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Titration-on-a-chip, chemical sensor–actuator systems from idea to commercial product

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Abstract

The earliest reports of integrated chemical sensor–actuator devices to perform coulometric acid–base titrations date back almost 20 years. Recently a first commercial instrument appeared that allows to perform very rapid, accurate acid–base determinations with a solid-state probe and no need for liquid titrants. This paper reviews some of the early developments and shows the effort that has been undertaken to bring this technology to routine use in the analytical laboratory and beyond.

Keywords: Sensor–actuator devices; Acid–base titration; Solid-state transducer; Coulometric titration; ISFET

1. Introduction

The area of solid-state transducers began its development about 40 years ago, more or less as a logical consequence of the emergence of planar photolithographic processes for microelectronic devices. At the beginning of the eighties the field really started to erupt with the realization that in order to take advantage of the rapid progress in microcomputers and microprocessors, peripheral devices, i.e., sensors and actuators, needed to follow suit. The interfacing of electronics to a non-electronic world [1] became a growing topic that by its very nature attracted scientist from many disciplines and to this day remains an exciting area. The conversion of signals into the electrical domain was nicely illustrated on the cover of the Transducers ’83 Abstract Book shown in Fig. 1. The diagram, that shows conversion in only one direction and thus symbolizes sensors, was made into the official flag for the conference series.

With the emergence of “transducer science” the idea that sensors and actuators could be regarded as electronic devices [2] and could be integrated into electronic systems slowly took hold. (It was not until the early nineties that the term *microsystem technology* started to come into vogue.) In one of the pioneering papers by Middelhoek and Noorlag [3], solid-state transducers are categorized according to the signal conversion from a physical (in the widest sense) to the electrical domain and vice versa, as illustrated in Fig. 2. It was Piet Bergveld who got inspired early on to exploit this reciprocity between sensors and actuators in order to create chemical systems to modulate pH [4]. Other than a unidirectional flow of information as illustrated in Fig. 3a, Bergveld proposed to integrate a chemical actuator with the sensor and use a closed loop control configuration as shown in Fig. 3b.

By feeding back information into the chemical domain, the integrated sensor–actuator system allows the monitoring of chemical reactions and thus not only changes the nature of, but also drastically increases the amount of information that can be obtained. The first reported application was an acid–base titration system integrated in a flow-through channel [5].

Following that initial work, chemical sensor–actuator systems have been utilized for a number of different applications, many of them in Bergveld’s group as summarized in a 1995 review [6] but also by others [7,8]. Only recently the original ideas reappeared in a commercial product by Thermo Electron, the Orion FLASH Titrator™ (patents applied). The success of the commercial product development can certainly be attributed to the creation of a large knowledge base and the possibility to program specific analysis methods in the instrument. Acceptance of a groundbreaking new analytical technique is only possible when the user does not have to become an expert before he can operate the instrument, a statement that can be held true for many other applications of advanced microsystem technology.

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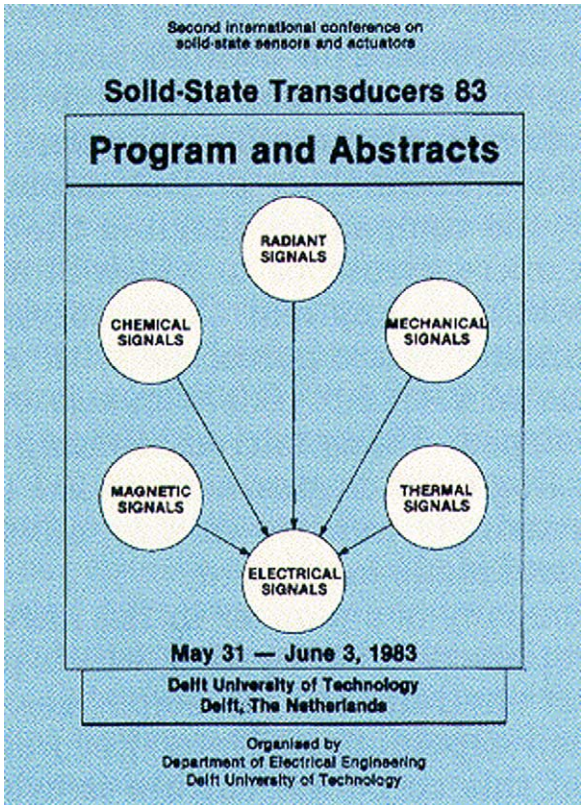

Fig. 1. Signal transduction in solid-state sensors.

