# Chapter 1

# Evolution of Sequential-Injection Analysis

## 1.1 FLOW-BASED ANALYSIS FOR PROCESS ANALYSIS

Process Analysis is a branch of Analytical Science, established in the 1950s in the petrochemical industry, which has enjoyed considerable interest and growth in recent years. This has manifested itself in several areas. Notably:

- In 1982 the Centre for Process Analysis (CPAC) was established as a joint industry / university venture with start up funding from the National Science Foundation (NSF). The aim of this venture was to stimulate research and technology transfer between academia and industry in the field of Process Analytical Chemistry
- In 1992, the journal Process Control and Quality was established to provide an outlet for technical papers, review articles, and case studies in the field of Process Analysis.
- Clevett, a renowned Process Analysis consultant and editor of the above mentioned journal, published a book entitled "Process Analyzer Technology" (John Wiley and Sons, New York, 1986) which is fast becoming a reference book for this emerging field.

- In 1994, the third international symposium on Process Analysis, Anatech will be held in Europe. The preceding two symposia were held in Europe (1990) and the United States (1992). In each case, delegates form all over the world listened to papers from authors originating on all five continents.
- Major corporations have established research programmes focused specifically at the development of technology in this field.
- Several international instrument manufacturers have established programmes to develop instrumentation for the field.
- Several small groups focused on the research, development, and technology transfer in this field have begun to appear in most industrialized countries.
- In South Africa, we have noticed an increased awareness in industry of the benefits of Process Analysis. Instrument suppliers are adding Process Analyzers to their product range.
- At Mintek, the decision was taken in 1992 to establish a Process Analytical Science research group. The aims of this group are to develop technology and instrumentation for Process Analysis in the metallurgical and associated chemical industries both locally and internationally.

From this we can see that Process Analysis is grounded on a strong research base. This base stretches across disciplines involving various analytical techniques, associated fields of engineering, and computational science.

One technique that has enjoyed attention in many of the avenues mentioned above is the field of flow-based analysis. At CPAC, the Flow-injection Analysis (FIA) group is highly successful and has, through a stimulating visiting researcher programme, had an impact on groups right around the world. In fact it was during a year long visit by the author to CPAC at the University of Washington that Sequential-injection Analysis (SIA) had its origin. The evolution of this technique from its roots in FIA is an interesting discussion and serves to illustrate the relationship between SIA and other flow-based analysis techniques. It will become clear from this discussion that FIA and SIA share many theoretical elements, instrumentation, and applications. It will also show what additional avenues and benefits have been realized by adopting this novel approach to flow-based analysis.

This discussion will begin by examining the origin, theory, and instrumentation of FIA. As this is developed, common elements which affect SIA will be highlighted. The discussion will then turn to gaining an understanding of the implementation of flow-based analysis in process analysis. This discussion will highlight the need for certain refinements to the then existing flow-based methods of analysis, that eventually led to the development of SIA. Having defined SIA, some of the major areas of research requiring attention in this new field of endeavour will be identified. These areas form the basis of this study.

## 1.2 PRINCIPLES OF FLOW-BASED ANALYSIS

### 1.2.1 *Birth of Flow-injection Analysis*

FIA may be defined as an automated sample manipulation method which relies on the injection of a well defined volume of sample solution into an unsegmented flowing stream with subsequent detection of an analyte in a suitable flow through detector. The term, Flow-injection Analysis, was coined by Ruzicka and Hansen[1] in 1975 and built on a steadily emerging realization that the previous requirement for homogenous mixing of the sample and reagent in the flow system and equilibrium conditions were indeed not true requirements.

A thorough review of the early history has been published by Stewart[2]. In this publication, the author makes the point that "when a new technique is introduced to the analytical chemistry community, it is usually the case that the process is the sum of many individual concepts developed by different investigators." This has indeed been true of FIA, in fact the technique continues to grow and develop with new aspects being added all the time. Of course, the danger of such development is that confusion can result particularly in the area of nomenclature, as different workers apply their own terminology. Some have even criticized the very term *Flow-injection Analysis*. However, the widespread use of the term will make the task of an IUPAC group investigating nomenclature in flow-based techniques a difficult one, particularly if they aim to make radical changes to the conventions which have become accepted through wide spread use.

Some debate also follows when variations of an existing technique are proposed and then given a new name. One example of this is the approach which has been termed *reversed Flow-injection Analysis (rFIA)* where the reagent is injected into a continuously flowing sample stream. Is this a new technique or simply a flavour of the existing technique? Arguments for both sides are equally convincing. It is the opinion of this author that heated debate on these subjects is counter productive and diverts attention from the natural growth and development of the field of study. Rather this energy should be channelled into proclaiming and investigating the benefits of the latest development.

This investigation reports on an interesting and potentially powerful development in the field of flow-based analysis. No space will be allocated to debating whether this development represents a fundamental advancement of the field to the point of justifying a new name or whether it is simply a variation on the existing technology. Rather it will be taken as a *fait accompli* and the potential that this new approach opens and the possibility for further development of the field that it unleashes will be highlighted. As further work is conducted in the field, the advantages that the new approach offers will determine whether the new terminology remains or disappears.

### 1.2.2 *Non-equilibrium conditions*

Practising analytical chemists must master a wide range of sample handling procedures. Aside from the mechanical task of weighing, these procedures include pipetting, mixing, decanting, separating, concentrating, diluting, and other volumetric functions. Despite the mundane nature of many of these operations, robotic sample handling has largely been limited to manipulations in a highly repetitive environment or where safety considerations preclude the presence of human operators.

Despite rapid and widespread advancement in the detectors used to measure components in prepared samples, until the mid 70s, few advancements had taken place in the field of automated sample handling. Sophisticated detectors and analytical instrumentation equipped with auto samplers were still dependant on the prowess (and speed) of the analyst responsible for sample preparation.

In wet chemical sample manipulation (see Figure 1a), flowing systems were seen to offer a means of simulating a conveyor belt of beakers to which various manipulation actions were applied (see Figure 1b), e.g. an aliquot of a required reagent was added. Samples in the simulated conveyor belt, were separated by air bubbles thereby ensuring the integrity of each sample (see Figure 1c). This mode of operation prevailed from 1966 when Skeggs[3] defined the concept of segmented-flow analysis. Essentially this approach still depended on homogenous mixing of the sample with the reagent – a concept which is engrained in wet chemists throughout their training as a the basis for reproducible measurement.

