robot is back into a safe position, the robot scheduler sets a signal which causes the downloading of operational parameters and the initiation of operation.
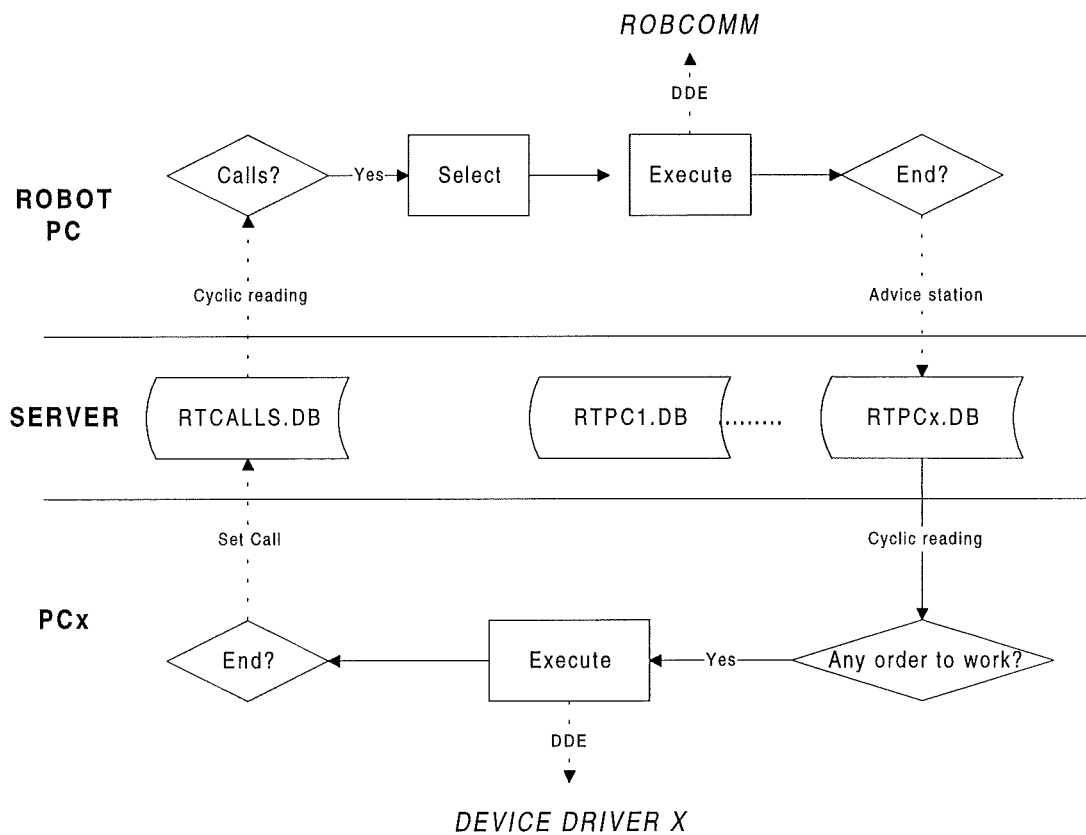
Figure 36. General algorithm for scheduling

5.4.1. Robot scheduler and priority rules

This application resides in the computer to which the robot controller is connected. Its main function is the scheduling of the robot, that is, the selection of the next pick and place operation among all those available.

Three are the possible sources of operations:

RTCALLS.DB,   were the stations record their requests for unloading.

SAMPSTIR.DB,   were extra operations derived from soil sample extractions are stored.

SAMPMACE.DB,   were extra operations derived from plant sample extractions are stored.

The selection is based on availability of the destination station and a series of priority rules. When a particular call is analysed, the scheduler must identify the station to which the sample needs to be transferred in order to execute the next step of its processing. This information is provided by RTFLOWS.DB. That destination station must be idle for a call to be classified as "possible". The status of a station is dynamically updated at runtime in RTPC1.DB if the instrument is connected to PC1, in RTPC2.DB if it is connected to PC2, etc. Among all possible calls, the selection is carried out according to their priority level.

Priority rules were set according to the results of the simulation exercise. Those stations with long operational times or those expected to have a high workload were considered as critical. The first ones because they have a

significant impact in the overall time required to process a batch of samples. The others because they could create bottlenecks.

Any call received from the LSC is immediately attended, freeing the station for the next vial. The same can be applied to the stirrer but a lower priority. The rest of the stations operate in the basis of first calling, first attended.

Critical station	Cause	Solution
Evaporation	Time	Multiplication (x4)
Extraction	Time	Priority 2
Pipette	Workload	Maximisation of pipette rack locations
LSC	Workload & Time	Priority 1
Robot	Workload	System layout & Dynamic scheduling

Table 6. Critical stations

This approach of 'first calling, first attended' was validated during simulation, offering satisfactory results. The introduction of a complex set of priorities was dismissed because it produced no significant savings in the overall time and did not add further value to the system control strategy.

Calls are automatically sorted in RTCALLS.DB in order of priority to facilitate the selection process. The scheduler analyses the first record. If it is accepted, the call is deleted from the database. If not, the scheduler evaluates the next one and so on.
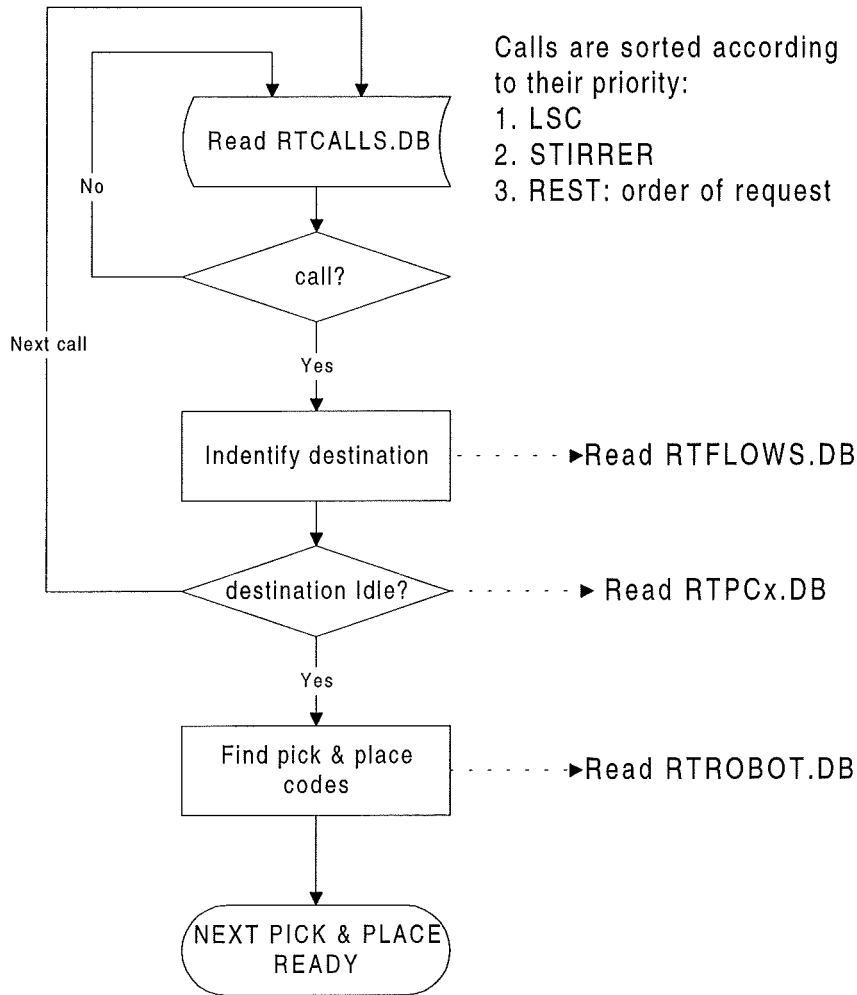
Figure 37. Selection of next robot operation

Once a particular pick and place operation is selected, the scheduler has to interact, via DDE, with the software device drivers involved in its execution:

The robot driver, ROBCOMM, was supplied by the robot manufacturer (CRS) to handle communications with the robot controller. The scheduler provides the pick and place codes as well as the operation type. There are three different operation types: direct, via balance and via Compudil. Those parameters and the order to move are transmitted by ROBCOMM to the robot controller through the RS232 link.
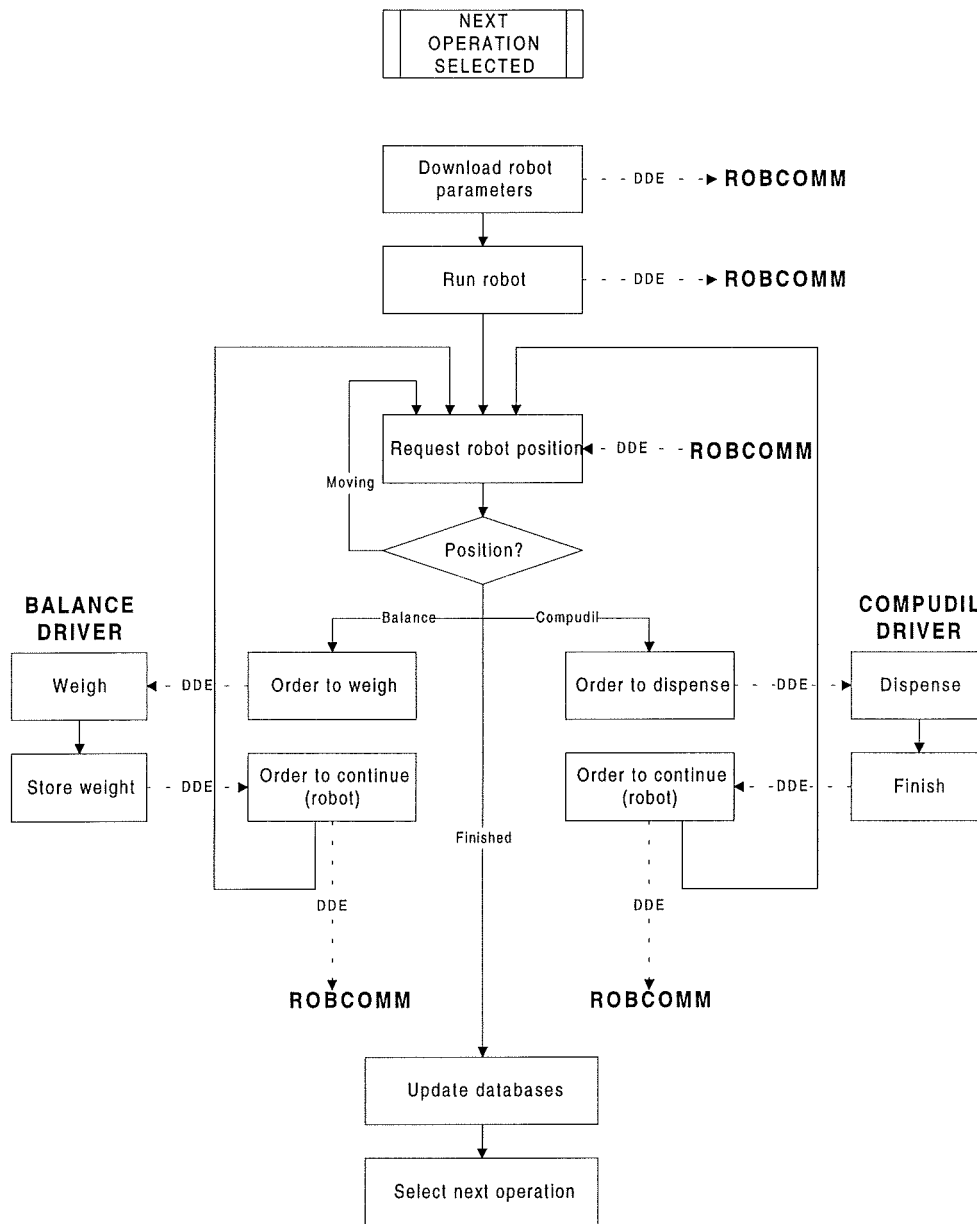
Figure 38. Algorithm for robot scheduler

Balance driver. Most of the time, a vessel is weighed during its transfer from station to station. The robot has to notify the scheduler when the vessel is in the balance, so that the information is forwarded to the balance driver and the weighing can take place. The communication flow runs in the opposite direction once the value has been stored, indicating the robot that the vessel can be moved to its final destination.

Compudil driver. The Compudil needs the robot to hold the vessel during solvent dispensing. A DDE "conversation", similar to the balance one, has to be maintained between ROBCOMM, the scheduler and the Compudil driver. The dispensing will start when the container is under the probe and the robot will continue once the operation has been completed.

Besides scheduling functions, this application acts as a man-machine interface by displaying the status of the modules under its responsibility.