This paper will reflect on a number of the developments in the chemical sensor–actuator field and describe some of the features of the Orion FLASH Titrator^{TM}.

2. Coulometric titration

Direct measurement of the pH of a sample with a potentiometric sensor such as a glass electrode or an ISFET only gives limited information about the composition of this sample. The actual pH depends on the nature of the protolytes present and also on the sample matrix. Moreover, the

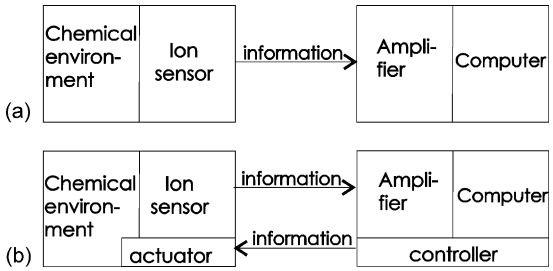

Fig. 3. Unidirectional information flow in a chemical sensor (a) and modulation of the chemical environment with an integrated sensor–actuator system (b).

accuracy of a direct measurement is limited since a 1 mV measurement error already represents an error of 4% in concentration for a mono-valent ion and potentiometric sensors therefore require a regular calibration. In many practical applications, the acid or base content of samples is therefore usually determined by titration with known standards, which results in a much better accuracy. In automated titration equipment, potentiometric sensors are often used as a convenient means to monitor pH changes as a function of reagent addition so that the end-point of the reaction can be accurately determined. In that case, only relative changes in pH are relevant so that calibration of the sensor becomes superfluous.

In a typical volumetric titration the volume of liquid titrant required to neutralize the acid or base in a sample, or to adjust its pH to a specified value, is measured. In a coulometric titration the titrant is generated electrochemically and the quantity of electric charge is measured.

Basic or acidic titrant is generated according to the following reactions:

Reaction 1 : Electrochemical generation of base

$$2H_2O \rightarrow 2OH^- + H_2 - 2e^-$$

Reaction 2 : Electrochemical generation of acid

$$H_2O \rightarrow 2H^+ + \tfrac{1}{2}O_2 + 2e^-$$

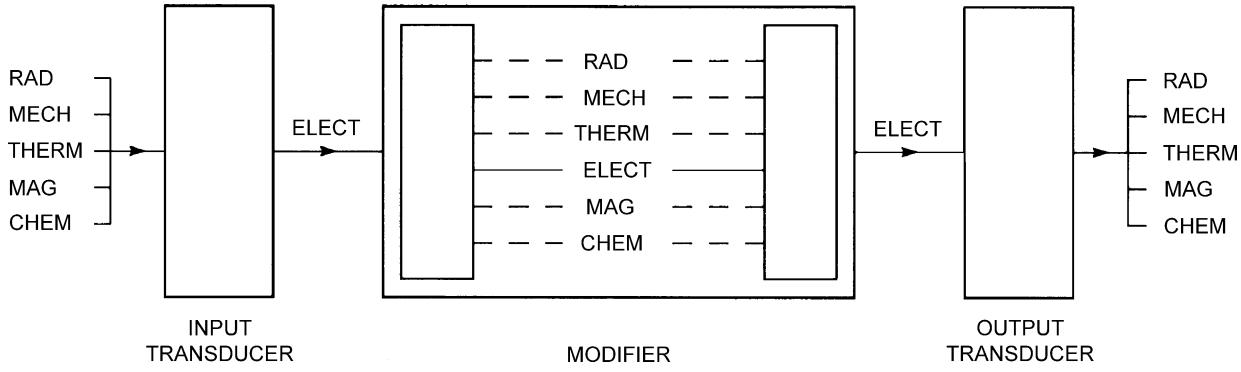

Fig. 2. General representation of the measurement and control-systems field (from [3]).

In a classical volumetric or coulometric titration all of the sample solution reacts with the titrant and the end-point of the titration is reached when the reaction is complete. The titrant has therefore to be homogeneously mixed by stirring the sample solution and a typical titration takes in the order of a number of minutes. On such a time scale, the response time of the end-point-detecting sensor can be in the order of seconds. It was recognized early on that a rapidly responding pH-ISFET can be advantageously used in place of a glass electrode [9] and in that case, mixing of the solution becomes the limiting factor.