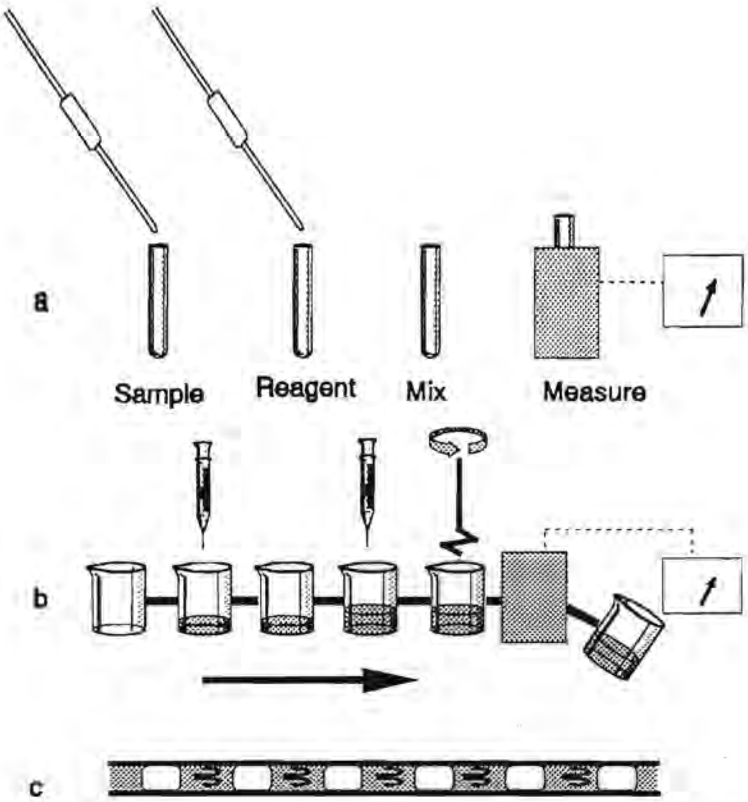

**Figure 1**: Development of automated sample manipulation procedures in wet chemistry. a. manual methods, b. conveyor belt, c. air segmented continuous flow methods

In contrast, FIA does not impose this limitation, in fact after injecting a well-defined sample into a continuously flowing stream and allowing the sample to be propelled down a flow conduit, a continuum of ratios between sample and reagent is achieved (Figure 2). Reproducible measurement is obtained because the geometry, flow rate, and timing of the system are kept constant.

This means that sub-stoichiometric conditions, or incomplete reactions, or other non-equilibrium conditions can prevail without compromising the reproducibility of the measurement. The implications of this have played a significant role in the wide

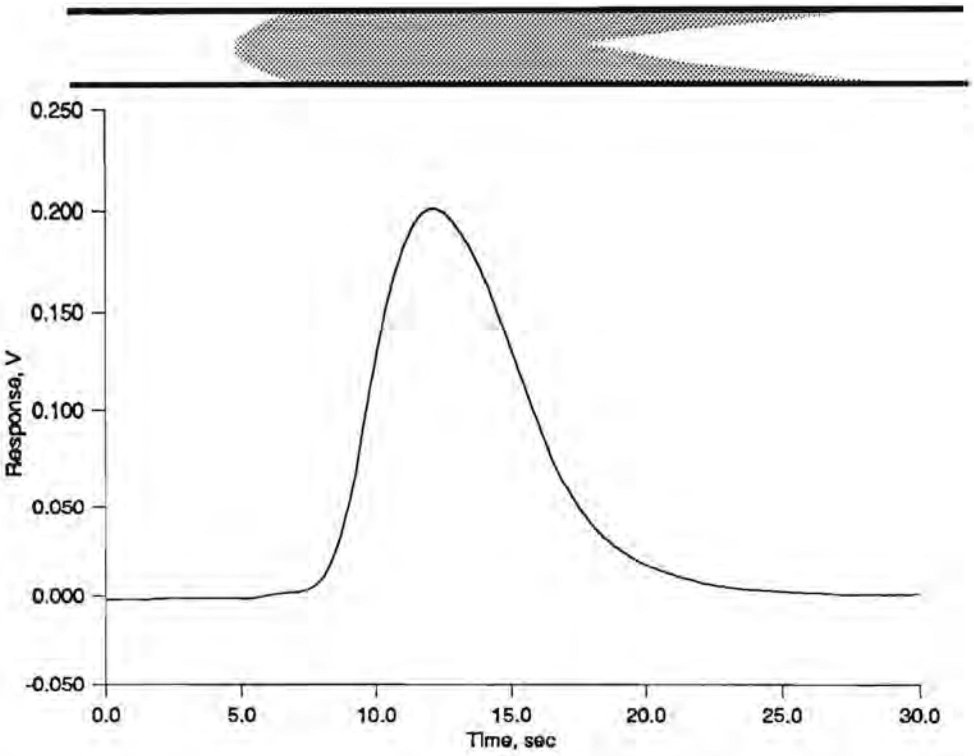

**Figure 2**: Dispersion of the sample zone into the carrier stream as it is propelled towards the detector under conditions of laminar flow. A continuum of ratios of sample to carrier concentration is achieved.

acceptance of FIA as a valuable tool in many areas of analysis. For example, measurements requiring lengthy colour developing times could be automated and speeded up because the requirement for complete colour development was removed. It also meant that unstable transient species could also be used in the detection process because these were reproducibly produced in the well-defined dispersion-controlled environs of a flow-injection manifold.

### 1.2.3 *Dispersion*

Reproducible dispersion is the basis for analysis by flow-injection methods. From the early days of FIA, dispersion was recognized as being fundamental to the optimum design and understanding of this approach to sample manipulation. Initially chemical engineering hydraulic models were employed as predictive estimators of the flow-injection response curve. These models are limited to the description of dispersion in the manifold (resultant from laminar flow) and do not consider the contribution from the injection valve, mixing and connection components, and detector flow cell. Furthermore, theoretical studies have been undertaken for systems where there is no chemical reaction and those where chemical reactions take place. DeLon Hull and co-workers[4] recently reviewed a wide spectrum of models that have been applied to the dispersion phenomenon in flow-injection systems and concluded that despite extensive efforts in the development of models, a uniformly acceptable understanding or description of dispersion is still not available.

Of course, while it was necessary for the theory to follow, the utility of FIA was not limited by the absence of a uniform theoretical description of the process and still today, an empirical approach is often adopted. In fact the technique was born out of a empirical approach despite certain errors in early thinking. For example, turbulent flow was initially assumed to govern mixing in flow manifolds. These incorrect assumptions were rectified as the theory was developed. Hence the development of a sound theoretical foundation is fundamental to the wide acceptance and universal application of key principles of operation. Also, a good understanding of some of the underlying principles, albeit in a fragmented approach, provides a basis for sound manifold design. A more important rationale for expending effort in the study of the theoretical principles behind a particular technique is that such studies often point the way to possible advances in the field.

This was in fact what led to the development of SIA. Conclusions drawn from the Random walk model suggested a course of action that eventually gave birth to SIA. This is discussed in detail in paragraph 1.5.2.

Ruzicka and Hansen[5] defined the conceptually simple and practically useful dispersion coefficient, $D = C^0/C$, where $C^0$ is the concentration of the sample material before the dispersion process begins and $C$ is the concentration of the sample after the dispersion process in the element of fluid that yields the analytical readout (refer to Figure 2). The special case, $D^{max}$ where $C = C^{max}$, the maximum of the recorded curve, was also defined. Subscripts indicating whether the dispersion coefficient refers to sample or reagent are also frequently used. It is important to remember that $D$ considers only the physical process of dispersion and not the ensuing chemical reactions. The use of this simple relationship has dominated experimental design and the development of the technique. Even when FIA advanced to the utilization of double injection modes which generated well defined stacks of samples and reagents, this parameter was used despite the more important concept of zone penetration which only emerged during the present study.

For convenience, sample dispersion has been defined as *limited* ($D$ = 1-3), *medium* ($D$ = 3-10), and *large* ($D$ >10). Flow-injection systems designed accordingly have been used to achieve a number of different sample manipulation unit operations. Zagatto *et al*[6] pointed out that in confluence systems, these parameters should be re-evaluated.