5.4.2. Co-ordinating Interfaces

These interfaces reside in every computer in charge of controlling laboratory equipment. They act as co-ordinators between instruments and the robot. At the same time, each one performs man-machine interface (MMI) functions by displaying the status of all the stations under its supervision.
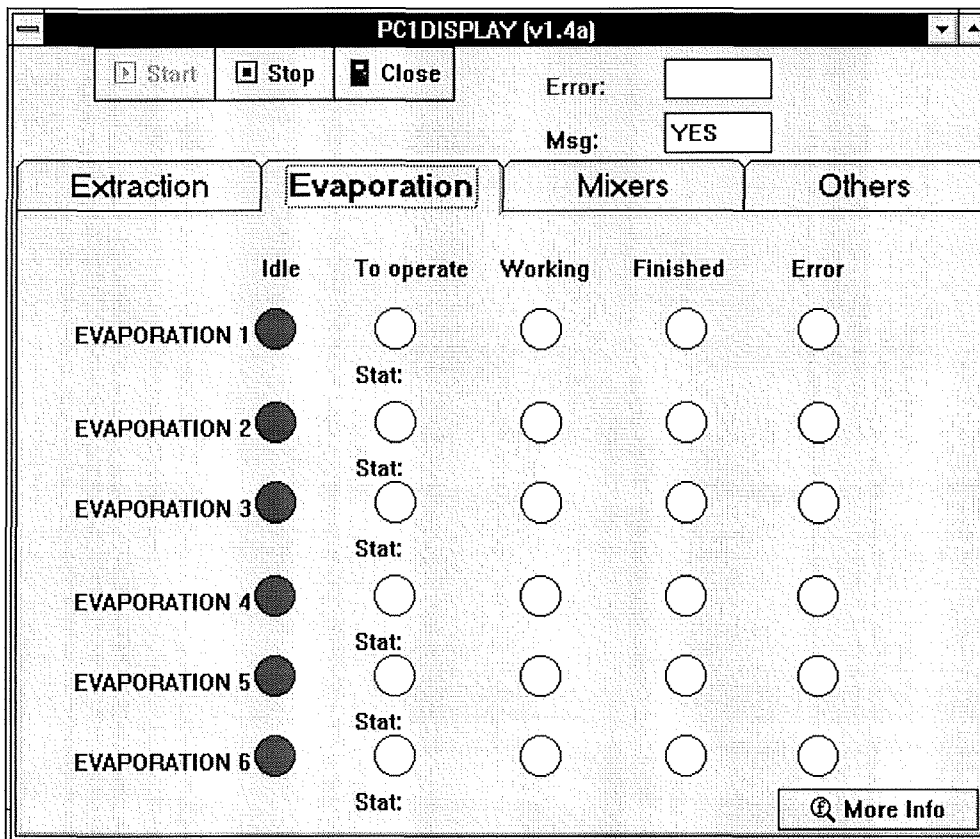
Figure 39. Co-ordinating interface as a man-machine interface

When these applications are first activated, they initialise the software device drivers associated with their connected instruments. Those drivers run in the background and act as slave applications to the master co-ordinating interface. The master interface is responsible for recognising the "whereabouts" of the manipulator and for transmitting that information to the device drivers. The former is achieved by cyclic reading of runtime databases, to be exact its associated RTPCx database, through the network. The latter, by sending an order to work to the device driver via DDE.
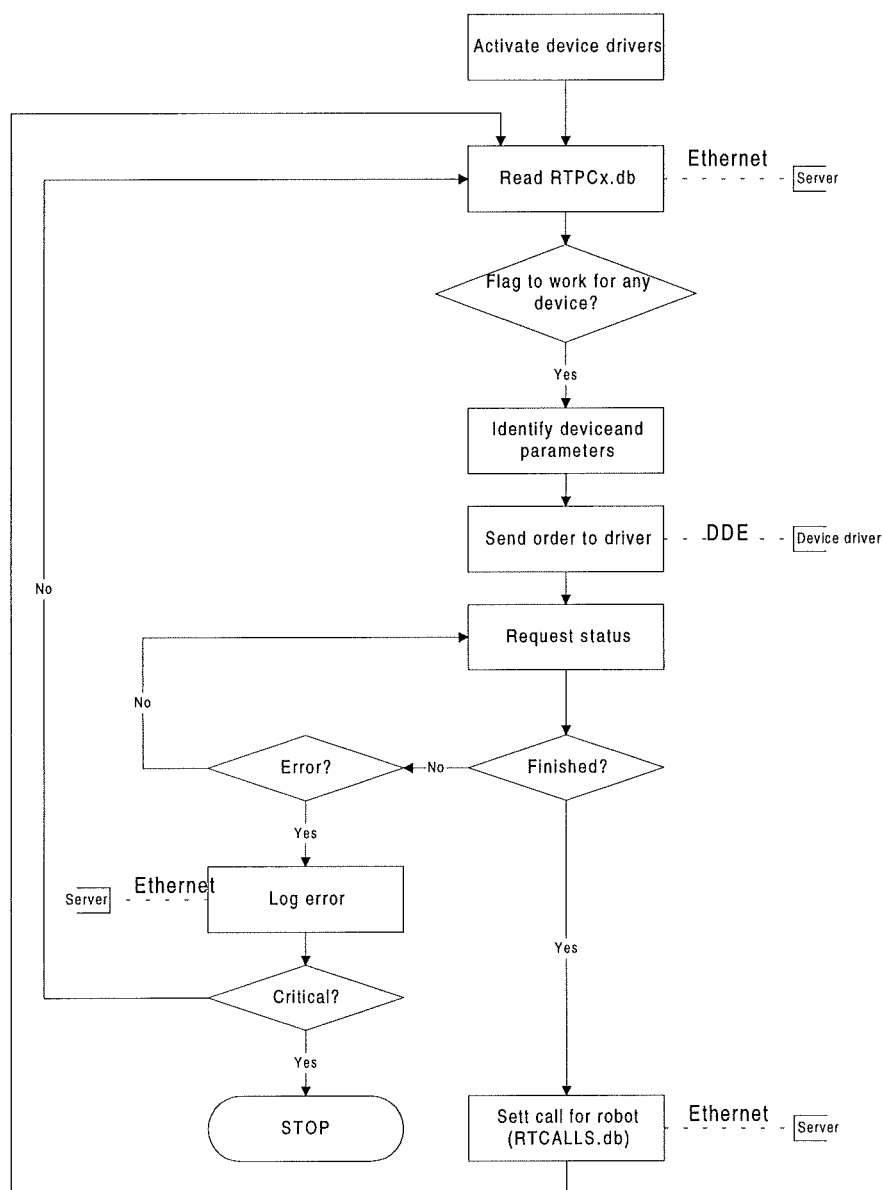
Figure 40. Algorithm for Co-ordination interfaces

5.5. Device Drivers

Software device drivers handle communications and control operation of serial laboratory instruments and low level controllers. There is a device driver per RS232 link in the computer. These applications run in the background and act as slave applications to the master co-ordination interface.

A request is sent by the master application via DDE. The request could be to start operation, to report status or to stop operation if fatal error. When an order to work is received, the driver must download the parameters and send the start signal.

Station	Parameters
Extraction	Speed, time, solvent types, solvent volumes.
Evaporation	Temperature, target level (volume)
Pipette	Number of aliquots, volume of each aliquot.
Vortex Mixer	Mixing time.
Compudil	Volume to dispense
Heating Block	Temperature, time.
Centrifuge	Speed, time, acceleration, deceleration.
Ultrasonic Bath	Time

Figure 41. Parameters to download

Two signals are required to start operation. One comes from the device driver, confirming that all parameters have been downloaded. The second signal is sent by the robot controller once the robot has loaded the station and has reached the nearest safe position. This robot signal avoids collisions between robot and mobile parts of workstations, reinforcing safety during operation.

```
  ┌─────────────┐   DDE                        ┌──────────────────┐
  │ Order to work│ - - - - - - - - - - - - - - -│   Acknowledge    │
  │with configuration ID                        └──────────────────┘
  └─────────────┘                                        │
                                                         ▼
                                               ┌──────────────────┐
                                               │  Find parameters  │
                                               │ (configuration ID)│
                                               └──────────────────┘
                                                         │
                                                         ▼
         ┌────────────────────────────────────►┌──────────────────┐
         │                                      │ Download parameters│
         │                                      └──────────────────┘
    No   │                                               │
         │                                               ▼
  ┌──────┘  ◇Third try?◇ ◄─No─ ◇ Downloading OK? ◇      ⟨ Robot safe? ⟩
                 │                    │                        │
                Yes                  Yes                      Yes
                 ▼                    ▼                        ▼
  ┌─────────────┐ DDE  ┌──────────┐  ┌──────────────────┐  ┌──────────────┐
  │Interface receives│-│Status= Error│  │Send delphi start signal│ │Send Robot signal│
  │      and acts│    └──────────┘  └──────────────────┘  └──────────────┘
  └─────────────┘                          │                  │
                                            └────────┬─────────┘
                                                     ▼
                                            ╭──────────────────╮
                                            │  Instrument works │
                                            ╰──────────────────╯
```
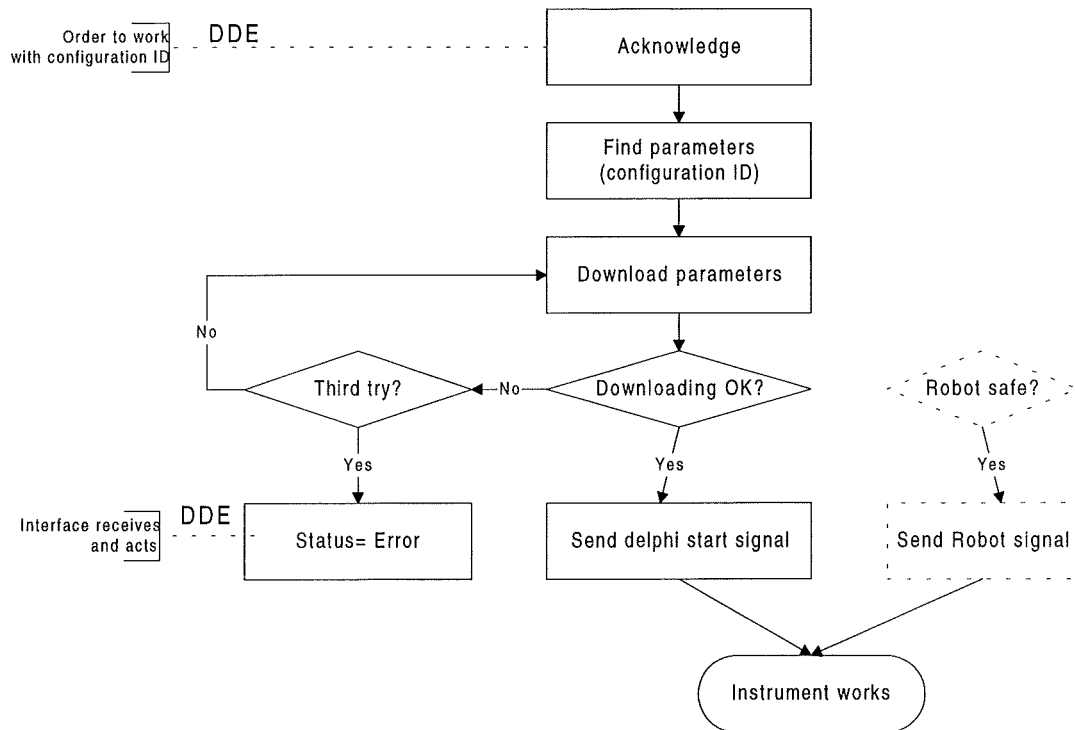
Figure 42. Algorithm for device drivers

Software drivers are also responsible for collecting and storing any generated data. Two instruments produce relevant information for the sample study: the balance and the LSC.

5.6. Robot controller programmes

Written in RAPLII and stored in the robot controller, their main function is to execute the pick and place movements requested by the robot scheduler via Robcomm (robot driver). All system locations were "taught" manually, named and stored in the robot controller memory using the teach pendant.

The only information received from the robot scheduler to perform a vessel transfer is the initial location, the final location and the operation type (direct, via balance or via Compudil). However, eight are the parameters needed to perform a successful pick or place operation. A set of generic programmes were stored in the robot controller to decode the scheduler information, assign values to the eight parameters and execute the movement in a safely

manner. The robot scheduler runs a programme, MAIN, which calls the other programmes as subroutines.

Parameter	Meaning
%0	Gripper opening distance
%1	Safe position on track
%2	Intermediate position (if required; if not same as %1)
%3	Side approach position (if required; if not same as %2)
%4	Final position
%5	Safe distance above
%6	Vessel with lip (0= no, 1= yes)
%7	Terraced rack (0= no, 1= yes, 2= Compudil). Determines how robot approaches (pick) or departs (place)

Table 7. List of parameters in robot programmes

The robot has the potential to damage equipment within its working envelope, and as such the movement of the robot must be carefully controlled. The concept of safe positions was introduced to ensure that the robot moves down the track in a safe and predictable manner. These safe positions are with the robot arm pointing forward and with the gripper in a horizontal configuration.
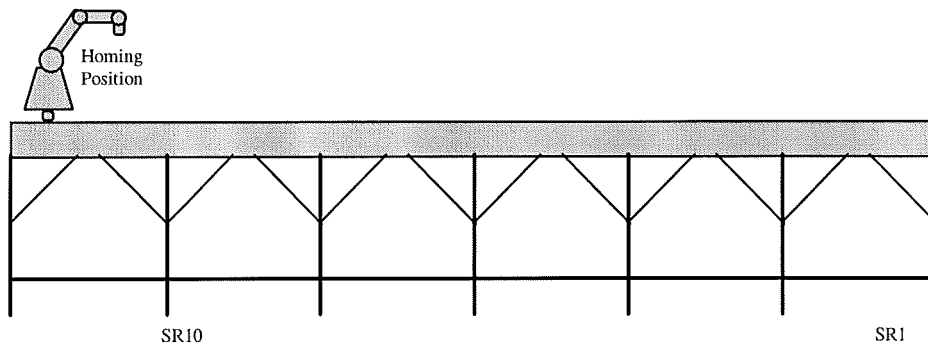
Figure 43. Safe positions in robot track

Safe positions enable the robot to travel between them without collision with equipment. The track has been divided into twelve 0.5 metre sections, numbered 1 to 12. The locations are called SR1 to SR12, S standing for Safe. The variable %1 is used within programmes to update the safe location.

In order to pick up a vessel the robot, starting from the safe position, must negotiate a safe route to the vessel in question, pick it up and return to the safe position by the same route. Similarly when placing a vessel the robot must negotiate a safe route between the safe position and the destination. In order to do this, intermediate points on its route to the final destination are defined. The variable parameters %2 (intermediate position), and %5 (safe distance above the destination) are used together with %4 for the final destination .

%1 → %2 → Approaches %4 by safe distance %5 →
%4
%1 ← %2 ← Departs %4 by safe distance %5 ←

In order to pick a vessel from a terraced rack, approach from the side, and departure vertically is required, and the reverse to place a vessel. This variable is defined as %3.