When the analysis volume is sufficiently scaled down, diffusion can be used as the principal way of mixing, which has two advantages. First of all it is very simple as it requires no mechanical means to agitate the solution but most importantly, under a given set of conditions, it is very reproducible.

The first coulometric micro titration experiments as described in Ref. [5] were performed in a constrained volume defined by the area of the generating electrode and the height of a flow channel. A number of defined current pulses were injected and the resulting pH changes were recorded after some seconds. The magnitude of the pH changes corresponded to a perfectly mixed volume as defined by the geometrical constraints so that in principle no calibration was required. The disadvantage of this "static" method was that the measurement of each point of the titration curve took several seconds so that the total analysis time was still in the order of minutes.

A faster titration method is to dynamically observe the pH change in the sample during the injection of a current pulse

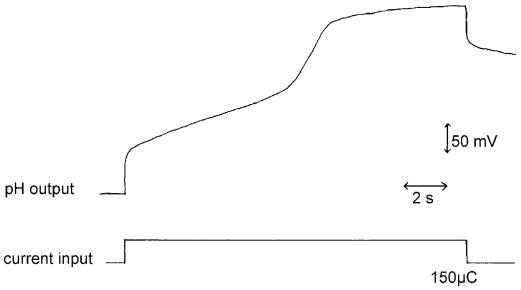

Fig. 4. Dynamic coulometric titration acetic acid (0.005 M) in a 30-µm high flow channel (from [5]).

as was demonstrated in the same paper [5] and illustrated in Fig. 4. With this so-called dynamic measurement, mixing is taking place during the recording of the pH change and while the titration times depend linearly on the acid concentration, the injected charge at the equivalence point no longer corresponds stoichiometrically to the acid present in the constrained volume. The time to reach the equivalence point is now determined by diffusion of the reacting species. When this is the case, a further step to simplify the titration set-up is to eliminate the flow channel and place the sensor–actuator chip in free solution so that the mass transfer now becomes completely defined by semi-infinite diffusion [10]. The volume in which the titration takes place is no longer fixed but expands with the length of the titration time. However, since diffusion in a given solution matrix at a given temperature is perfectly reproducible, the accuracy of this titration method is excellent. Recently,

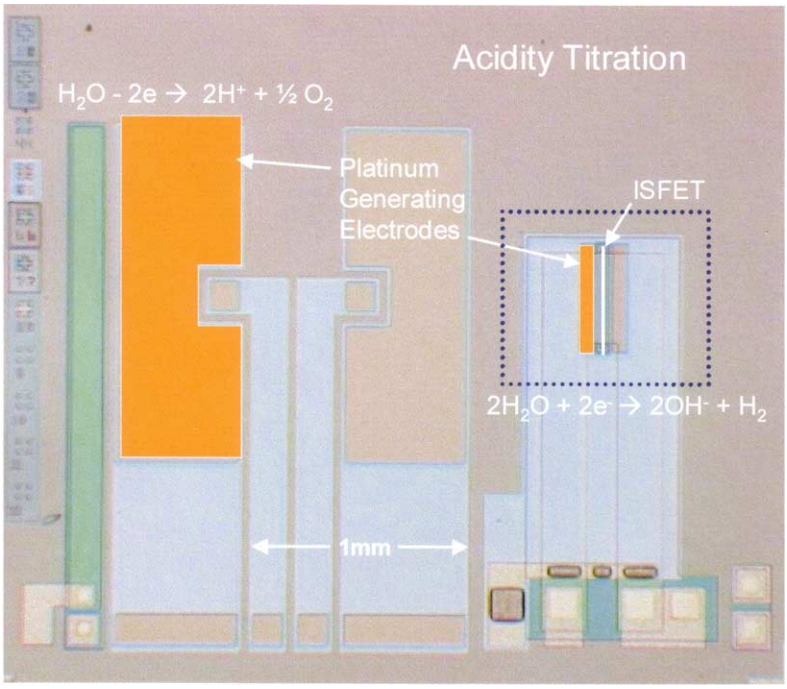

Fig. 5. FLASH Titration chip layout. The dotted line delineates the section of the chip shown in Fig. 6a–d.

the "titration-on-a-chip" has become available as a commercial product, the Orion FLASH Titrator™ by Thermo Electron. In the next section a number of the features of this instrument will be described, some of the following figures and descriptions appeared previously in reference [11].