Zagatto *et al*[6] proposed a generalized parameter, volumetric fraction, to describe the composition of specific element of fluid after a dispersion process. They defined volumetric fraction $X_{s,t,k}$, where $s$ is the solution considered, $t$ is a temporal coordinate, and $k$ is a spatial coordinate. $X$ without subscripts refers to the volumetric fraction of the sample at the time corresponding to peak maximum at the detector. This parameter offers the possibility of evaluating more complex manifolds.

Although Ruzicka and Hansen always recognized the limitations of their approach to theoretical modelling with respect to the influence of chemical reactions[7], it was not until 1981 that the kinetic implications of a chemical reaction were included in theoretical models by Pardue and Fields[8,9], and Painton and Mottola[10,11].

Betteridge *et al.*[12] took a different approach by developing a model which operates on individual molecules. The so-called Random walk model was chosen because it is well suited to investigating sample size, chemical kinetics, and the combination of reaction rate and physical dispersion. This model successfully predicted many observations made with real flow-injection systems. For example, peak height decreases exponentially with time when no chemical reaction is occurring, and high flow rates produced rapid mixing and high longitudinal dispersion. Most important for this investigation into SIA though, the Random walk model suggested that mixing, the fundamental requirement for FIA, could take place with no nett displacement of the sample; i.e. it is possible to have $D > 1$ without traversing a manifold of length, $L$. This important concept is discussed in more detail in paragraph 1.5.2 and is the foundation on which SIA is built.

### 1.2.4 *Manifold Design Criteria*

Having identified that dispersion was an important criteria in the design of flow-injection manifolds, workers set about defining rules and guidelines for the design of effective manifolds. These criteria have been summarized in a series of rules by Ruzicka and Hansen[5]. These rules govern the effect of sample volume, reactor length, flow rate, and reactor geometry on dispersion. They also address means of increasing sampling frequency while maximizing sensitivity and other measurement phenomenon, e.g. FIA titration.

While a good understanding of these principles is helpful in the design of effective flow-injection manifolds, many practitioners prefer to rely on a straight forward empirical approach. In this regard, FIA is quite forgiving and a system which has not been optimized can yield absolutely satisfactory results. There are nevertheless, dangers associated with such an approach. Again this illustrates the tremendous power of a reproducible sample handling procedure. A less than optimized sequence, if carried out in a reproducible fashion can (and often does) yield reliable results.

## 1.3 HARDWARE

One of the factors which ensured FIA's initial widespread acceptance has also hampered its long term development. Components needed to put together a flow-injection manifold can be inexpensive and are commonly found in most laboratories. To assemble a flow-injection manifold, a minimum configuration would include

- some means of propelling the sample - (gravity feed should not be excluded),
- a means of introducing the sample - early systems though not ideal made use of a hypodermic syringe and a length of silicone tubing to act as a septum,
- a flow through detector - a simple LED-based photometer can be assembled in most electronic workshops, and
- a recording device - an inexpensive laboratory recorder is the obvious choice.

While such an arrangement would deliver a crude system with small chance of application in a routine fashion, it illustrates the point that FIA has low capital requirements. Even if one were to go for a more sophisticated system making use of a good peristaltic pump, electrically actuated injection valve, simple detector, and microprocessor control, the individual components would cost approximately US$6 000 (R20 000).

There are a few instrument manufacturers who supply good commercial laboratory analyzers, one or two who cater for the process environment and then only for specific applications, and one with a specific application who offers a portable field analyzer for environmental monitoring.

It is estimated that in the USA, there are about 50 flow-injection analyzers in the process environment. All of these are home built systems. Instrument suppliers are reticent to get involved in this area. The following reasons for this are given:

- Providing the equipment is not enough, it is necessary to also supply methodology. Individual users have specific requirements and low volume applications cost money to develop and support. Industry is generally not prepared to pay the price necessary to cover these costs.
- Components are readily available either off the shelf or borrowed from chromatographers. Many laboratories have opted for the development of their own systems. Time and again this has proved to be a costly exercise as an important and often overlooked aspect of reliable systems is the software and hardware necessary for reliable and versatile data acquisition and device control.
- Process analyzers are strongly dependent on custom made sampling systems.

While early investigations of the technique can happily be undertaken with a minimum outlay of capital, a sound approach is to quickly identify a reputable vendor of complete systems. This frees the laboratory to concentrate efforts on the development of suitable chemistries of measurement and leave the instrument design and software development to instrument vendors. Such vendors can afford to offer a versatile and thoroughly debugged system which is configurable to meet individual requirements.

Also in the early development of SIA, hardware (specifically the pump) had a negative impact on progress. While the sinusoidal flow syringe pump was suitable for demonstrating the principle, the sinusoidal flow pattern complicated operation of the analyzer. Several investigators reverted to the use of peristaltic pumps. Considering that SIA was developed specifically (though not exclusively) with the process environment in mind and peristaltic pumps are not ideally suited to the process environment, this is a step backwards rather than an advancement. The specification for ideal SIA instrumentation is set out in paragraph 1.6.5.

## 1.4 FLOW-BASED ANALYSIS FOR PROCESS ANALYSIS

### 1.4.1 *Automated Wet Chemical Analysis*

Automation in the laboratory environment received a considerable boost with the introduction of FIA by Ruzicka and Hansen in 1975[1]. This approach to sample manipulation gained world-wide popularity in both industrialized and developing countries. Instrumentation costs were small compared to many other methodologies, and the assembly of flow-injection manifolds from components borrowed from chromatographers or machined by in-house machine shops meant that even laboratories with a limited budget could participate.

It was the wet chemical laboratory which benefitted most from the power and versatility of FIA. The classical literature was scoured for suitable wet-chemical procedures that could be implemented in flow-injection manifolds. Separation, trace enrichment, dilution, and many other typical unit operations carried out in a wet chemical laboratory were adapted for use in flow-injection manifolds. Colorimetric, electrochemical, and other detectors were equipped with suitable flow cells and incorporated into manifolds. Many classical methods of analysis, which over the years had been replaced by instrumental techniques such as atomic-absorption spectrophotometry, obtained a new lease on life. Also, methods which had been discarded because it was difficult to ensure reproducible handling of a sample or which made use of unstable reagents that could be prepared *in situ*, could again be explored in the controlled environment of a flow-injection manifold. Electrochemists, beginning to feel the impact of sensitive instrumental techniques, found new avenues opening to them as flow-injection provided them with novel options in the manipulation of samples prior to electrochemical detection.

FIA was not just a curiosity for the researcher. Rather there is a growing trend to replace the tedium of manual sample manipulation in service laboratories with flow-injection analyzers fed by autosamplers. A dramatic new approach to wet-chemical analysis is emerging[47].