Pick :

%1 → %2 → %3 →
%4
%1 ← %2 ← Departs %4 by safe distance %5 ←

Place:

%1 → %2 → Approaches %4 by safe distance %5 →
%4
%1 ← %2 ← %3 ←

The gripper is used to pick vessels and so the distance it opens is critical if breakage is not to occur (%0). The force with which it closes is also important if a vessel is not to be dropped on route. A force of 40% of maximum has proven appropriate for the weights we handle. Lipped vessels, that is extraction and collection vessels, are a special case. When picking one of those, the robot applies enough force so that the force sensor detects the presence of a vessel (around 5% of maximum). The gripper then relaxes, allowing the vessel to slide down during lifting until the lip rests on top of the gripper. The final force is then applied to secure the tube. Lipped vessels happen to be the most heaviest ones. By using this gripping technique, the lip supports some of the weight of the vessel.

Moves to %4   Closes 5% force   Departs 10 mm   Closes 40% force
                                               in a straight line

1	2	3	4
MOVE %4,S	CLOSE 5	DEPART 10,S	CLOSE 40
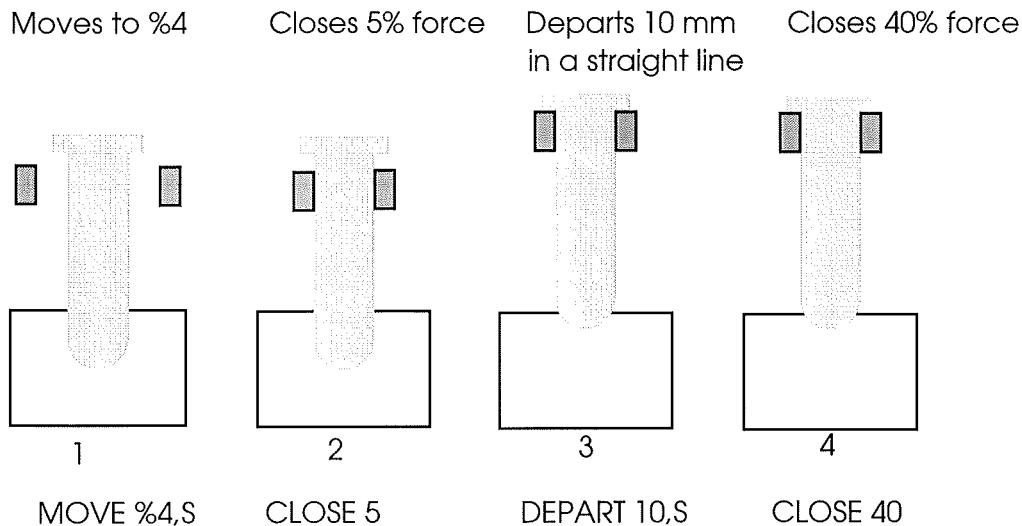
Figure 44. Gripping technique for lipped vessels

5.7. PLC program

The PLC program, written in Ladder Logic and stored in the PLC, handles all those stations or their subsystems (manifolds, pumps, air, sensors, actuators, etc) requiring digital and/or analogue control (refer to Table 2 for details).

The sequential ladder logic program is organised in blocks. In general terms, each station has related five blocks: monitoring, status, operation, output, and errors.

Block	Function
Monitoring	Reading of inputs
Status	External monitoring by the high level control programs (Delphi)
Operation	Handling of normal operation
Output	Setting of outputs
Errors	Fault detection

Table 8. Blocks for low level station control

Five different status are used for each station: "idle" if it is not in use, "ready" if the vessels have been loaded, "busy" if the station starts its operation, "finished" when the instrument is ready for unloading and "error" if a fault occurs.

When a station is selected for operation by the scheduler, the host computer interrogates the PLC about the status of the instrument. If idle, it sends a start signal after the operational parameters have been successfully downloaded. Once the vessels have been loaded and the robot is back into a safe position, the robot controller provides the last signal required to start the operation. The status will remain busy until the process finishes or an error is detected. The station will go back to idle only when all vessels have been unloaded.

6. OVERALL SYSTEM CONSIDERATIONS

6.1. Safety measures

The workcell is situated in a restricted access area and it is surrounded by a cage to isolate any mobile part in the system from human reach. Only authorised users who have received appropriate training are allowed in the area. Input and output racks are accessible through interlocked windows. Those windows cannot be open if the robot is moving and, reciprocally, the robot does not move if the windows are open. If after requesting access to the racks, the windows are not open in 10 seconds, they will be automatically locked again. In the same way, if the windows are open during more than 5 minutes, an error light will flash.

Stations are linked to a emergency stop circuit. In case of danger, the user can press any of the emergency stop buttons strategically distributed around the cage and the power to the system will be automatically cut.

A UPS protects the system against possible accidents caused by power failures. If power does not return in five minutes, the system initiates a safe shutdown routine.

A modem connects the system to the outside world. In case of error or power failure during overnight operation, a message can be sent to security officers or overnight personnel. They should then go to the robot area, asses the problem and contact relevant personnel if necessary.

6.2. System operation

6.2.1. Preliminary preparation

The first step is to design and save the method of analysis with the GUI. After that, the analyst has to book a slot for robot use.

Samples have to be prepared and placed into extraction vessels. LSC vials also require preliminary preparation. Scintillant has to be manually added into the vials which are fitted with specially drilled caps. No other glassware require special preparation.

Before processing, the analyst has to perform a series of safety checks. He or she has to ensure that there is no glassware left in stations, required solvent bottles are full, waste bottles empty and the robot is in a safe location on the track.

If the system was previously shut down, the user has to follow the switch on procedure to power up the PLC, the robot controller and the computers. Computers are managed with a unique screen, keyboard and mouse due to the existence of a CPU switch. They are password protected to avoid unauthorised users. The switch on procedure is completed with the homing routine of the robot. The system is now ready for operation.

6.2.2. Operation

The user specifies the method to run by using the RTDBCRE application in the server. As it has been mentioned before, this application will convert the analysis method into a working recipe by creating the set of run-time databases. It also calculates a unique 'run number' for that method, since a method can be run lots of times.

A mapping of the required glassware and the rack locations will be shown. The user has now to access the input racks through the interlocked windows built on the safety surroundings and place samples and glassware in the specified locations.

Once the windows are closed and all resources in place, the co-ordinating interfaces and the robot scheduler, each one in a different controlling PC, can be run by clicking their icons in the computer screens. They will automatically activate their relevant device drivers and the laboratory instruments will initialise.

A calibration routine takes place before the system processes the batch of samples to guarantee instrument performance. The calibration screen of the robot scheduler allows for individual station calibration or full system calibration.
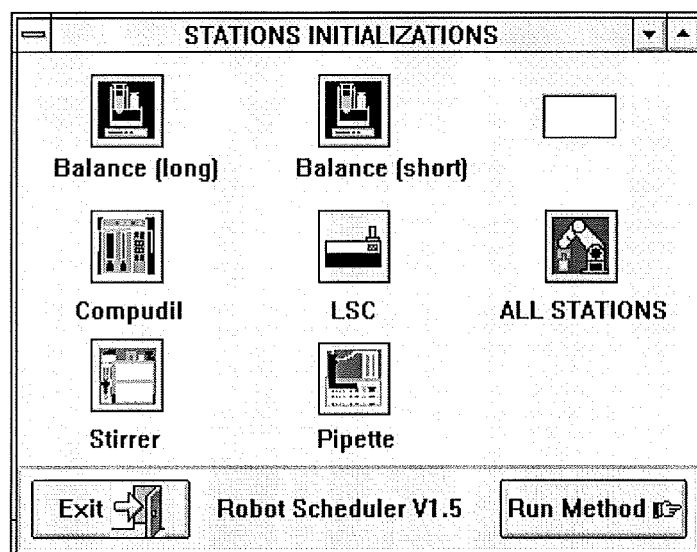
Figure 45. Calibration screen

Full system calibration lasts for about 20 minutes. The result of this calibration is displayed on screen and has to be repeated if a particular

station fails. After a successful calibration, the processing of samples will initiate.

The robotic cell runs totally unattended so the system software has to drive the process by controlling and scheduling the instruments, managing communications and storing data. But it also has to provide with monitoring capabilities. The status of each instrument, the remaining number of operations and any generated error, are shown through man-machine interfaces located on every PC. The shared screen sequentially displays them thanks to the scanning feature of the CPU switch.

Once the samples have been processed the system automatically creates the set of post-runtime databases, parks the robot in its home location, and closes all control applications. The system is ready for another user.

6.2.3. After Use

Printouts of methods employed for analysis and any other data generated during runtime are accessible through the reporting tool integrated in the GUI.
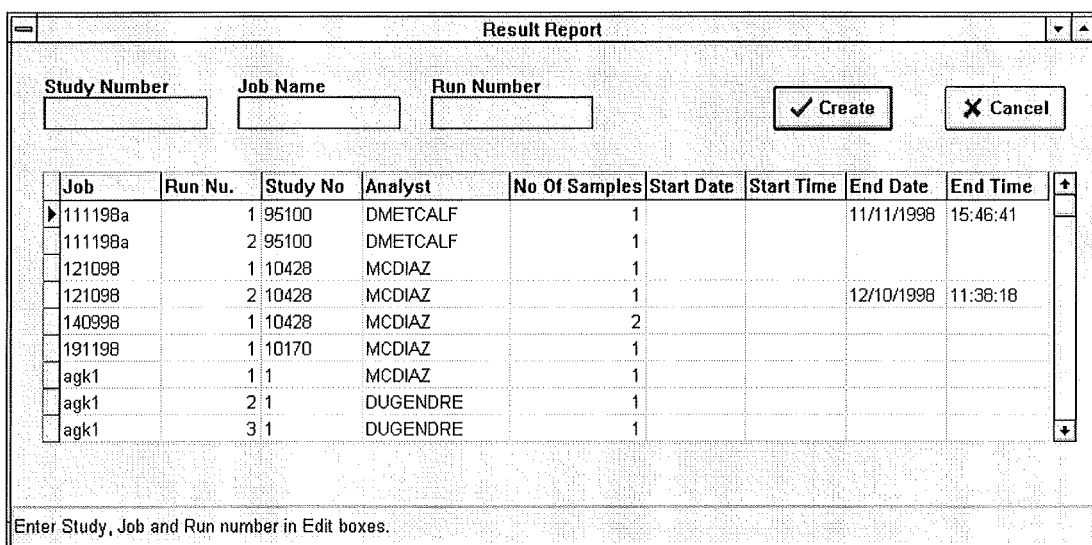
Figure 46. Report request screen in GUI

Users only have to enter the study number, the method name and the specific 'run number' and the report is automatically created and printed for them.

Samples and any used glassware have to be removed from system racks. Every user is responsible for cleaning the vessels and return them to the robot area for further use.

If the system is no longer used that day, the shut down procedure has to be performed to switch off the robot, the PLC and the computer network.

6.3. Error response

All software has been developed prioritising safety to promote the prevention of runtime errors. Finding the balance between flexibility and robustness was a difficult task.

The method design stage is critical in the avoidance of dangerous occurrences during operation. The GUI continually performs checks to ensure that the final workflow is feasible and robust: values for operational parameters in the laboratory instruments, compatibility between solvent volumes and vessel capacities to avoid overflows, etc. If an illegal command is entered the system does not accept it and warns the user. This restricts the execution of some operations. For example, the vortex mixer requires the solvent volume to be inside a defined range. If the vessel contains less solvent than the accepted minimum, a vortex will not be created and therefore, the liquid will not be properly mixed. If, on the other hand, the tube contains too much liquid, spillage could happen. As a consequence, the user needs to introduce an extra step, solvent addition or reduction, in the method. This could be seen as unnecessary by users, but it guaranties the performance of the system and the quality of the analysis while reducing the possibility of problems during operation.

Runtime failure can be originated by hardware malfunction, programming bugs, operator error or unexpected situations. Preventive maintenance schemes, extensive software testing and user training help reducing the chances of these situations. We tried to prevent them even further by other means.

Firstly, by providing a simple standard operation procedure (SOP). This is particularly difficult in a system of such size and complexity since higher number of routines and decisions have to be automatically performed without user input. An example to illustrates this is the dynamic scheduler. The common practice in automation is to automate repetitive processes, where batches of samples are processed following always the same procedure. If a new batch needs to be analysed in a different way, the system has to be re-programmed to accommodate the changes. This philosophy would require extensive training for users, demand specialised skills, produce frequent system downtime and increase enormously the number of potential errors. All those reasons influenced the overall control strategy followed for the system. Different methods of analysis had to be executed without requiring any reprogramming.

The second action taken was the establishment of two different user access levels: super-users and normal-users. By maximising the number of decisions a user can make, the system would gain in flexibility. However, some of those decisions could lead to dangerous situations or reduction in performance when taken by non specialised operators (e.g. acceleration and deceleration rates in centrifuges, stirring or mixing speeds, increments in pressures). Super-users have a deeper knowledge and understanding of the system due to their involvement in the implementation phase or in the day to day running of the system. Only developers, maintenance personnel, analyst in charge and his deputy have those privileges.

Despite all those preventive measures, runtime errors can occur. Brainstorming sessions and risk assessment studies took place to identify the highest number of scenarios in which something could go wrong. As a consequence, a net of error detection procedures were implemented both at low level and high level control. In all instances, errors are displayed and recorded.

There are different levels of system response to errors. Critical errors are those that could lead to dangerous situations or affect the outcome of the analysis. Most of runtime errors fall under this category : instrument malfunctions, vessels not found in expected locations, illegal commands received, etc. Due to the nature of the process and the fact that the system runs unattended while processing radioactive samples, it would be too dangerous or totally useless to continue with the process. The system response to critical, unrecoverable errors is to notify and stop.

Non critical errors can be resolved by operator or system actions. During the initialisation phase, system checks are performed to ensure equipment and supplies are connected and functioning correctly (mains, air, vacuum, mobile parts, etc.). If a problem is detected, the system advises the operator to perform some checks and retry. As another example, if the washdown vessel for the stirrer is absent (maintenance, sensor failure), the system questions the user about performing the process without washing the station between samples. It will continue if an affirmative answer is received.

If the control system identifies the failure as a communication problem (DDE, serial, network), it responds by re-attempting for three more times. If the problem is solved, the process continues as normal. If not, it assumes that a critical error is the cause of the problem so it warns the user and stops. Other self-corrected actions are failures in cloned stations. If Evaporation 1 is registered as "out of order", the system will use evaporators 2 to 4 for operation.