3. The Orion *FLASH* Titrator

Fig. 5 shows the layout of the *FLASH* Titration chip with key titration features identified. The two critical elements are the pH-sensitive ISFET gate and the adjacent platinum generating electrode. The reaction scheme shown is a total acidity titration with *Reaction* 1, generation of basic titrant, occurring at the electrode adjacent to the ISFET, and *Reaction* 2 occurring at the remote counter electrode. The chip is mounted at the end of 12-mm probe that is dipped in solution like a conventional pH electrode. The solution is then allowed to become quiescent. The titration process is illustrated in Fig. 6a–d. At 1, 2, 3, and 4 s into the titration, a *zone of neutralization* can be seen spreading by diffusion from the generating electrode. This zone spreads into more and more of the *nano-volume* element sensed by the ISFET. Below each illustration is a developing titration curve—a plot of pH versus time—and its first derivative. At 3 s, the end-point has just been passed—the titration is complete. The peak on the first-derivative curve indicates the time coordinate of the inflection. The rate at which the pH change radiates depends in a predictable way on the sample total acidity (or alkalinity). Fig. 7 shows *FLASH* Titration curves and first derivatives for three concentrations of the weak

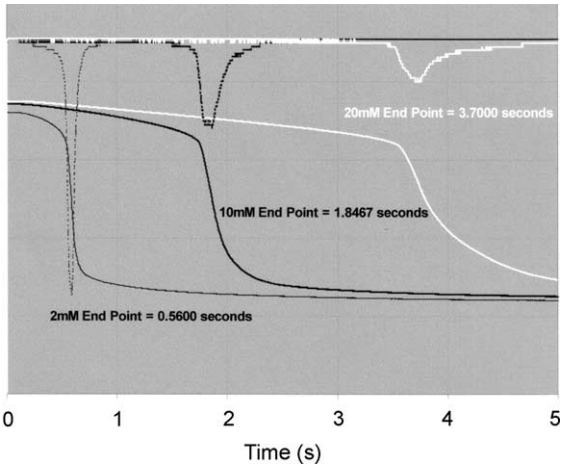

Fig. 7. *FLASH* Titration curves and first derivatives for 2, 10, and 20 mM HIBA (background electrolyte, 0.1 M KNO_3; current, 20 μA).

acid hydroxyisobutyric acid (HIBA). End-point time (EP) is plotted versus concentration in Fig. 8. Reasonable linearity is seen over the range of 2–20 mM HIBA with a titration current of 20 μ. Depending on the composition of the sample solution, parameters such as viscosity and ionic strength may vary and have some influence on the end-point time. Therefore, for particular applications a matrix factor adjustment is utilized as will be explained in more detail in a later section.

Unlike a coulometric titration, there is no attempt in *FLASH* Titration to equate a quantity of electric charge with a chemical quantity or concentration—it is *time* that is measured, not *charge*. So long as calibration is carried out,