Part of the reason for its growing popularity is evident when examining the steps required to develop a flow-injection method (Figure 2). When confronted with a particular measurement request, the *modes operandi* for the flow-injection method developer is as follows:

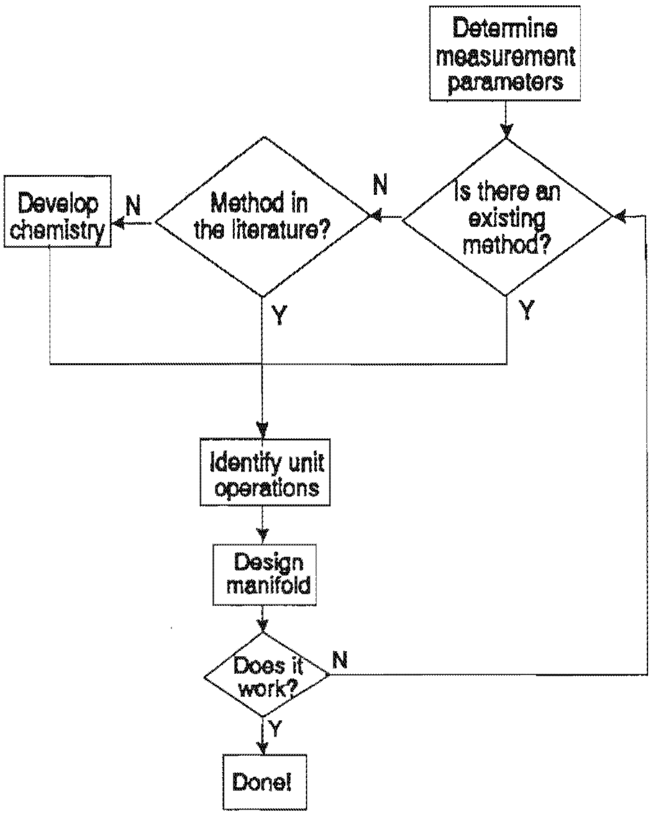

**Figure 3**: Application development flow diagram

- Determine the measurement parameters, e.g. analytical range, required precision, etc.
- Establish whether an existing wet chemical method is suitable.
- If not, search the literature for a suitable measurement chemistry.
- If none, can be found develop a chemistry from scratch.
- Identify the unit operation which together form the method. In this regard, a proven battery of flow-injection unit operations, and flow-injection components such as dialysis units, phase separators, flow-through stirrers, etc. is of great assistance.
- Design an FIA manifold that will achieve the desired sample manipulation.
- Test the methodology in the flow-injection manifold. Pay special attention to the optimization of manifold parameters and reagent concentrations, and interferences.

A closer look at this sequence of events reveals two important considerations.

(1) An established "tool box" of unit operations and flow-injection components is invaluable to the method developer.

(2) Established and proven chemistries of measurement, where available, can be used. This cuts down development time significantly and also contributes a high degree of confidence to the final methodology.

These considerations proved equally important when FIA began to make its way into the process environment. Equipped with suitable robust instrumentation and proven chemistries of measurement, process analysts could keep development time to a minimum and efficiently demonstrate the versatility of FIA in the process environment.

As is the case in their laboratory counter parts, flow-injection process analyzers are often in-house developed systems. There are presently numerous flow-injection process analyzers in daily use in the United States and Europe. The first systems in South Africa began field tests last year and the first full commercial installations were commissioned early in 1994. All indications are that the use of this approach will continue to increase in the future particularly as reliable commercial systems come onto the market. Frequently, end-users consider reliability and robustness as prime criteria when selecting instrumentation. In this regard flow-based analyzers have much to offer.

### 1.4.2 *Advantages*

Flow-based process analyzers provide several excellent features that are absent in many continuous analyzers and sensors[5,13]. Of note are the advantages in the area of automated calibration, self-diagnosis, and self-cleaning:

- Calibrants are subjected to the same treatment as the samples.
- The baseline provides an immediate indication of a drifting detector or fouling of the system.
- Because a small sample bolus is injected into a continuously flowing stream, the analyzer is constantly flushed with a clean solution.
- The ability to make use of highly reactive, oxidizable, light-sensitive, or otherwise unstable reagents which can be generated *in situ* sometimes makes this approach the only possible solution to the monitoring of a particular process stream.
- There are several additional advantages such as a high sampling frequency, good reproducibility, and computer-compatible hardware which ensures that process analyzers are conveniently incorporated into existing or planned distributed process control systems.

With such advantages, it did not take long for these flow-injection analyzers to make their way into the plant environment. Many successful installations followed[14-17].

### 1.4.3 *Disadvantages*

Nevertheless, there is always the need for improvement. Despite the above mentioned successes in areas as varied as the monitoring of fermentation processes, sea water, and redox scrubbers, there still exist some barriers to the extensive wide scale deployment of flow-injection process analyzers. These may be summarized as follows:

- Usually a new manifold must be developed for each application. Manifolds are often complex and prone to blocking.
- Most flow-injection methods are suitable for the determination of single elements. Few multi-element detectors are presently used.
- In spite of the fact that FIA uses pump speed typically of the order of 1 $cm^3.min^{-1}$, this still translates into about 10 $dm^3$ of reagent per stream per week. This can prove to be excessive particularly when expensive reagents are being used wastefully essentially as carrier solution.
- There is a lack of robust commercial instrumentation, system devices, and manifold components.

Of course these barriers do not apply to all applications and flow-injection process analyzers will continue to enjoy wide application.

While sensors continue to enjoy much research funding it would appear that the their wide scale use is not eminent. Experts in the field point to early in the 21st century as being the time when we can expect to begin to enjoy the fruits of research into the field of sensors[21]. This is a long time to wait and presently, the overwhelming conclusion of process analysts is that most chemical sensors can not be relied upon without some level of sample preconditioning or manipulation. Many sensor researchers would agree. Chemical sensors are simply not robust enough yet. Furthermore the resources required for their development make all but the highest volume applications quite beyond economic viability.

An assessment of these barriers and a broad consideration of process monitoring requirements indicated the need for a more versatile flow-based sample manipulation technique. The development of such a technique and its application is the subject of this study.

### 1.4.4 *Instrumentation*

The last barrier mentioned above, that of inadequate commercial instrumentation, will not be addressed in this study. Instead, some of the minimum specifications for future commercial systems will be highlighted, with specific reference to the process environment. It is hoped that this will hasten their development and thereby ensure the future wider utilization of flow-based process analyzers.

A characteristic of FIA since its inception has been the use of home-built systems. While commercial systems have been available, these have often focused on a particular application. This goes contrary to one of FIA's major benefits - its usefulness for a host of different measurements. Also, fittings and components are frequently borrowed from the chromatographer despite significant difference in operating conditions, notably pressure.

While the absence of versatile commercial systems can usually be tolerated in the laboratory, in the process environment it has severely limited the wide spread application of FIA as a process analyzer technique. Only organizations with large research departments and budgets can afford to develop their own in-house flow-injection process analyzers.

Instrument suppliers seeking to address this need should heed the following guiding specifications.

### 1.4.4.1 Sampling system

Generally, sampling systems are developed to meet the requirements of the particular process being monitored. The following desirable options should be provided for:

- The sample may have to be pumped out of the process.
- The sample may have to pass through a polishing filter.
- For high value or toxic sample there should be a provision to return unused sample to the process.
- The ability to monitor multiple streams should be incorporated.
- In some cases it may be necessary to carry out some form of sample conditioning, e.g. cooling.

- Maintenance requirements should be kept to a minimum and should be conveniently undertaken.
- Some form of self diagnosis should be considered.
- High dissolved solids and particulate material must be handled in an unattended fashion for extended periods of time.