If despite all those precautions a dangerous occurrence takes place, operators can use the E-stop buttons distributed along the safety surrounding to cut the power to the system. Manual recovery will have to take place afterwards.

6.4. Training

Training is a crucial step to guaranty the success of any new piece of equipment. It is not only necessary to transfer the 'know-how' from manufacturers to users but, in our environment, is also compulsory due to GLP directives (Good Laboratory Practice). We put a lot of effort in developing an interactive and hands-on training program which offered every user the right amount of information in the friendliest possible way. Different training programmes were designed to meet the needs of different groups of users. SOPs (Standard Operating Procedures) as well as manuals were produced to help the process.

6.4.1. Developers training

The importance of training was identified even at developers level. As a team, we worked together and had frequent meetings to discuss issues and lines of actions. However each of us had assigned specific tasks, in my case all those related to software development, and were becoming too specialised in one area of the project. It was agreed that a formal procedure should be produced to realise that knowledge transfer and create a truly multi-skilled team in which nobody was the only owner of his project share.

6.4.2. 'Normal Users' training

Training is required to teach users how to operate the machinery but also to build their confidence. We have seen too many examples of instruments siting around the lab without being used at all. This could end up being the case of the system described here, since novices can easily feel intimidated

by its size and technology. Moving robots around can be a exciting experience but also terribly scary for fear of doing something wrong.

The training programme was divided in several stages: off-line training, on-line training, data handling and advanced system use.

During the one day off-line sessions, 25 people, distributed in groups of five, learned about all preliminary preparation steps prior to the running of the system: Overview of system, sample preparation, extraction vessel assembly and method design with GUI.

11 key users were identified for the first round of on-line training. 6 more followed three months later. During those half day hand-on sessions, authorised users learned how to run the system and gained knowledge about system resources, start up and shutdown procedures, error occurrence and emergency procedures.

The data handling sessions were mainly oriented to Study Directors plus Team Leaders and included reporting and data interpretation, archiving and GLP.

Advanced system use involved training in stand-alone workstation use and troubleshooting at basic level.

6.4.3. 'Super-Users' training

A system champion (Analyst in Charge or AIC) and his deputy were nominated. They are the first point of contact in case of doubt or system failure. As a consequence, their training program had to be much more extensive. On top of the 'Normal User' sessions they received lessons in preventive maintenance and hardware repair, error diagnosis and recovery, robot recovery, system backup and advanced level troubleshooting. It took place over a period of one month.

6.4.4. Security and overnight personnel training

Overnight staff should know how to respond to a problem during unattended operation. An overview of the system as well as the existing emergency procedures were included on those sessions.

6.5. Validation

While accuracy of results is the goal for a particular analysis under development, the ultimate goal of validation is to ensure that something does what is intended to do, precisely and reliably (Dugendre, 1996). Validation of automated systems is required before its release for routine use.

According to GLP/GALP regulations, validation efforts should be broken down into separate components addressing the equipment (both instrument and the computer controlling it) and the analytical method run on that equipment. After they have been verified separately they should be checked together, as an integrated unit, to confirm expected performance limits (system suitability testing). Finally, the generated analysis data should be authenticated by comparison with predefined expected results.
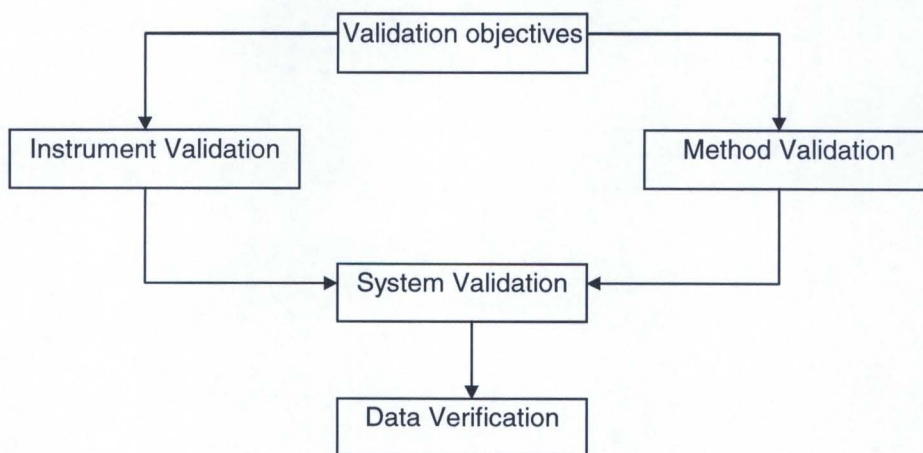
Figure 47. Validation stages

The validation process probed to be very demanding in terms of time and personnel. Three people had to be present during any system validation test to be able to record every event and respond to any unexpected problem. Each test was repeated until all its acceptance criteria were met. The process included the following stages:

1. Design, documentation and approval of validation strategy and procedures. Those documents collected all tests to be performed as well as their acceptance criterias.

2. Testing of individual elements or workstations of the robotic system as stand-alone modules.

3. Testing of the robotic system, as an integrated unit under direct software control. Several tests were performed to validate all specified system objectives.

   3.1 Calibration tests to ensure that calibration routines are successfully performed.

   3.2 A 'wet test' in which extraction vessels should not contain any soil, only the assembled vessel. The purpose was to prove the performance of the system.

   3.3 A 'soil test' in which the extraction vessel contained at least 50 gr. of soil. Otherwise the procedure was identical to the system 'wet test'. This test tried was oriented to prove the reliability and quality of the analysis.

   3.4 A 'safety test' where all the different safety features of the system were checked: interlocked windows, UPS (for power failure) and emergency stop.

   3.5 A 'contamination test', using radioactive samples, to prove that no cross-contamination exists between samples.

4. Writing up of validation report, GLP audit, approval and archiving.

The validation process was finalised after almost a year. Instrument hardware should be re-validated after any repair or modification and software after any upgrade.

7. DISCUSSIONS, RECOMMENDATIONS AND FUTURE WORK

One of the things learned is that it is very difficult to make people change the way they work. The 'we have been doing it for years and it worked so...Why change?' is commonly heard. The system here described represented a major change in the Environmental Sciences department of RPAL, so it was a challenging task for us to replace scepticism with enthusiasm. Users are now in a phase of 'trust building' in which they are gaining familiarity with the system as a day-to-day tool, increasing their confidence in the quality of the results and perceiving the benefits of its use.

A project of such a magnitude should not be over once the system is ready for operation. Upgrades and further system optimisation add value to the investment made. Through daily use monitoring and analyst feedback several enhancements were soon identified:

- Vial shaker to improve cocktail and sample mixture in LSC vials.
- Removal of GPC and SPE for its use off-line.
- Replacement of the 0.1 ml pipette syringe by a 0.5 ml one, so the most common volumes could be transferred with improved accuracy.
- Replacement of the existing balance (2 decimal place reading) by a 0.1 mg readability one, so the 2% accuracy could be ensured for even smaller aliquots (all checks are done by weight).
- Upgrading of computers for Year 2K compliance.

At present, the system is fitted with limited intelligence. It helps the user during the design stage so only robust and physically possible methods of analysis are stored for further process. However, once a method is accepted, the robot will run it exactly as the user has specified. The fact that the method is 'possible', does not mean that it is 'optimum'. There could be some redundant, unnecessary or even inappropriate operations that the

analyst included due to a shortage of available data, knowledge or confidence.

An intelligent system should learn from its experience and use this information to optimise throughput and utilisation of resources (Felder, 1996). Experts systems are a sub-speciality in artificial intelligence (AI). The term is generally understood to mean a "knowledge-based" or "knowledge-driven" system designed to represent and apply factual knowledge in specific, very limited areas of expertise. The goal is to make intelligent programs by providing them with high quality, domain-specific knowledge about some limited problem area. It is, somehow, a way of capturing human expertise to make it permanent, widely available and easily portable, while providing consistent and objective answers. Regardless of the details of implementation, the expert system is, in the limit, a process involving a cleverly ordered series of "if tests" within a knowledge database. The great advantage is that the knowledge base can continually be updated by the system using results of experiments (Isenhour, 1988).

Isenhour and his colleagues from Kansas State University have reported the application of those principles to the analytical laboratory (Isenhour, 1988; Bleyberg 1990; Lee 1992). The same trend could be followed by our system. All experimental data and expertise accumulated during operation over the time should be used as a source of information to evolve towards an expert system which combines knowledge about analytical chemistry with laboratory robotics. The system would be able to modify or even create optimum and efficient procedures for analysis, process them and finally archive them for future reference.

On-line quantification steps, such as LSC, together with knowledge databases will allow the use of software-driven logical decisions to determine the best procedure to adopt. Analysts would still design their methods with the GUI, but, at runtime, the system will use its expertise to decide if a

particular step is unnecessary or inappropriate. Results from quantification steps combined with available data can be fed into decision trees to decide the next step in the process. Those decision trees as well as the knowledge base will be developed and validated in conjunction with experienced analysts.

The system network is completely independent from the company network. Their interconnection has already been planned for the year 2000. Several organisational steps have to be finished before its realisation: migration from company VAX to NT servers, rewiring of building and replacement of system server by NT machine. The adoption of Windows NT as the prime operating system for the whole enterprise helps to bridge the gap between the laboratory and the office.

A high degree of security will be implemented to guarantee total insulation during system operation. The system should run independently from the Company network so it is not affected by its problems and there is not a decrease in performance during runtime. However, at the management layer level, the connection provides many benefits.

At the moment users have to go to the lab to design their methods by using the GUI in the system server. In the near future, they will be able to access the GUI form their desktops in the office so method design and report production is facilitated.

The new Company LIMS (Laboratory Information Management System) will be finalised soon. LIMS are used to standardise the collection of information generated in the analytical laboratory and provide general access to that data. As any other analytical research tool, the robotic system should also interact with the LIMS system so sample data is automatically uploaded from LIMS and, in the same way, generated data is formatted and downloaded into it.

Besides looking into the future, a review of the project cycle is equally useful. The experience gained while developing the system should lead to the identification of those aspects that would have been done differently if commencing now. This will have a positive impact in future automation projects and, at a more personal level, in our professional development.

The in-house development had many advantages that have been explained over the thesis but it also required a long time for its implementation. From my personal point of view the main lesson learned is that the benefits of automation are more easily proven and the technology better assimilated by deploying automation in stages.

Some workstations, such as the extraction, could have been installed as stand-alone modules for its use in the lab. The process could have continued by developing a small automated cell including the first steps in the analysis: extraction, pipetting and LS counting. That basic system could have been expanded to include concentration and mixing, and so on. This strategy also presents disadvantages as for example more validation phases but it would have simplified the development phase and provide tangible benefits faster.

Another reason for in-house development was to provide enough flexibility to respond to changes. But this also made our task more difficult since a change in system requirements meant re-thinking and re-implementing some of the work already done. Although capability to adapt to new circumstances is important, enough quality time should be spent by users to decide real requirements and produce serious specifications.

This project, developed under a Teaching Company Scheme, has been a very beneficial experience not only for the Company, as it has been shown along the thesis, but a personal level too.

Extensive training, both on the job and by going to externally run courses, helped to develop my technical knowledge into effective and practical skills, applicable not only to the scheme but also transferable to future employment.

Besides technical skills, experience was gained in business related issues, project management, communication and presentations, to name a few. It also gave me the opportunity to enrol for this MPhil. Other aspects as team work, international exposure and friendship cannot be forgotten.

To sum up, this project has been a challenging and rewarding experience and, due to the success of the scheme, I was offered a permanent position with the Company as an Automated Systems Consultant.

8. CONCLUSIONS

A robotic system for sample analysis has been developed and successfully validated at Rhone-Poulenc Agriculture Ltd. It consists of a robot mounted on a six metre track with twenty two laboratory instruments and several racks distributed at both sides. Some workstations have a RS232 interface and can be remotely controlled by a computer. The rest, requiring analogue or digital signalling, are interfaced to a PLC. The cell layout was optimised using Visual Interactive Simulation (VIS).

Due to the nature of the processes involved it is likely that no two runs will ever be identical. We are dealing with the automation of a non repetitive process involving non deterministic operations, such as evaporation or filtration. Parallel batch processing, as oppose to sequential, is also required since the overall time has to be minimised to increase productivity. A high level of operational flexibility is involved compared to a typical Flexible Manufacturing System (FMS) installation. As a consequence, classical control strategies could not be applied and the system has to be dynamically scheduled at runtime.

A Distributed Computer Environment (DCE), comprised of five networked computers, shares the control workload. This architectural strategy multiplies CPU power, provides a global multitasking environment, facilitates the integration of different vendor software standards, provides modularity and allows expandability. Each computer in the network is in charge of the scheduling, the supervisory control and the serial communication management of the instruments physically attached to it. Dynamic Data Exchange is used for inter-communication between applications residing in the same PC. The different scheduling programmes, distributed along the network, communicate through the server resident runtime databases rather that directly with each other.

Four are the key modules in the control system: A Graphical user interface (GUI), a multi-application dynamic scheduler, software device drivers and a real-time database system.

The Graphical User Interface (GUI) brings the power of computer aided design to the reconfiguration of equipment and sample analysis recipes. Through interactive graphics and immediate feedback, complex method of analysis can be developed easily, naturally and safely. Prior to a run, this master recipe is converted into a working recipe accessible and understandable to all modules of the dynamic scheduler. The process starts once the system calibration routine has taken place.

When a workstation has finished its operation it sets a call in a given runtime database notifying the robot application that the unloading process can take place. The next pick and place operation is selected among all these calls according to the availability of their destination and a set of priority rules. The scheduling application in charge of the destination workstation is notified that a loading sequence is going to be initiated. Transfer of control to the device driver takes place via DDE for the downloading of operational parameters in the instrument. The station then awaits two signals to begin the task. The first comes from the computer after a successful downloading of parameters. The second, from the robot controller once the manipulator has loaded the station and has reached the nearest safe position.

All generated data is reported back to the user at the end of a run according to the standards of Good Laboratory Practise (GLP).