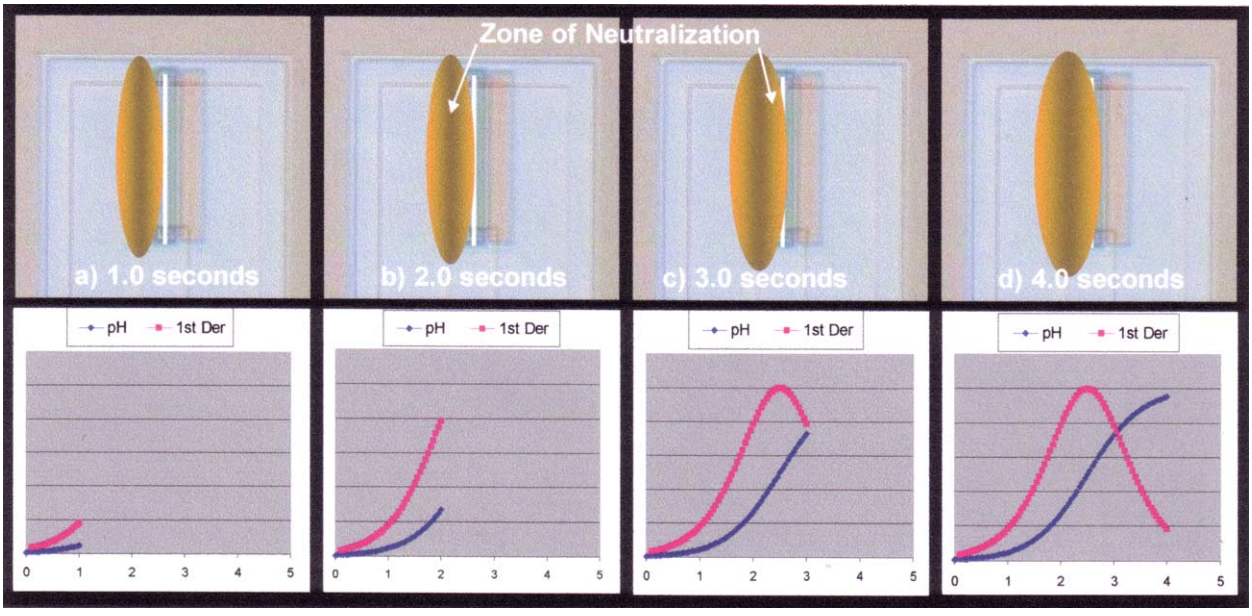

Fig. 6. Dynamic *FLASH* titration process. The upper four frames show the section of chip surrounded by the dotted line in Fig. 5. As the titration proceeds, the "*zone of neutralization*" spreads by diffusion into the volume element contacting the ISFET. An inflection time in the pH vs. time curve is proportional to total total acidity.

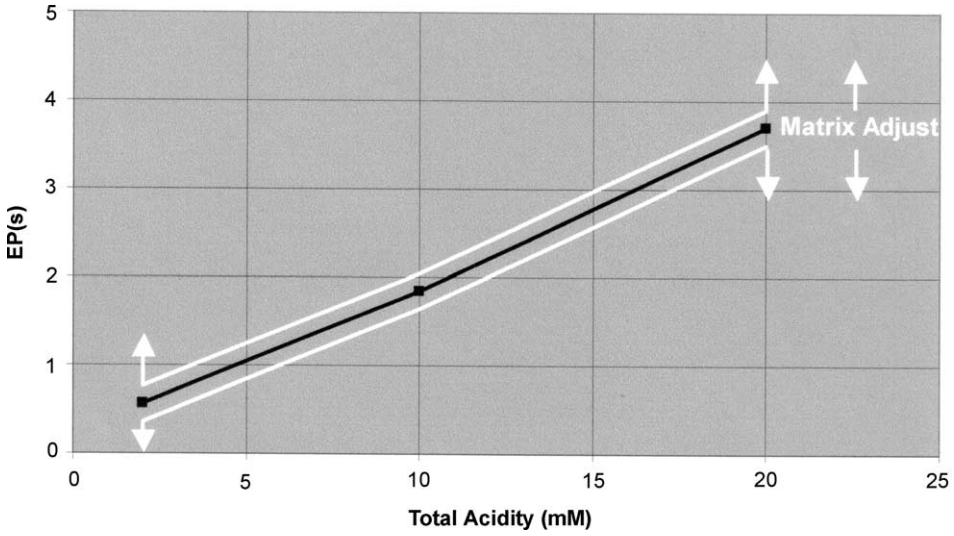

Fig. 8. Calibration curve with matrix factor adjustment.

FLASH Titration does not require 100% current efficiency. And because products generated at the counter electrode do not have time to diffuse to the ISFET during the titration, there is no need to provide an ion barrier such as a salt bridge or membrane as is required in a conventional coulometric titration.

4. Practical application of *FLASH* Titration

Fig. 9 is a depiction of the *FLASH* Titration apparatus. The basic elements are a probe and a meter—as simple as the equipment used to measure pH. A probe stand and stirrer are included and will be discussed below. Autosampler and computer/printer interface accessories are shown but are not necessary to perform *FLASH* Titration. In addition to titration, the system can be used to measure pH, conductivity, and temperature.

Fig. 9. Orion FLASH Titration equipment by Thermo Electron.