#### 1.4.4.2 Calibration

Most detectors used in flow-based analysis require regular calibration. The mechanical system used should be as simple as possible, probably dependant on a multi-position selection valve. Of greater importance, the calibration algorithms and strategies require careful thought and attention. Some options which should be handled by the controlling software include the ability to:

- Intersperse calibration measurements with sample measurements.
- Average replicate measurements after sensible outlier rejection.
- Select the number of calibrants.
- Apply one of several curve fitting algorithms and even multi-variable calibration techniques. This option will become more important as there is a move towards multi-element techniques based on detector arrays.
- Periodically check the validity of the calibration.
- Waive calibration if the previous calibration is still valid.
- Include statistical measures to establish the goodness of fit of the calibration curve.

### 1.4.4.3 Pump

The means of propelling streams is one of the weakest components in present flow-based process analyzers. One of two options are generally applied. Either chromatographic reciprocating pumps or peristaltic pumps are used. Both of these have their limitations. One commercial system makes use of a pressurized reagent container to propel the carrier stream. Included in the specifications for the ideal pump are the following:

- robust - able to withstand continual use for extended periods of time with little or no scheduled maintenance,
- all wetted parts to be able to withstand corrosive solutions and organic solvents.
- not prone to blockage,
- be easily controlled using TTL or switch controls (forward, reverse, and stop),
- device actions should be rapid and without significant inertia,
- flow rates in the range 0.5 to 15 $cm^3.min^{-1}$,
- constant flow rates over extended periods,
- smooth, reproducible, and pulseless flow,
- pressures of up to 700 kPa,
- small and compact in size,
- multiple pumping channels (± 4 channels per pump),
- self priming,
- low power consumption, and
- have the option of inherent safety.

A pump which satisfies all of these criteria is still to be developed. It is unlikely that all requirements will be satisfied in a single pump. rather it is expected that a range of pumps will cover the various desired features.

### 1.4.4.4 Valves

Various valves are required in flow-injection analyzers. These range from simple two way valves, to multi-position selection valves (3 to 10 ports), and multiport (usually 6, 8 or 10) injection valves. These valves should have the following characteristics:

- robust - able to withstand continual use for extended periods of time with little or no scheduled maintenance,
- small and compact in size,
- be able to withstand pressures of up to 700 kPa,
- be easily controlled using TTL or switch controls,
- ports should be of the same diameter as the manifold tubing,
- flow channels should not be torturous,
- all wetted parts should be resistant to corrosive solutions and organic solvents,
- switching should be rapid and reproducible,
- low power consumption, and
- have the option of inherent safety.

Valves which satisfy most of these criteria are already available.

### 1.4.4.5 Detectors

There is a dangerous tendency to simply move reliable laboratory detectors into the process environment. This practice often fails. A superior approach is to develop a whole new range of detectors which are based on proven analytical concepts used in laboratory analyzers. These detectors should be designed with process conditions in mind with a minimum number of vulnerable parts, and requiring negligible scheduled maintenance. Because these detectors can be configured for a specific analyte, it is often possible to simplify their design. One of the most important components in any flow-injection detector is the flow-cell. Time spent in ensuring a sound design is well spent. In this regard, strong guiding principles are:

- minimize dead volume,
- simplify flow paths,
- avoid bubble traps, and
- ensure convenient maintenance schedule.

To date most detectors are single channel devices. This is seen as a short coming in present analyzer designs. Diode array spectrophotometers (uv, vis, and ir regions), and electrode arrays for electrochemical detectors promise to be important detectors in future multi-component analyzers. Robust commercial systems, specifically diode array detectors, are beginning to make their way into the market.

### 1.4.4.6 Device Control and Data Acquisition

In the design of a device control and data acquisition system, the main consideration should be versatility. The ability to easily swop devices and detectors and programme the device events in a convenient fashion is of paramount importance.

The rate of change of the detector response is such that a data acquisition rate of 10 $sec^{-1}$ per channel is more than adequate. Some redundancy to allow for statistical smoothing of the data is desirable, though not essential. There is a need to allow for different input voltages from the detector. A reliable amplifier and facility for offset adjustment is quite adequate.

Devices may require either transistor-transistor-logic (TTL) or switch control and both options must be available. Analyzer diagnostic systems often rely on digital inputs. These requirements have been adequately addressed in the FlowTEK™ software package which will be discussed in more detail in Chapter 2.

### 1.4.4.7 Data output

While most process control systems have sophisticated calculation capabilities, it is most advantageous to carry out all calculations at the process analyzer itself and only release final concentration data (for samples and where required, calibrants) to the process control system. Either a 4 to 20 mA signal or ASCII data compliant with one of the serial communications protocols is regarded as a minimum requirement. Convenient access to raw signals at the analyzer facilitates debugging during commissioning and analyzer breakdowns.

#### 1.4.4.8 Housing

Some process analyzers are installed in specially constructed analyzer shelters and then the demands on the analyzer housing are fairly lenient. Where this is not the case, protection from the elements and plant environment is required. Generally, an IP55 coded housing is sufficient. In the choice of the analyzer housing material, careful cognisance of the plant environment is required. This is particularly important in corrosive environments. In explosive environments (Div 1 Class 1) where inherently safe instrumentation is required, it may be necessary to purge the analyzer housing and equip the door of the housing with a cut off switch that powers the analyzer down when the housing is opened.

### 1.4.5 *Future of FIA in Process Analysis*

While this study focuses on SIA, it is worth considering the future of FIA in the process environment because it highlights important considerations for the future of SIA as well. Weaknesses and opportunities in this area could impact on SIA. These ideas have been developed through various discussions both with members of industry and with fellow researchers and colleagues in the United States of America

It is most likely that as the merits of FIA become more widely known, this mode of plant monitoring will gain rapid acceptance. Where instrument suppliers offer robust and generic instrumentation, plant laboratories will often be in a position to suggest a suitable measurement chemistry or even develop the methodology themselves. This is a most desirable options and represents an efficient means of meeting process monitoring requirements. This development presents an interesting challenge for the analytical chemist. In many other areas of development in analytical science, instrumentation plays a dominant role and a good understanding of physics and computer science is necessary. As FIA finds wider acceptance there will be a growing need to apply sound chemistry in the development of innovative measurement solutions.

It can be expected that there will be a growing interest and effort in the direction of the development of multi-element methodology. This will necessitate studies using detector arrays such as diode array spectrophotometers, electrode arrays, and multi-dimensional sensors. Chemometric data handling procedures will form vital components of such systems. The need for carefully designed chemistries of measurement will inevitably become more important as selectivity is derived from both the detector, the data handling, and the chemistry of measurement.

Miniaturization is a logical development in the evolution of flow-based process analyzers. Not only will this assist in reducing reagent consumption, but smaller devices will advance the progression towards chemical sensors. Also FIA is seen as a useful tool for environmental monitoring. In this area there is a growing tendency to move the monitoring device to the sample source or make use of portable systems.