The system aims to process 70% of the samples entering the Environmental Sciences department. In addition, it can be used as a research tool in method development studies dedicated to the definition of optimum and robust protocols of analysis. Analysts have traditionally dedicated more than 50% of their time to those tedious and time consuming tasks. All that time

can now be used to do more creative and intellectual work. Safety has also been improved by reducing the exposure of personnel to chemicals.

Due to the success of this scheme, I was offered a permanent position in the Company and further co-operative ventures are being planned between Rhone-Poulenc and Middlesex University in both the UK and France.

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APPENDIX A. Published work

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FLEXIBLE LABORATORY ROBOTICS SYSTEM: HARDWARE AND SOFTWARE OVERVIEW

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Abstract: Automation using workstations appears to be the answer for performing many of the repetitive tasks in analytical laboratories. Integrating these automated stations using robotics is a logical progression. There are many potential benefits, but, because different technologies must be integrated, a high level of complexity is related to these kinds of projects. In addition, flexibility, expandability, ease of use and set-up, as well as maximising robot time, are required in order to provide a reliable and efficient system. This paper gives an overview of the different hardware and software components in the Rhône-Poulenc Agriculture Ltd. robotics cell.

Keywords: flexible automation, robotics, hardware, software engineering, user interface, database system, scheduling, network.

1. INTRODUCTION

Increased productivity and throughput, automatic data collection and documentation, and most effective use of chemists' time are some of the benefits of applying automation. However, a high level of complexity is

related to these kinds of projects because different technologies, such as robotics, data acquisition, instrument interfacing, process control and LIMS (Laboratory Information Management System), must be integrated. In addition, as techniques become more complex, their automation requires higher levels of sophistication (Donzel and Hamilton, 1993).

Partial automation of discrete operations is commonly used in laboratory environments (solid phase extraction, autosamplers, etc.). In some cases robots have been used to link these small automated cells. However, until recently, robot based systems have required too much programming effort, been too inflexible in operation, and too expensive to use (Isenhour and Eckert, 1989). This has meant that only the most repetitive analysis has been automated, as for example water analysis (Cockburn-Price, 1995), routine pesticide residue or soil analysis (Laws and Jones, 1988; Koskinen *et al.,*1991).

However, all the potential benefits that can be obtained and recent technological advances, have lead automation not only to small or rigid processes, but to more complex and ambitious ones.

The variety of compounds and matrices found in sample analysis of trace pesticides and metabolites, necessitate the use of a wide variety of techniques and, usually, different process recipes for different samples. A high level of flexibility is required to bring these techniques into an integrated system because it involves automating a non repetitive process. In addition, in order to perform all the required operations, a high number of laboratory instruments from different vendors must be integrated in the robotics cell. It means that several signalling and communication protocols (RS232, IEEE488, RS485, digital/analogue signals) have to be harmonised and that a large workspace is needed.

As these systems are not presently available commercially, customisation is

required to get the maximum benefits in productivity (Owens and Eckstein, 1988). As a result, RPAL (Rhône-Poulenc Agriculture Ltd.) is developing an automated cell for sample analysis. As one of its functions will be method development, it is important that this cell does not need to be reprogrammed to run a different procedure. This is a big difference if compared with similar systems (Laws and Jones, 1987).

To protect the financial investments made, the RPAL system has to be: *flexible* to allow processing of different process recipes; *modular* to allow future expansion and modification (Buhlman *et al.*,1992); and has to *optimise robot time* to increase capacity and throughput (Little, 1993).

The purpose of this paper is to give a brief overview of the hardware selected and the software applications developed for the RPAL system. It gives a general outline of the problems encountered and the solutions addressed.

2. SYSTEM HARDWARE

2.1 Robot

Traditionally, fixed-base robotics arms have been used, with all the instruments located around it in a highly constricted work space (Isenhour *et al.*, 1989). As the process being automated here is complex, a high number of workstations need to be integrated to perform all the required operations. In addition, intelligent instruments running as 'stand-alone' modules are usually relatively large. The consequence is that additional workspace is required and, therefore, the volume of space that the robot has to reach must be larger. This problem led to the choice of a track-mounted robot. The track also allows expandability, assuring modernisation and adaptation to new technologies and the possibility of solving bottlenecks by including additional units.

An articulated A465 robotics arm (CRS Plus, Burlington, Ontario, Canada) with six degrees of freedom and 711 mm reach was selected because of its versatility, relative ease of programming and teaching of locations. The robot is mounted on a six metres linear track and is interfaced to the Host through a C-500 controller (CRS), where programs to control robot movements are stored.

Variations in vessel size present no problem when chemists are handling samples manually, but in robotics procedures this is a difficult problem. Limiting vessels helps, but due to the nature of sample analysis, different workstations use different vessel sizes (in this case from 16 to 70 mm.). Changeable grippers have been used (Ahmed and Sowmya, 1994), however, this is an extra operation requiring time and substantial costs. A multipurpose gripper with several fingers pairs to handle the whole containers range was designed. This was a major and complicated task, but crucial for optimum operation of the system.

2.2 Workstations

An important factor to achieve increased capacity is the use of semi-autonomous workstations instead of devices that require the robot to work them (Little, 1993). The 'stand-alone' modules operate on their own so that the robot can carry out other functions. In this way, the robot becomes a 'pick and place' manipulator, whose only function is to transfer sample containers between workstations where the different operations are performed. The result is that many procedures can occur simultaneously on samples at different stages of a procedure. However, these stand-alone modules are not independent. Their performance has to be synchronised and controlled by a host PC.

The RPAL system integrates twenty two workstations. Some of them are off-the-shelf serial devices fitted with bi-directional RS-232 interfaces which can be connected directly to a computer. However, older instruments or custom built workstations, do not have RS-232. These workstations are instead controlled through digital or/and analogue signals. DA&C (Data Acquisition and Control) cards, PLC (Programmable Logic Controller) and micro-controllers, were the interface options studied. A Sysmac C200HS PLC (Omrom Co, Tokyo, Japan) was chosen based on the high number of I/O and timers required. The need for analogue signals, and other factors such as cost, development time and expandability were also considered. As this PLC is fitted with an RS-232 interface, it can be easily integrated into the system.

In summary, the system consists of a robot mounted on a 6 metre linear track with twenty two semi-autonomous workstations situated down both sides. The optimum instrument distribution along the track was determined using simulation (Smartt and Gill, 1997)

2.3 Computer hardware

In the RPAL system, ten serial devices plus the PLC and the robot controller had to be connected to a Host PC. In addition to handle the serial communications, the host PC had to control each workstation through software device drivers, execute overall supervisory control, carry out robot scheduling, manage databases, display the user interface and develop reports. Even with sufficient memory, the computer could fail to cope with so many tasks due to a lack of system resources.

The RPAL system uses five networked computers as shown in Figure 1. The first one is the User interface. Here, analysts will enter all the required information to run the system and will be able to automatically produce reports of the results. This will be the only computer accessible for users

avoiding possible security problems, unauthorised system running or 'crashes'. Three other PCs will be the sub-processing units. They will be connected to all the serial instruments (including PLC and robot controller) and will control them directly. The last one, the main PC, is the hub of the system, containing the databases, and acting as a server for the three sub-processing units.
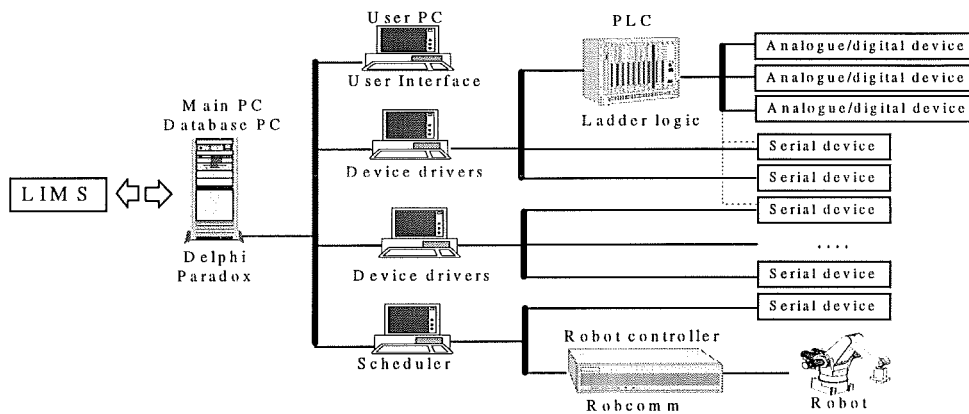
Fig. 1. Hardware and Software distribution

The network increases the CPU capability of the system and its speed, distributes the workload, allows automatic sharing of data and reduces the probability of error.

3. SYSTEM SOFTWARE

Programs to control the robot movements are written in RAPL-II (Robot Automation Programming Language, CRS Plus) and stored in the C-500 controller. PLC programs to control the digital/analogue instruments are written in ladder logic. If a different package is used to elaborate each application it will have a disadvantageous impact in the learning time, cost, compatibility issues and troubleshooting. Therefore, it was advantageous to

find a complete programming environment to develop all the other applications.

Delphi for Windows (Borland International, Inc., CA, USA) was chosen as the programming environment due to its fast compiler, graphical environment, integrated database support, reporting capabilities and object-oriented programming language.

3.1 User Interface Software

The Interface has been designed to be graphical and user-friendly, with workstation descriptions representing each process in a method. Analysts will use it to design sample procedures. To do so, they only have to add the desired workstations to the graphical screen, connect them together (see Figure 2), and configure them, for set-up time, speed or other parameter. No detailed computing knowledge is required to run it. The user only has to be aware of some basic rules to work with it. The User Interface has been written using Delphi and is stored in the User PC.

3.2 Database System

All the information entered by the user will be stored directly in databases, not only for reports and safety but also for control purposes. From these 'user-time' databases, a set of run-time databases is created when the system is running. This is a key part of the system. Borland Paradox is used for the databases, and they are stored in the main PC, which acts as a server for the instrument computers.
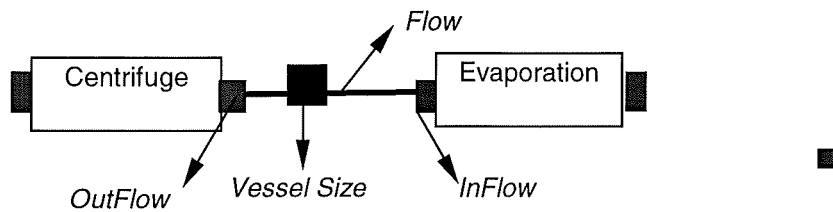
Fig. 2. Station connection in User Interface

3.4 Software Device Drivers

Modular software device drivers, placed in the sub-processing units, handle the serial communications with the workstations. This modularity protects financial investments because it allows for replacement of instruments, integration of new ones and problem detection. The result is a flexible system which can be upgraded with new technologies with a minimal impact on the existing one.

3.3 Control routines and robot scheduler

Control routines reside in the sub-processing units. In general terms, the purpose of these routines is to look at in the server databases until a switch field is set by the robot control application. This indicates that the vessel has been placed and the instrument is ready to work. When this occurs, the related operational parameters are taken and downloaded to the device driver using DDE (Dynamic Data Exchange). When the station has finished working, the control routine collects the signal from the driver and sets a call for the robot in the server. The control routine in the robot PC reads this 'database call' to select the next 'pick and place' operation for the robot.

Scheduling is a key factor in optimising robot time, and increases system capacity and throughput. If a number of samples have to be processed, the

simplest way of doing it is sequentially. However, the system is unlikely to be working efficiently and at full capacity. A parallel process of samples will optimise the robot time and subsequently, the system or process time. This could be achieved using complex algorithms before the system starts running. However, as different types of samples are analysed in parallel, the complexity of the algorithms increases. In addition, it is impossible to predict, accurately, the actual times for some of the processes. An on-line scheduling of robot movements is a better solution for the RPAL cell-Workstations call the robot when they finish their operation and a procedure of priorities select the next robot destination.

3.5 Reporting Tool

When the system has finished running a method, all user information, run-time information and data produced by the instruments are available in datasets. A reporting tool, included as a feature in the User Interface, allows analysts to choose the format and data to include in the report. After that, it will be created and printed automatically.

4. CONCLUSIONS

Laboratory automation provides a large number of benefits including increased capacity and throughput, freeing human resources for more intellectual tasks. RPAL has developed a flexible system for sample analysis of trace pesticides and metabolites. It is a non-repetitive procedure requiring parallel processing of samples with different assays. In addition, a large number of workstations are involved in the process. For these reasons, traditional approaches did not suit this robotics system. The hardware selected and the software developed for controlling and interfacing the system were made in order to meet RPAL's objectives.

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Robotic System for Analytical Method Development with On-line Quantification and a Graphical Interface.

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A robotic system has been developed, jointly between Rhône-Poulenc Agriculture Limited (RPAL) and Middlesex University, which automates method development, and performs simultaneous multiple-method, routine sample analysis. The system consists of twenty-one discrete workstations of varying complexity. Three different types were used: off-the-shelf ready to use, those requiring modifications, and purpose built. In order to achieve such a system, many of the discrete processes in the analytical laboratory have been automated in separate work-cells. A Programable Logic Controller and Serial interfaces are used to control and communicate with a distributed controlling computer system. A small industrial robot mounted on a six metre length of track, feeds the workstations as a pick and place manipulator. The control system gives the analyst full control of all the parameters

associated with each workstation. A Graphical User Interface (GUI) allows analysts to use the system with minimal training, and to graphically represent the process in a familiar form.

INTRODUCTION

The analysis of pesticide residues in plant and soil matrices involves the extraction, clean-up and quantitation of parts per billion (ppb) amounts of molecules from samples which are complex in nature. As a result the steps are labour intensive, and the quantitation step generally involves the use of sophisticated instrumentation. In order to register new active ingredients environmental studies using soils and crops are required. This generally involves the use of radio-labelled molecules to aid following the degradation path. These studies are also labour intensive as analysis of the samples is required, using similar techniques and quantitation methods to residue studies. Combination of the study of degradation with developing a suitable method of analysis is beneficial in terms of efficiency of the process. Development of a fully automated system to achieve this objective, which has not been reported before, is described in this paper.

The use of robotic systems in laboratory applications has been reviewed by Majors [26] and Crook [5,6]. There are numerous references to the use of Zymark robotic equipment for the analysis of pesticide residues between 1985 and 1997, including Law and Jones [16, 18-20], Owens [30], Lemme [24], Koskinen [17]. Between 1988 and 1994 Isenhour and his group have

reported the use of expert system software to control robotic systems using the Zymark robot [2,10,12-15,21-23,36-38]. Once a system reaches a certain size, scheduling of tasks becomes important consideration. Corkan and Lindsey [4,25] and Murray [28] have discussed many of these issues.

AUTOMATION OF ANALYTICAL PROCESSES

The cost of automated analysis requires a significant capital and resource investment. However, the benefits of automated analysis are potentially immense, enabling reduced analysis costs, improved precision and minimising analyst contact with chemicals. Many analytical techniques have been automated, and although transferring manual procedures to automated systems is, on paper, feasible, there are technical problems with automating an entire process. These technical problems need to be overcome in order to maintain flexibility of operation, and in the systems use, in the future, to justify the capital investment. These problems revolve around the integration of equipment, not specifically designed to be integrated into systems. Extensive electronic and software engineering is required in order to be able to satisfactorily control the equipment. In addition, many workstations are not available and so require development.

Automated turn-key systems for the analysis of routine samples in the laboratory have been available since 1982, mainly utilising Zymark robots. Alternative robotic equipment systems, such as the HP ORCA, have also been used. The use of systems integrators is the usual route for major

projects, due to the specialist engineering, computing, and resources required to achieve a rapid development. However, as technology is rapidly changing, any future modifications cannot be easily done in house. The software code is unlikely to be available, and so a delivered turn-key system cannot be modified easily. A system with sufficient flexibility to be modified cannot be justified due to the high cost, and long development time to achieve it.

AVAILABLE EQUIPMENT

The advancement of computers, robotics and control systems has, in recent years, allowed rapid advances in laboratory automation. Stand-alone automated pipette and solid-phase workstations, as well as analytical quantification techniques, are available commercially from several manufacturers and have, over the last decade, made significant impacts into the analytical laboratory. However, stand-alone workstations invariably have not been designed to be integrated into larger robotic systems, and can be deficient in several areas. Most notably communications, robot access, and safety control are problem areas, requiring specialist engineering knowledge. To achieve satisfactory reliability for a complex system, the reliability over normal use of individual components or workstations need to be improved in order to minimise accumulative errors reducing the overall reliability of the system. At minimum, they may require some modifications by the equipment manufacturer, and further in-house customisation, to enable some form of safety control in the automated system. Even if the equipment has a bi-

directional RS232 interface, the protocol enabling communications may not be readily available. The available access area for samples may not be suitable for the robot, and some further customisation may be required to the equipment, or robot gripper, in order to access the sample area.

AUTOMATED ANALYSIS

Automation often requires the changing of traditional manual procedures so that they can be automated more easily. Method development is usually done off-line using traditional manual procedures, and then transferred to the robotic system, which can result in problems. As a consequence, the time taken to establish a new automated method is often considerable. Re-validation is then required, in the automated system, before routine analysis can commence. In addition, the sample preparation stage of an analytical method has always been a limiting step in automation, due to the difficulties associated with its automation. Although this step has been automated, it was with limited control of the process [18-20]. Thus the need to develop analytical methods, on robotic systems, is vital, especially if flexibility is required. These problems, and numerous others, have limited the effectiveness, so far, of automation in analytical chemistry applications.

METHOD DEVELOPMENT

Expert systems, using logical decision trees, enable method development to be automated, but requires the quantification of results in order to make the decision. Full integration of such systems has been limited and it is rare for

an analytical method to have been fully optimised due to the considerable time taken to achieve such a situation. For example, optimisation, using automation of liquid-liquid extraction, has been reported [34]. Although chromatographic method development software packages have been around for some time, it is only the final step in what can often be a long and time consuming process. Using a flexible system, all of these factors can be combined into a truly automated system. Once multiple samples are introduced into an automated system, scheduling becomes a problem, so a suitable way of scheduling the robot was required. The safety of analysts exposed to chemicals is also a consideration of increasing concern.

CONSIDERATIONS

Robots suitable for laboratory applications have become more reliable and easier to incorporate into complex integrated systems. Some of the earlier problems associated with laboratory robotics are discussed by Shealey [32]. In order to provide a high degree of flexibility in an automated system, sophisticated programs are required. As the development of software is both expensive and time-consuming, turn-key systems are invariably rigid in their application. Writing the code in-house allows future modifications to be carried out and thus allows control without the need for re-negotiations with systems integrators. The optimisation of robot time between workstations using scheduling software is also an important consideration, as the running of complex systems is difficult to envisage. Although such software packages are available, they are usually tied to the systems integrator and

come as part of a turn-key solution. Specifications may not sufficiently detail the users' requirements since as automation evolves the user sees the benefits and requests modifications, thus changing the original specifications. Unless regular communications between engineers and analysts are good, then misunderstandings of the requirements can result.

The availability of instrumentation with the capability to communicate (bi-directionally) with computer systems has advanced rapidly in recent years, with RS232 being the usual standard. Manufacturers in many cases provide the software required to drive the instrumentation, and the necessary protocols to communicate with computers, but they are not usually designed to be integrated into robotic systems. Consecuently, there are several problems that are often encountered. First, even though different robot manipulators are available, moving a sample between workstations is often problematic, requiring a change of hand or vessel, or workstation access is restricted. Second, the compatibility of stand-alone systems with other systems is invariably poor leading to software and hardware operating problems. Thus the integration of many stand-alone workstations into a total automation package is very difficult, requiring specialist expertise, and support from the manufacturer. The integration of robotics, with analytical equipment, including instrumentation also requires specialist engineering and computing skills. The use of companies specialising in this area is the traditional route to obtain such a system. Turn-key solutions provide the answer to many automation projects, but these invariably rely on the

automation of set procedures, with large numbers of samples. In order to automate a non-repetitive process each workstation needs to be configurable by the software in run time. The automation of non-repetitive processes is also impossible using traditional scheduling and control tools as workstations may be busy at the time required leading to delays.

PROJECT MANAGEMENT

A project was set-up to identify the major time consuming tasks performed in the laboratory, and those suitable for automation. As part of the project, off-the-shelf solutions for a number of tasks were identified and implemented immediately. These included data capture, temperature recording of sample storage areas, and the purchase of stand-alone automated workstations. The automated system described in this paper was the outcome of the remaining part of the project. The users were involved, at the outset, with the design of the system in order to guarantee the projects success. Initial ideas and concepts were discussed with automation integrating companies with regard to the feasibility of the concept, cost, and time to design and build. Although several companies were able to provide turn-key solutions, the risks associated with such a venture were deemed to be too high, such that future requirements could not be guaranteed without additional, unknown, costs. Access to the software code, and having in-house development expertise, was also another consideration. Thus, in order to be in control of the project and phase the development, it was decided to proceed in-house. As Rhône-Poulenc did not have the necessary

engineering and computing expertise, the final stage of the project was conducted in conjunction with Middlesex University. The University provided the expertise and technical support, and Rhone-Poulenc the funding. In addition the University was able to obtain external funding under the Teaching Company Scheme (TCS). This scheme is designed to introduce new graduates to industry, and train them to be effective, benefiting all parties. For this project three specialist engineers were recruited, each on a two year contract, and became part of a multi-discipline team with the analytical chemists at Rhône-Poulenc, and engineers at Middlesex University.

SIMULATION OF PROCESS

In order to estimate the size of the system, the number of workstations required, and the performance of the integrated system to a range of different scenarios, a graphical simulation of manual processes in the laboratory was initially performed, using a discrete event simulation software package (Witness) [33]. This enabled an embryonic system to be developed prior to going into the expensive build stage. The workstations have been arranged in a logical sequence based on the results of the simulation exercises and integrated together in the robotic system (Figure 1). The purpose of the robot simply is to act as a pick and place manipulator, feeding the workstations with samples and vessels. The workstations are designated 'idle', 'busy', 'finished' or 'unavailable', and so using a simple system of workstation calls, the robot can be scheduled to move the vessels between

workstations or racks. The simulation showed that a six metre length of track, with a 6 degree of freedom (DoF) robot would be required with twenty-one workstations arranged down both sides of the track. Several workstations required cloning in order to minimise bottle-necks. In particular the evaporation workstation was cloned to give several discrete evaporation units.
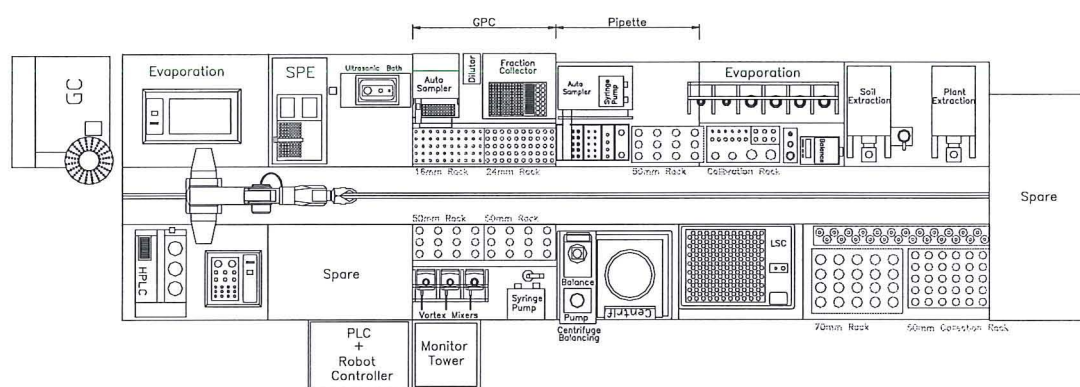
Figure 1. Layout of Cell showing positions of specific workstations

SELECTION OF ROBOT

Robots designed specifically for laboratory applications have limitations over small general purpose industrial robots. The Zymark robot is a cylindrical robot with three degrees of freedom (DoF), and although suitable for many applications, it cannot easily be mounted on a track. The four DoF Hewlett-Packard ORCA robots promised much, with its superior software and control capabilities [8,11,27,31]. However, the lack of a waist, small pay-load (0.5 kg), and limitations on track length (2 m) again made it unsuitable for our application. Many industrial robots are designed for the heavy end of

industrial applications, but the CRS small industrial robot combines all of the criteria that were required. It has a high degree of accuracy (±0.05mm), high pay-load (3 kg), 5 or 6 DoF, 6 m track length, and relatively low cost. It also comes with a teach pendant, and is easy to integrate into complex systems (programming, programmable logic controller, anthropomorphic configuration, software, and path movement). This robot has also been used successfully for other laboratory automation applications [3,29] most notable by North West Water, and is a prime component of Robocon systems. These factors were enough to satisfy us that this was the type of robot that we should use for our application [9]. The robot is controlled, using a series of generic programs, to move to a particular location. This involves a set sequence of movements to guide it to retrieve or place a vessel, and then safely move away to a safe position. The concept of 'safe positions' allows the robot to move between any two safe positions, without fear of collision. Vessels have been specially designed to fit with the workstations and be easily moved by the robot. A uniquely designed gripper allows the robot to manipulate all sizes of vessels and to interact with any workstation.

GRIPPER DESIGN

Although the robot came with a servo gripper, a pair of gripper fingers needed to be designed. The variety of vessels that were used in the manual processes was large, and incompatible with automation. In addition, access for some workstations, such as the centrifuge, was already pre-determined by the limited access available. Workstations that had to be developed

would have to be designed around the gripper, and so they became constrained by the gripper configuration. The gripper design, the vessels used, and workstations thus became inter-connected, such that any change in one affected whether the other was acceptable. As a result the system design would need to be thought about early in the project in order to ensure that the gripper design was close to ideal.

Optimisation of the shape and size of the vessels went a long way towards finalising of the gripper design, the final vessels being cylindrical in shape. This enables the robot gripper to grip the vessel, regardless of size in the same manner. The vessels were, wherever possible, selected with a round-bottom as accuracy became less of an issue. The round-bottom aids placing by guiding the vessel into the support rack during the placing operation, whereas a flat-bottom vessel needs to be more accurately placed, and the rack location bevelled (Figure 2).
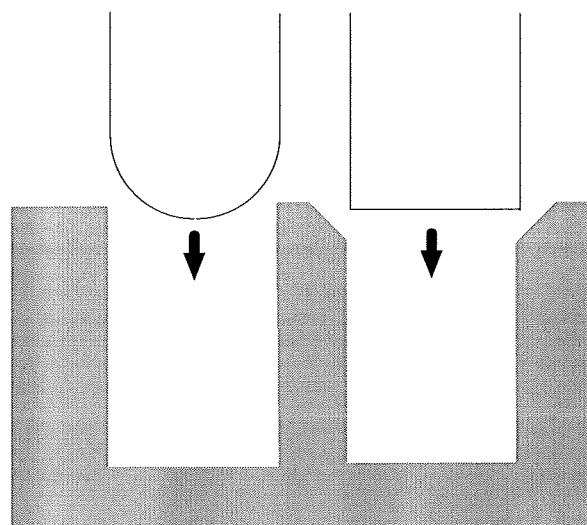
Figure 2. Round-bottom Vessel alignment

In addition, the larger, heavier, vessels were designed with a lip to aid robot lifting. The servo gripper, supplied with the robot, had a maximum opening distance of 50 mm, but the vessel diameters ranged from 12 to 70 mm. In order to over come the problem of lifting the largest vessel, the gripper hand had to be open by a least 20 mm. This made it impossible to lift the smaller vessel, so two lifting positions were required on the same hand. Another solution was to use inter-changeable gripper hands, but the additional costs, and time delays in switching hands during use, did not look an attractive proposition, so considerable effort was put into the gripper design. Prototypes were made out of wood in order to obtain a satisfactory working gripper before the final design was machined in aluminium (Figure 3). The design evolved over a period, and was orientated at an angle of 25° from the vertical, in order to achieve the maximum vertical lift, which was required for the extraction workstation. In addition, rubber pads were added to protect vessels from damage by the aluminium. The front part of the gripper handles the large vessels, the rear the remaining smaller vessels.