As more chemical sensors are developed and come onto the market, it can be expected that these will be used in FIA manifolds in the beginning. To date, many sensors, particular in the field of biochemistry, have relied on FIA to present the sample to the transducer. This will be discussed in more detail in a subsequent chapter. Some would argue that FIA will provide the launch point for the extensive use of chemical sensors in distributed process monitoring systems. In fact, it is not inconceivable that flow-based analyzers as we know them today, or some variation of them, will form the basis of true in-line process chemical sensors in the future.

## 1.5 EVOLUTION OF A NEW FLOW-BASED ANALYSIS TECHNIQUE

We have noted successful applications of FIA in a number of different applications, and for the foreseeable future, we can expect flow-injection process analyzers to proliferate in modern chemical, biochemical, metallurgical, and environmental applications. The use of chemical analyzers in the process control strategy represents a significant shift in thinking for many process control engineers. For the most part, process control systems are based on physical measurements such as flow-rate, pressure, electrical resistance, etc. While this has resulted in processes which are operated under statistical control, verification of the process performance can only really be achieved by chemical analysis, usually in a remote plant laboratory. This approach is seen as unacceptable in the design of quality management systems for the production process, e.g. ISO 9000. In such systems, the emphasis is on quality assurance during the process rather than after-the-fact. Process analysis brings the process controller a step closer to ensuring excellent control of the plant and real time quality assurance. At this stage, lengthy development times, the cost of these analyzers, and their maintenance requirements mean that only a few critical streams are monitored.

What process control engineers really want is a whole battery of chemical sensors in a fully distributed system. A high degree of redundancy would ensure reliability and facilities for cross validation. Calls for such capabilities have resulted in considerable research activity in the area of sensor design. Yet researchers will clearly have to come up with novel ways of addressing several severe recurring problems. A case in point is the fibre optic sensor, where quoted disadvantages[19] include long response times, limited long-term stability, limited dynamic range, and the absence of automated verification of the sensor response.

It is worth noting that at present sensors are operated in a mode which strives for steady state response. In some cases this is appropriate and successful in sensors that measure physical phenomenon such as temperature. However, where fragile sensing elements are used that are prone to decomposition or change, a different approach is required. Two principles evident in living organisms apply.

(1) The first makes use of a high degree of redundancy, where the sensing elements are constantly being renewed and old and failing elements are decommissioned on an ongoing basis to be replaced by new sensing elements.

(2) The second operates on an impulse-response basis where two distinct states can be identified for the sensor. The sensing element is subjected to some or other stimulus - it receives an impulse. The sensor in turn generates a response which is transmitted via the nervous system to the brain where it is interpreted. The response is not a continuous signal. Rather it is modulated allowing the sensing surface to re-establish itself between each impulse-response couple. In this way, longevity, reliability, and repeatability is ensured.

Focusing on this approach in Nature and applying it to process analysis, the taste bud provides an excellent model for the next generation of automated wet-chemical analyzer. Process solution (saliva), which has solubilized the analyte (flavour), washes over an array of minute sensors (taste buds). A central processor (the brain) receives and combines data from various process analyzers (senses such as taste, smell, sight, and touch), and through a process of pattern recognition, identifies a taste. The saliva continues to flush the sensors in preparation for the next analysis. During this time, the taste sensors are also calibrated using the saliva as calibrant.

This model suggests an exciting route for the development of future generations of process analyzers. Unlike its predecessor, continuous flow analysis, FIA (and SIA) are impulse-response measurement types and represent the first step in the progression to the model suggested above. Between injections (impulses), the baseline and chemical environment is returned to a known state. The output from the detector (response) is recorded for transmission to some interpretative device. In FIA, the period between impulses is used simply to re-establish the baseline by flushing away the previous reaction products.

Using a chemical sensor as the detection device in an flow-based manifold now opens up some interesting options. Between impulses, the sensing surface can be renewed. This principle was demonstrated in the development of flow-optrodes[20,21]. Considering these devices, and Nature's example in the taste bud, it became apparent that a further development of the flow-injection concept was in order and could lead to a more advantageous use of sensors in flow-based analyzers. A different approach to solution sequencing was required.

### 1.5.1 *Flow Programming*

The development of FIA from its inception is based on the introduction of a well defined sample zone into a continuously flowing carrier stream. During the passage to the detector, the sample, being subjected to various physical and chemical interactions, is converted into a detectable species. The success of this technique is totally dependant on a reliable and well designed solvent delivery system.

A review of the FIA literature[5,22-24] soon reveals that an overwhelming majority of applications favour the use of a constant flow rate. Indeed, the ease with which such an environment is obtained when using a simple peristaltic pump, has contributed significantly to the wide acceptance of FIA. There are however several recognized disadvantages of FIA *per se*[25]:

(1) It is wasteful. Reagents are pumped continuously irrespective of whether they are being used or not. Although this action also serves to flush the flow manifold and detector between measurements, where the reagent is costly, this is not a desirable arrangement.

(2) A requirement for increased reaction time implies the use of longer reaction coils. Longer reaction coils result in increased dispersion which may be undesirable.

(3) The chemical kinetics are concealed within the physical process of dispersion. While most chemistries are extremely rapid and so kinetic studies are not practical, kinetic differences in slower reactions can be employed to add a measure of selectivity to otherwise unspecific methods[26]. Constant flow conditions preclude this approach.

(4) It is difficult to maintain a constant flow rate for extended periods of time. Differences in temperature, solution viscosity, and elasticity of pump tubing result in variations in the flow rate.

Wider use of computerized device control has allowed for the development of sequencing techniques which can collectively be termed flow programming. Broadly speaking, two concepts apply, *viz*, stopped-flow FIA[27,28] and reversed or oscillating flow[29,30]. These two techniques address the above mentioned disadvantages in most instances and raise questions around the requirement for monotonous flow.

It is apparent that the only reason why this mode of thinking has become entrenched is due to the dominance of linear, preferably constant, and forward flow in the theory of FIA. The convenience of being able to inject the sample into the continuously flowing carrier stream at any time has had a strong influence on the development of FIA and its supporting theory.

Rios *et al*[31] and Toei[32] were the first to deviate from this approach. They demonstrated in experiments where the flow rate was varied (positive or negative ramp), that as long as the injection is synchronized with the start of the flow change cycle, reproducible results can be obtained. This observation holds important implications for addressing some of the limitations experienced with systems based on monotonous flow.

### 1.5.2 *The Random Walk Model*

A theoretical description of the zone dispersion process in the analyzer tubing is a central issue in flow-based techniques. As dispersion is a random process, the random walk model can be used to describe it. Einstein used the random walk model to explain Brownian motion[33]. He showed that a group of molecules taking a series of random steps will finally reach a Gausian distribution around the origin, the spread being determined by the number of steps and the mean size of each step. For a molecule experiencing laminar flow, the total displacement per step can be considered a combination of the laminar flow and the random walk.

It was Giddings[34] who laid the foundation for providing a theoretical basis for the dispersion process long before flow-injection was even conceptualized, when he applied the random walk model to describe the dynamics of chromatographic processes. Betteridge and co-workers[12,35] built on this to use this model to describe zone dispersion in FIA, albeit for conditions of constant linear forward flow. They pointed out that because this model deals with individual molecules and not assemblages, it is easy to simulate the effects of sample size, chemical kinetics, and the competing effects of the rate of chemical reaction and physical dispersion. Furthermore, conceptually it is easier than theories based on a series of imaginary tanks[36]. In a series of simulations they simulated the dispersion process both in the presence and absence of a chemical reaction and showed the agreement with experimental observations.