Side View   Front View

Plan View
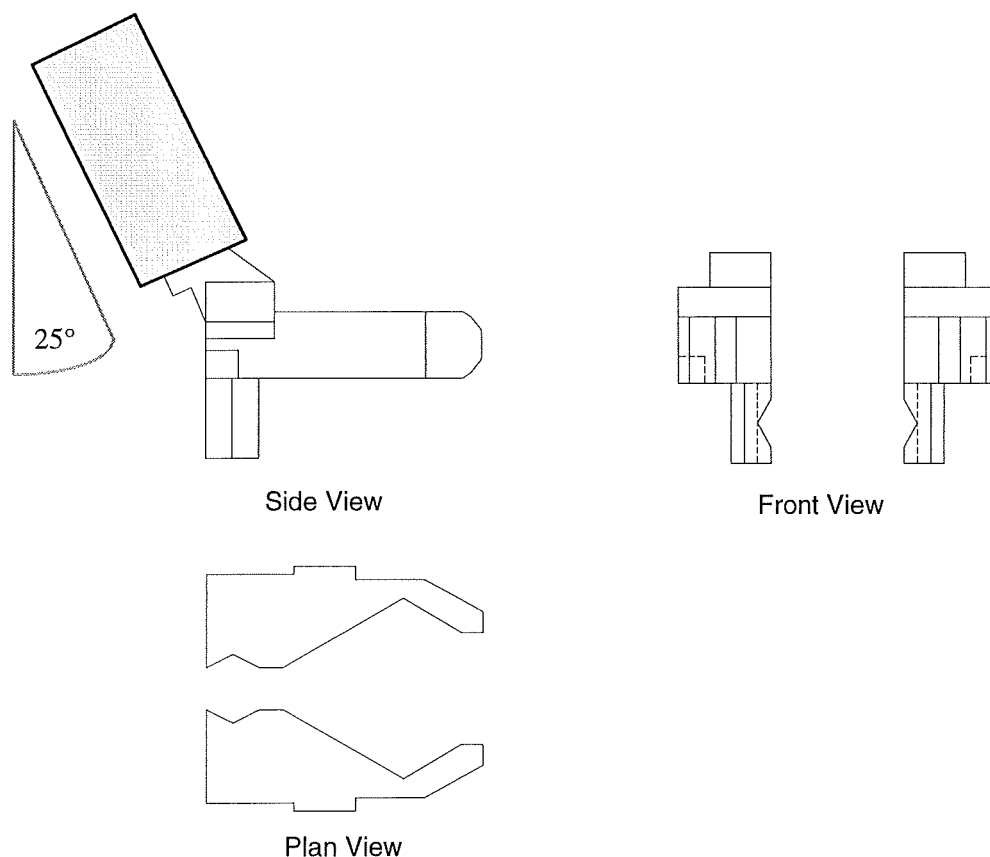
Figure 3. AutoCAD drawing of Robot Gripper.

SELECTION OF VESSELS

The vessels were optimised for the system, during the design stage, but the selection was, wherever possible, based on standard laboratory glassware. A total of six vessels were selected, based on the volumes of sample extracts used, and to optimise the transfer of aliquots (Figure 4). The extraction vessel is the initial vessel, containing the sample, and consists of a modified Schott Buchner funnel. The lower part is a polypropylene base funnel that holds a slotted polypropylene disc sandwiched between two solvent resistant seals, and secured with a screw-in Pyrex glass filter head. On top of the slotted disc is placed a suitable glass-fibre filter disc that is held

in place with a stainless steel mesh. The soil or plant material is then added prior to running on the system. Up to 100 g of soil can be extracted in this vessel. Three intermediate vessels are used in the system for the bulk of the sample work-up, and consist of carefully selected vessels enabling the minimum number of vessels, yet allowing the maximum flexibility of extract manipulation. The volume ratios between consecutive vessels are approximately five to one, allowing between 200 ml and 8 ml of solvent to be manipulated at the two thirds full mark. These tubes are 50 x 150mm, 24 x150mm, and 16x100mm, the last two being standard test-tubes. Final extract vessels are the LSC vial, and a standard 12mm vial suitable for most automated chromatographic instruments (GC or HPLC). On-line GC and HPLC were incorporated into the design, and is the next phase of the project. The final vessels selected are shown in figure 4.
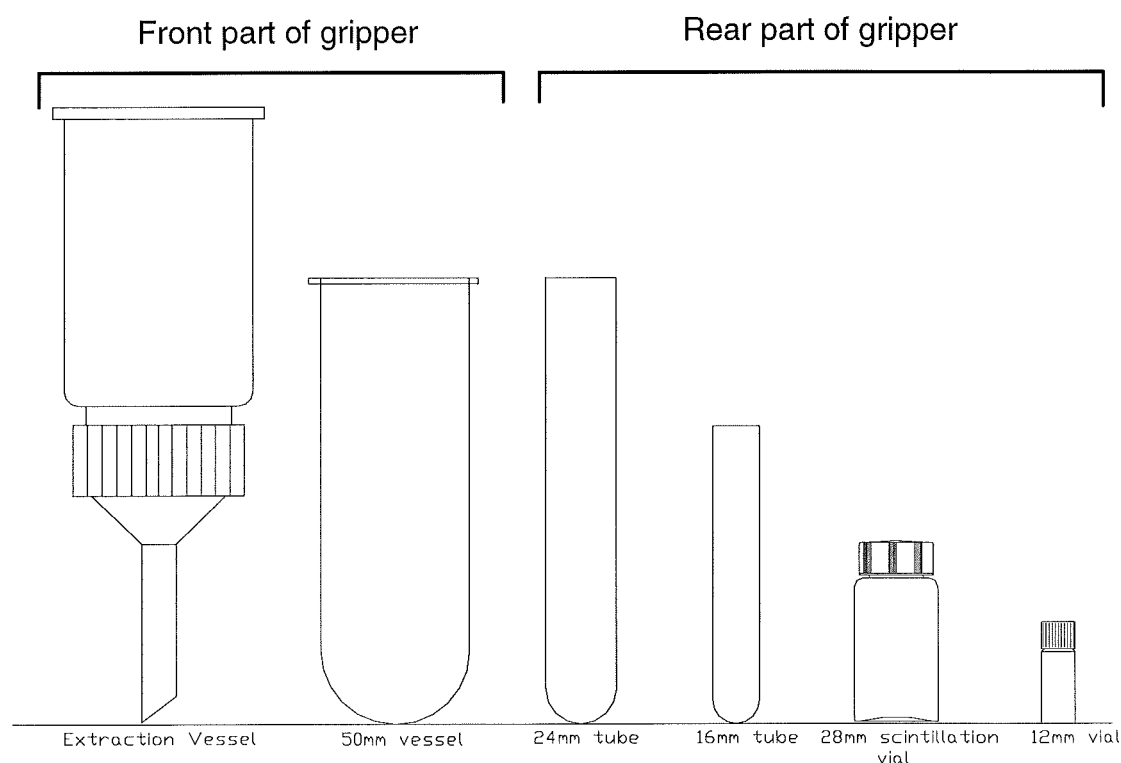
Figure 4. AutoCAD drawing of vessels used

WORKSTATION DESIGNS

In order to replicate the manual processes performed in the laboratory, and be able to automate them, modifications were required in the way that some processes were performed. It was felt that as long as the chemistry of the process was unaffected, the changes were deemed acceptable although, of course, validation of the modified process was performed. This resulted in a list of key workstations that would be required in the automated system (Table 1). Once the type of workstation had been defined, the next stage was to approach commercial laboratory equipment suppliers in the hope that they would be able to supply suitable equipment. Unfortunately very few manufacturers were able to help, and so many workstations were unavailable. The list was then split into commercially available equipment, and equipment not available. This second list then required the design and fabrication of workstations around the user specifications. Due to the large number of workstations that fell into the latter category, these workstations were either designed, in-house by the project team, or as student projects at Middlesex University, either by final year degree, or ERASMUS exchange students. These provided a number of interesting design solutions and prototypes, some of which formed the basis of final workstation designs. In particular, the evaporation workstation design, was a major break through for the system.

TABLE 1. Workstation availability and degree of customisation required

Workstation	Available (off-the-shelf) & Supplier	Degree of Hardware Customisation
Balance	Mettler	Minimal (rack only)
Extraction	No	Extensive
Evaporation	No	Extensive
Centrifuge	Sigma with modifications by V.A.Howe.	Minimal + Balancing workstation required.
Centrifuge balancing	No	Extensive
LSC	Packard	None
Pipette	Gilson	Minimal
Vortex mixer	Heidolph	Extensive
Ultrasonic bath	No	Extensive
Solvent Dispensing	Hook & Tucker	Minimal

EXTRACTION WORKSTATION

Extraction is usually the first step of any analytical process, and as a workstation was not available commercially it had to be designed. Wright [35] developed an extraction workstation, but it was not suitable for high volume use. Existing manual extraction procedures were numerous, and generally not suitable for automation. Physical agitation and filtering seemed

to be the easiest method that could be automated, as long as control of the process could be achieved. The criteria for extraction, in combination with ease of automation, lead to the extraction workstation design being one in which soil was physically stirred, or plant material macerated, using over head devices, with solvent addition under semi-autonomous control (Figure 5). The type, number and proportions of solvent, extraction speed and time are user configurable in the GUI. The extraction and collection vessels are loaded by the robot, the collection vessel is then raised to meet the extraction vessel, and both are raised to the stirring paddle or macerator head. Solvents are then added automatically, and a slight positive pressure is applied to prevent solvent dripping through the filter. The process then starts, and after a set time vacuum is applied and the filtrate collected in the collection vessel. The vacuum is monitored to enable the end-point, or problems, such as blockage, to be detected. To achieve the necessary control a programmable logic controller program was written in which the valves, micro-switches, sensors, etc were controlled automatically.
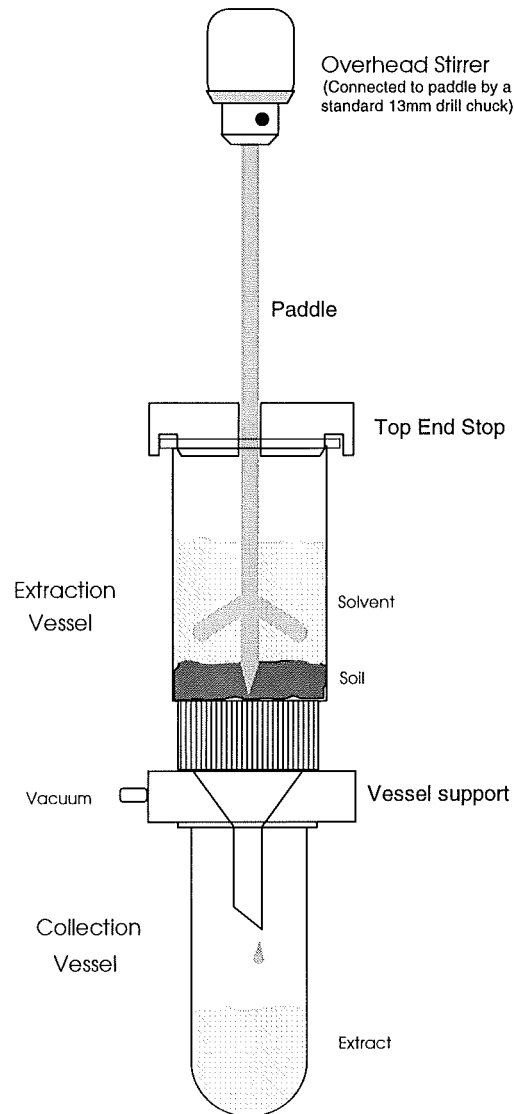
Figure 5. Soil Extraction Workstation Schematic

SYSTEM SOFTWARE REQUIREMENTS

In order to establish the hardware and software requirements a review of the

different available options was performed in order to arrive at a control

strategy [7]. The control hardware consists of a network of five computers, a

Programmable Logic Controller (PLC) and the Robot Controller (Figure 6).

The PLC, programmed in Ladder Logic, is used to control custom designed

and built workstations using analogue and digital control, and to interface them to the computer network. The pick and place robot routines were written in RAPL-II (CRS, Ontario, Canada) and stored in the robot controller. Drivers for serial equipment and overall control routines were implemented using Borland Delphi as the programming environment and Borland Paradox for the database. The software has evolved around the concepts of safety, flexibility of operation, and modularity for expansion.
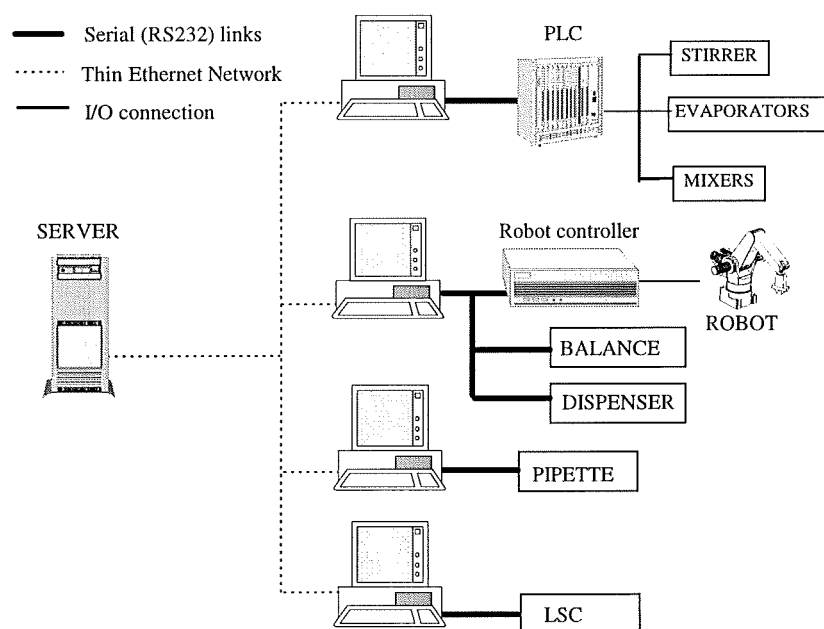
Figure 6. Communications Configuration

The system is managed through three main modules, developed in-house: Graphical User Interface (GUI), Database System and Run-time control Programs.