Each molecule in their simulated sample plug is represented by $x$,$y$, and $z$ co-ordinates constrained within the boundaries of the hypothetical tube in such a fashion as to give a uniform number of molecules per unit volume. The molecules were moved so as to simulate both random dispersion ($\Delta d$) and longitudinal transport by laminar flow ($\Delta f$). Thus for each cycle, $(x_i, y_i, z_i)_{\mathrm{new}} = (x_i, y_i, z_i)_{\mathrm{old}} + \Delta d + \Delta f$. Without flow, random dispersion causes the initial rectangular injection to become Gausian. In the presence of laminar flow, the resultant sample peak becomes skewed Gausian as is frequently observed in flow-injection profiles. The real value of the random walk model is that it leads to the conclusion that efficient mixing of the reacting components can be achieved without actually travelling any nett distance: efficient mixing can be achieved simply by oscillating the injected zone back and forth.

Although Betteridge and co-workers confined themselves to conditions of constant linear forward flow, this is not a requirement for the random walk model - the two terms in the equation above are independent. Thus it became evident that these same principles would hold for a system where linear flow programming was applied. The contribution from the longitudinal transport ($\Delta f$) would simply be altered to reflect the changing flow conditions defined in the flow programme. The dispersion contribution ($\Delta d$) would remain the same.

In classical FIA the need to travel the full length of the channel is only necessary because the sample zone has to be transported from the injector past a mixing point, through a detector, and then to waste. Use of a flow programme, rather than constant monotonous flow, requires synchronization of sample zone injection with the start of each flow cycle. A system configuration was required which will allow sample zone injection, reagent addition, mixing, measurement, and ejection of the reacted mixture by a combination of forward and reversed flow steps.

While linear flow programming traditionally refers only to the flow pattern employed, i.e., the rate and direction of flow, the inclusion of a mechanism of selecting different streams to be subject to the flow programme may also be added. (Of course, if the composition of the different streams altered the diffusion constant, this would have an effect on the $\Delta d$ term.)

The group at the University of Washington[25] used these ideas for the basis of an extension to FIA which was called Sequential-injection Analysis (SIA)[37].

### 1.5.3 *Sensor Injection*

SIA provides a robust methodology for performing automated wet-chemical analysis. Reagents, samples, and wash solution are selected sequentially using a selection valve and are drawn into a reaction coil. The reaction products are then expelled through the flow cell of a suitable detector giving rise in the process to a measurable signal. Although the new methodology falls short of the standard of our optimized and extremely versatile taste buds, it takes us one step closer to this example of an idealised process analyzer. The major deviation of a sequential-injection analyzer from the model from Nature can be found in the need for a selection valve. The selection valve provides the system with the capability to sequence reagents, samples, and calibrants. In the taste bud this is not necessary as the selectivity of the taste bud is built into the array of sparingly selective sensors that together provide the required level of selectivity through a process of pattern recognition. In SIA, selectivity comes primarily from the chemistry employed. Future work should address the development of sensors that incorporate the chemistry, and therefore have built-in selectivity. The use of solid interfaces and membranes in this regard will prove invaluable.

It is not unreasonable to envisage an instrumental arrangement that presents process solutions, after suitable physical modification, to an array of sparingly selective sensors. The responses from these sensors would then be manipulated to yield selective information on critical plant constituents. Such an approach offers some hope for the wide scale utilization of chemical sensors as it offers a means of overcoming existing limitations in the areas of calibration, reagent renewal, sensor lifetime, and sensor diagnostics.

### 1.5.4 *Instrumental Layout*

The instrumentation used in SIA is quite similar to that used by FIA and includes a pump, selection valve, reaction coils, and a detector equipped with a flow-through cell. Components are linked with narrow-bore teflon tubing and one of several connector types. Several arrangements of these components have been used. Initially the detector was placed between the pump and selection valve (see Figure 4). Later this arrangement was altered to place the detector in one of the arms of the selection valve. The reason for this will be discussed in a subsequent chapter. Also some workers have used a peristaltic pump or micro volume piston pump called a Tecuria pump (Figure 4c). The advantages and implications of this approach will also be discussed in a subsequent chapter.

Each measurement starts by drawing wash solution into the manifold. This solution flushes the reaction products from the manifold at the end of the experiment. The selection valve is then advanced and successive aliquots of sample and reagent solution are drawn into the manifold. In the manifold the resultant stack of reagents and sample are transported (with oscillation or stopped flow, if required) through a reaction coil to the detector by reversing the flow of the pump. As the detectable species passes through the detector flow cell, the signal is registered and can then be related to concentration using normal calibration procedures.

## 1.6 RESEARCH REQUIREMENTS FOR SEQUENTIAL-INJECTION ANALYSIS

Once the initial concept of SIA had been demonstrated[37], several areas of research became apparent and form the body of this study.

### 1.6.1 *Device Control and Data Acquisition*

The effective and reliable use of flow programming implies the requirement for a highly reproducible means of generating the flow programme. While early FIA analyzers were often manually operated and data acquisition and display was typically achieved by means of a chart recorder, this is clearly not adequate in SIA. SIA relies implicitly on flow programming for the determination of volumes of reagents and samples. Where a non-linear flow rate profile is used the need to synchronize the start of an experiment with a specific instant in the flow cycle is of paramount importance.