GRAPHICAL USER INTERFACE

Barnett described the principle of the user interface as long ago as 1988 [1], and the Windows programming environment is ideally suited to the development of a user friendly interface. The off-line Graphical User Interface allows analysts, with minimal training, to develop a method via the computer screen. All workstations are represented graphically, giving the user complete flexibility for the analysis. Samples can be split into aliquots and processed with any of the analytical techniques that have been integrated into the system. Methods are built by dropping workstations in the desktop, configuring them, and joining them to previous stations (Figure 7). The GUI interacts with the user in order to guide the analyst through the method design process. The system checks sample volumes, vessel compatibility and workstation parameters at every step of the process. This ensures that only feasible methods are stored for running. An integrated reporting tool that generates formatted reports containing all the data, after the method is run is also avaialble.
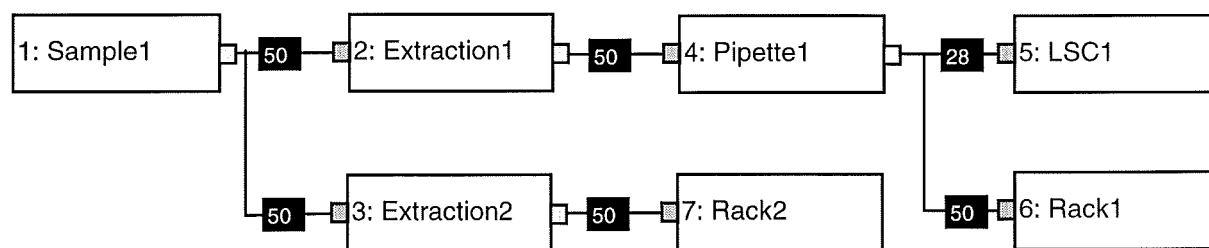
Figure 7. Method entered with GUI

DATABASE STRUCTURE

The Database structure is more than a data storage tool because it has control purposes and maintains GLP. It consists of a net of databases distributed in three sets. The first one, the "User-time" set, is functional at the design stage. These permanent databases store all the information related to methods designed with the GUI, such as user, station parameters and connections. The temporary "Run-time" set is used by the control programs. When a method is run, its related information is transferred from user-time databases to run-time ones. Controlling computers use these databases firstly as a source of information to know which operational parameters to download each time and secondly, to synchronise and schedule instruments and robot operations. In addition, on-line generated data, in the form of weights, times, counts per minute (LSC), errors, etc. are stored here. Once the process is finished, all the relevant data from the run-time set is transferred to a permanent set of "post-run" databases. These are exclusively related to the particular run of that method and are used for reporting purposes.

RUN-TIME PROGRAMS

Once a method has been developed with the GUI, the software calculates the resources required. After the samples and resources have been put in place by the user, the processes are scheduled in real time by the system. Traditional pre-runtime scheduling was not applicable for the system because this is a non-repetitive and non-deterministic process. The aim was

to be able to analyse several samples at the same time, in parallel, using different analytical methods and different operational parameters in the workstations. Method development strategies can be applied, and each step optimised. Optimisation of processes has been reported by Wieling[34] but on a limited scale. Another advantage of such a system is that the use of on-line quantification steps (such as LSC) will allow the evolution of an expert system. At each step, the results will make the decision for the next step, via a decision tree developed by experienced analysts. Software device drivers were implemented to control and communicate with each RS232 interfaced instrument. When a station completes the task, the driver sets a call for the robot. A dynamic scheduler selects the next pick and place robot operation from all those calls, based on a set of priority rules. Once the sample is placed in the next station and the robot is back into a safe position, the scheduler sets a signal for the driver which downloads the operational parameters and starts the instrument. The interaction that occurs at run-time is shown in Figure 8.

Software Drivers
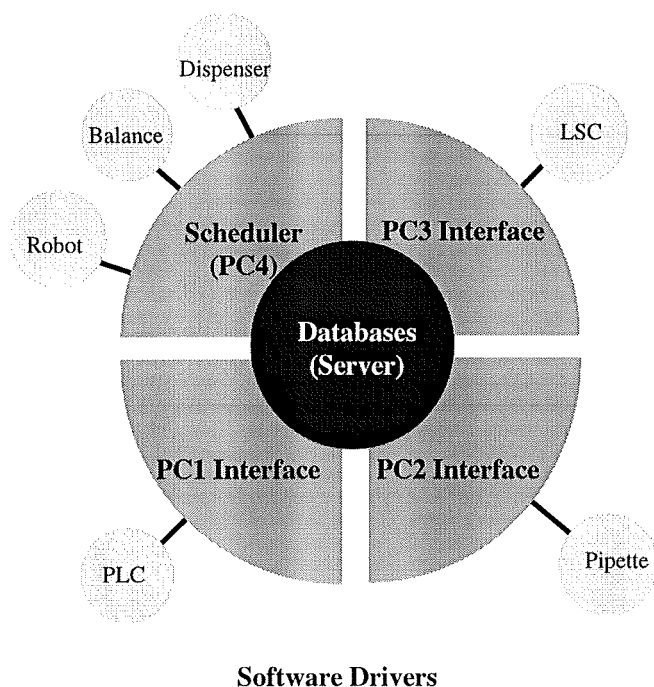
Figure 8. Interaction of run-time programs

CONCLUSION

The development of a fully automated robotic system, which uses on-line quantification and a user friendly graphical interface, allows greater flexibility in the analytical laboratory. Users are able to set up a series of analytical procedures with full control of the parameters associated with each step in the procedure. A graphical interface allows users to easily use the system, with only minimal training. On-line quantification will allow operation of an expert system by using software-driven logical decisions to determine the best procedure to adopt. Method development can then be fully automated using a simple set of these decision trees.

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APPENDIX B. Databases

USER TIME DATABASES

Database name	Storage of
PASS.DB	authorised users and their security information
OLDPASS.DB	Two last passwords
LOGONFIL.DB	All accesses to the GUI
STUDIES.DB	Existing study numbers

Table 9. User related databases

Database name	Storage of
CENTRI.DB	configuration parameters for centrifuge
COMPUD.DB	configuration parameters for Compudil
EVAP.DB	configuration parameters for Evaporators
HEATBL.DB	configuration parameters for Heating Blocks
PIPETTE.DB	configuration parameters for pipette
STIRRER.DB	configuration parameters for stirrer and macerator
UBATH.DB	configuration parameters for ultrasonic bath
VORMIX.DB	configuration parameters for vortex mixers
INITSAM.DB	description of samples

Table 10. Instrument related databases

Database name	Storage of information about
GENERAL.DB	all existing methods (job name, Study, analyst, etc.)
GLSTATI.DB	all the steps (equipment) used in every method
GLFLOWS.DB	how those station are connected (sequence) in every method
GDRAST.D	every method graphical representation (screen co-ordinates, etc.)

Table 11 Method related databases

Database name	Storage of information about
STATIONS.DB	all the steps (equipment) used in the method being developed
FLOWS.DB	how those station are connected (sequence) in the method being developed
DESSTAT.D	graphical representation (screen co-ordinates, etc.) of the method being developed

Table 12. Temporary databases

RUNTIME DATABASES

Database name	Existing information	Generated runtime data
RTCENTRI.DB	all centrifuge operations	none
RTCOMPUD.DB	all Compudil operations	none
RTEVAP.DB	all evaporators' operations	none
RTHEATBL.DB	all heating blocks' operations	none
RTPIPET.DB	all pipette operations	Locations for vessels involved
RTEXTRAC.DB	all stirrer & macerator operations	none
RTUBATH.DB	all ultrasonic bath operations	none
RTMIXER.DB	all mixers' operations	none
RTSAMPLE.DB	all samples being analysed	sample weights
RTLSC.DB	Stations' Ids (no parameters required)	LSC data & aliquots weights
RTROBOT.DB	List of all system locations and their robot controller codes	none
VESSELS.DB	all vessels' involved in the process	empty vessels weights

Table 13. Instrument related databases (runtime)

Database name	Existing information	Generated runtime data
RTGENERA.DB	method general information	start & end times
RTSTATI.DB	all steps (equipment) used in the method	operation start & end times
RTFLOWS.DB	robot pick & place operations	intermediate weights

Table 14. Method related databases (runtime)

Database name	Function
RTPC1.DB	Status of all instruments controlled by PC1
RTPC2.DB	Status of all instruments controlled by PC2
RTPC3.DB	Status of all instruments controlled by PC3
RTCALLS.DB	Storage of instrument "calls" for the robot
SAMPSTIR.DB	Extra robot transfers required for stirrer operation
SAMPMACE.DB	Extra robot transfers required for macerator operation
RTERRLOG.DB	Records runtime errors

Table 15. Scheduling databases

Database name	Function
BALCALIB.DB	results of balance calibration
COMCALIB.DB	results of Compudil calibration
STICALIB.DB	results of stirrer calibration
MACCALIB.DB	results of macerator calibration
PIPCALIB.DB	results of pipette calibration
LSCCALIB.DB	results of LSC calibration

Table 16. Calibration databases

POST RUNTIME DATABASES

Database name	Key data stored
*C.DB	LSC information (aliquot weights, DPMs, etc.)
*E.DB	Runtime errors
*F.DB	Intermediate weights
*R.DB	Vessel weights
*S.DB	Sample weights
*W.DB	Operation times

Table 17. Post-run databases

Notes:

Post-run data sets are saved in a directory named after the method (C:\...\method name\).

* stands for the "run number" (the same method can be executed over and over)

APPENDIX C. Example of Report

1: Sample1

2: Extraction1

3: Pipette1

4: LSC1

5: Evaporate1

6: Pipette2

7: LSC2

8: Mixer1

9: Pipette3

10: LSC3

11: Rack1

METHOD:	val095	METHOD CREATED BY:	MCDIAZ
STUDY:	1	CREATION DATE:	04/03/99
NUMBER OF SAMPLES:	1	REPORT REQUESTED BY:	MCDIAZ

SAMPLES

Station ID	Sample Type	Device	Number of Extractions
1	Soil	Stirrer	1

EXTRACTIONS

Solvent A =A (Unknown)   **Solvent B =Acetonitrile**   **Solvent C =C (Unknown)**

Station ID	A Solvent %	B Solvent %	C Solvent %	Time (min.)
2	0	100	0	20

EVAPORATIONS

Station ID	Temperature(°C)	Target Vol. (µl)
5	50	49000

MIXINGS

Station ID	Time (min.)
8	3

LSC   (one shot counter with fixed protocol. Not user configurable)

Station ID	Vials	Vol/vial (µl)
4	2	1000
7	2	1000
10	2	1000

GENERAL INFORMATION

Study No.:   1

Method: val095

Run No.:   1

Samples in batch: 1

Batch run by :   MCDIAZ

Start Date: 10/03/99   **Start Time:** 11:25:30

End Date: 10/03/99   **End Time:** 12:32:40

List of runtime errors (if any):

Sample	Stat. ID	Error Code	Time	Comments
1	2.00	33	12:30:35	Washdown

SAMPLE: 1

Sample Type:	Soil
Rack Location:	7001
Initial Weight (g):	291.74 *(including vessel)*
Final Weight (g):	302.88 *(including vessel)*

Sample Description (user entry):

Sample for contamination test
Flask number A12
Total Dose = 27710708

Notes: *All DPM values shown are corrected with a constant background value of (DPM) : 0*

Extracts

1 *extractions performed with the* Stirrer
Total Volume applied was 100 *Ml.*
Solvents used were: , Acetonitrile,

Station ID: 2
Flask Location: 5001
Extract Weight (g):   65.03

Aliquot Loc.	Weight (g)	DPM	DPM/g	Mean DPM/g	C.V. (%)	Total DPM
3001	0.84	191845	228387	229399	0.44	14917817
3002	0.85	195849	230411			

Concentrates

Station ID: 5
Flask Location: 5001
Concentrate Weight (g):   40.66

Aliquot Loc.	Weight (g)	DPM	DPM/g	Mean DPM/g	C.V. (%)	Total DPM
3003	0.83	300673	362257	361751	0.28	14708775
3004	0.86	310670	361244			

Mixings

Station ID: 8
Flask Loc.: 5001
Weight: 37.40

Aliquot Loc.	Weight (g)	DPM	DPM/g		Mean DPM/g	C.V. (%)	Total DPM
3005	0.85	289082	340096		356028	4.47	13315447
3006	0.84	312446	371960				

Additional data for Sample 1 (Raw data)

LSC DATA

* All DPM values shown are corrected with the constant background value (see Sample header)
* TSIE is the quenching parameter

Aliquot Loc.	LSC Station ID	Date	Time	Protocol	Counting Time (min.)	CPM	2S%	FLAG	DPM	TSIE	%LUM	Source Stat.	Stat. ID
3001	4	10/03/99	12:45:25	1	.23	180513	.98		191845	494	0	Extra	2
3002	4	10/03/99	12:48:45	1	.22	184322	.99		195849	497	0	Extra	2
3003	7	10/03/99	13:17:51	1	.15	282406	.97		300673	472	0	Evapo	5
3004	7	10/03/99	13:21:22	1	.14	291992	.99		310670	480	0	Evapo	5
3005	10	10/03/99	13:29:53	1	.15	271606	.99		289082	476	0	Vorte	8
3006	10	10/03/99	13:33:12	1	.14	293442	.99		312446	471	0	Vorte	8

INTERMEDIATE WEIGHTS

From (Stat. ID)	From (Type)	To (Stat. ID)	To (Type)	Contents Weight (g)	Time
2	Extra	3	Pipet	65.03	11:34:55
3	Pipet	5	Evapo	63.40	11:44:21
5	Evapo	6	Pipet	40.66	12:09:43
6	Pipet	8	Vorte	38.75	12:16:50
8	Vorte	9	Pipet	37.40	12:21:56
9	Pipet	11	Rack	35.74	12:28:52