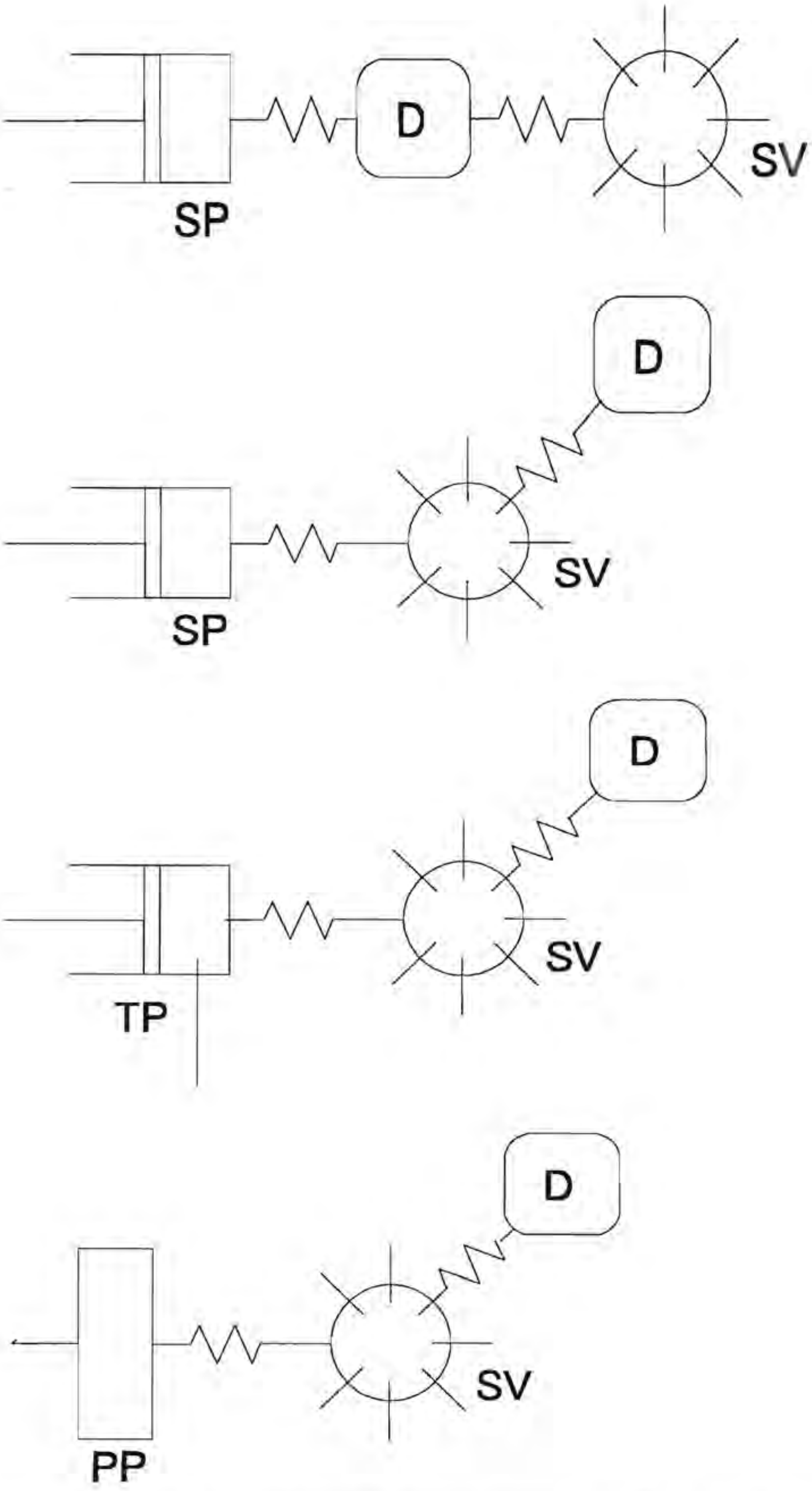

**Figure 4**: Some variations in initial manifold arrangements. SP - Syringe Pump, TP - Tecuria Pump, PP - Peristaltic pump, D - Detector, SV - Selection Valve

Volumes in SIA are frequently determined by the time that a particular stream is selected or on the number of strokes a pump executes. Control of such parameters is best achieved under micro processor control. Also in the research environment, the ability to alter the sequencing order and relative volumes is most important and should be executed conveniently.

Data acquisition from one or more detectors and subsequent manipulation of the data is also best achieved electronically. Subsequent examination of the data and the execution of various diagnostic procedures requires data to be in an electronic format, (typically as an ASCII file).

These specifications were used as a starting point for the design of a PC-based device control and data acquisition package called FlowTEK™.

### 1.6.2 *Manifold Design Principles*

Although meaningful results were obtained using the initial manifold design, that manifold was clearly in no ways optimized. Workers at the University of Washington and Mintek investigated basic manifold design principles. Parameters that were investigated included flow reversal, sample and reagent volumes, and factors that had a direct bearing on the degree of zone penetration. Whereas dispersion proved to be a key parameter in the description of flow-injection manifolds, zone penetration is a more important parameter in SIA. It is interesting to note that many of the principles established in this study are directly applicable in flow-injection manifolds that make use of double injection techniques to achieve a stack of well defined sample and reagent zones.

This investigation also began to highlight some of the important considerations for suitable devices such as pumps, selection valves, and flow-through detector cells.

### 1.6.3 *Application to Measurement Problems*

Having examined the principles of good manifold design, the developed theories must be tested with some real applications. Trace enrichment and separation using sorbent extraction was selected as interesting typical sample manipulations that an SIA system would have to tackle. The suitability of SIA for this application is demonstrated.

### 1.6.4 *Sensor Injection*

SIA will doubtless find application in certain specific areas, particularly in the field of process analysis. In fact already, Shell Development Company makes use of SIA to monitor pH. Its true application though will probably be as a front end to sensors. To date sensors have been notoriously unreliable. Already in the biochemical field, analysts are requiring sensors to be part of flow-injection manifolds particularly when operated in the process environment. SIA offers a more versatile sample manipulation strategy for chemical sensors than does FIA. This is demonstrated by investigating a cyanide selective sensor and its operation in an SIA manifold.

### 1.6.5 *Design Criteria for Instrumentation*

As is the case for FIA, SIA instrumentation is generally borrowed from chromatographers or built from scratch in precision machine shops. One company in the United States advertises itself as being a supplier of components for FIA and SIA. This represents a significant step forward for the technique and heralds the wide acceptance of the technology by a broad spectrum of users. Nevertheless, catalogues are still thin in this area and the following specification are an attempt to set out some important requirements for future commercial components and SIA systems. The similarity to specifications for similar devices for flow-injection process analyzers is quite evident.

#### 1.6.5.1 Pump

- The flow rate must be highly reproducible and reliable. Continuous maintenance free operation for periods of weeks is necessary for process applications.
- Remote control via TTL or switch contacts should enable immediate stop, start, forward, and reverse pump actions. Pump inertia should be negligible. The ability to control the pump speed via an analog input is seen as a desirable though

not essential option. In this regard, the option of having either a high or normal pump speed may be adequate.

- Flow rates of between 0.5 and 10 $cm^3.min^{-1}$ are seen as being optimal.
- Pump pulsing should be kept to a minimum.
- All wetted parts resistant to a broad range of solvents and acids. It is unlikely that a single material would be able to satisfy all requirements for inertness and therefore two or three options should be available. While this is an important criteria, it is not as critical as for FIA as by far the majority of time, only the wash solution will be in contact with pump components.
- The pump should not be adversely affected if it runs dry. It should also be self priming.
- Connection to typical 0.5 mm, 0.8 mm, and 1.5 mm i.d. tubing should be by means of standard fittings
- Power requirements should be low enabling the pump to be incorporated in portable systems. It would be desirable to offer a 12 V version.
- An intrinsically safe option would be required for certain applications.
- Physical size should be kept as small as possible.

#### 1.6.5.2 Selection Valve

- Continuous maintenance free operation for periods of weeks is necessary for process applications.
- Flow paths should have a minimal effect on dispersion.

- Various flow path options should be available, including dead stop, flow through individual, flow through to common.
- All wetted parts resistant to a broad range of solvents and acids. It is unlikely that a single material would be able to satisfy all requirements for inertness and therefore two or three options should be available.
- Valve ports should match the dimensions of the flow manifold and should not include torturous paths.
- Remote control via TTL or switch contacts should enable random selection of ports using 4 bit digital control. The ability to sequentially step through ports should also be available. Some means of feed back indicating the present valve position is required.
- Power requirements should be low enabling the valve to be incorporated in portable systems. It would be desirable to offer a 12 V version.
- Back pressures of up to 700 kPa must be accommodated. For some applications 2000 kPa would be desirable.
- Connection to typical 0.5 mm, 0.8 mm, and 1.5 mm i.d. tubing should be by means of standard fittings.
- An intrinsically safe option would be required for certain applications.
- Physical size should be kept as small as possible.

### 1.6.5.3 Detectors

The same criteria as for FIA hold (see paragraph 1.4.4.5).

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