A typical *FLASH* Titration run using the described apparatus takes about 30–10 s of stirring to disperse carryover from the previous sample, 15 s waiting to allow the solution to become quiescent, and 5 s for the titration. A unique aspect of *FLASH* Titration is that it is non-destructive, unlike volumetric or coulometric titrations where the acid (or base) in the sample is neutralized after the titration. In this case only some tens of nanoliters are converted in a total sample volume of several milliliters, which allows a user to repeat the titration in the same beaker when the solution at the surface of the probe is replaced by stirring. Although not exactly equivalent to running a duplicate sample where errors in sample preparation or dilution might be uncovered, repeating the titration does give an improvement in precision. Precision improves in proportion to $\sqrt{n}$, where n is the number of runs. A typical precision for *FLASH* Titration is less than 1%. If a 1% titration is repeated three times ($n = 4$), a precision of 0.5% can be expected. In other words, by allowing the time per sample to increase from 30 s to 2 min, precision can be improved by a factor of two. As discussed further below, the *FLASH* Titration apparatus is autosampler-compatible. In automated titrations, the disadvantage of longer analysis times per sample is mitigated by the advantage of unattended operation.

Calibration of the *FLASH* Titration probe consists of running two or more known total acidity (or alkalinity) solutions, and allowing the meter to calculate the slope and intercept values of a calibration curve. In simple cases, probe calibration is all that is necessary before moving on to sample analysis. For example, the curve in Fig. 8 could obviously serve as calibration for the determination of the total acidity of HIBA solutions.

Analysis of complex samples requires an additional step. *FLASH* Titration is a diffusion-regulated process. The rate at which the zone of neutralization spreads from the generating electrode depends upon the diffusion coefficients of the electrolysis products that are diffusing outward as well as the diffusion coefficients of the sample acids or bases that are diffusing into the zone of neutralization. Therefore, the end-point times for the same concentration of different acids or bases can differ slightly. Also, more general sample *matrix effects* can occur. For example, diffusion rates are affected by viscosity, so viscous samples may read differently from non-viscous samples even if the total acidity (or basicity) is the same. Temperature also affects diffusion rates and although this effect is not large, it is best, just as in an ISE measurement, to calibrate and measure at approximately the same temperature. Finally, the titrant generation current efficiency may be less than 100% in some samples.

All of the above effects are taken care of by a procedure known as *matrix factor adjustment*. Matrix factor adjustment is a calibration step that is specific to a particular application. It consists of running a sample of the product to be tested that has been titrated volumetrically and labeled with the correct total acidity or alkalinity value. In Fig. 7 the matrix adjustment factor can be seen graphically as a shift or offset in the calibration curve that brings *FLASH* Titration results into close correlation with volumetric titration results for a particular type of sample.

Probe calibration and matrix adjustment can often be combined into a single procedure. One user controls the blending of a soft drink syrup concentrate with water by determining the total acidity of the product. Instead of calibrating the *FLASH* Titration system with three known standards, such as HIBA solutions, and then adjusting the matrix factor with a volumetrically titrated soft drink, she keeps a sample of properly diluted syrup, one that is 50% of the target, and one that is 200%. She labels them 50, 100, and 200 and does a three-point calibration inputting those values. The instrument then reads out her unknown samples directly in units of percent of target value. Any sample with a reading between 95 and 105 is OK.

In the *FLASH* Titration system the titration current can be manipulated in three ways. It's *sign* or *polarity* can be changed, its *magnitude* can be increased or decreased, and the user can choose between a *constant current* and *current ramp*.

The desired polarity of the titration current depends simply on whether one is titrating an acidic or basic sample. A cathodic current is chosen for titrating acids since base will be generated according to *Reaction* 1. An anodic current is chosen for titrating bases with acids generated in *Reaction* 2.

The magnitude of the titration current depends on the range of acid or base concentrations in the samples to be analyzed. It has been found that best results are obtained when the end-point times range between about 0.5 and 10 s. At less than 0.5 s the accuracy suffers because the time measured is so short. At greater than 10 s, the diffusion zone in which the titration takes place penetrates more and more into the sample solution and at some point the result becomes sensitive to uncontrolled convection and therefore less accurate. The *FLASH* Titration system allows the user to choose between 3, 20, and 100 μA constant current and 4, 8, or 12 μA/s current ramp in order to encompass a wide range of concentrations.

The mathematics of diffusion is complex but very effective in describing the behavior of simple systems such as *FLASH* Titration. Olthuis et al. [12] have shown that a relatively simple one-dimensional model is perfectly adequate to predict end-point times for different samples. The simplest case for a FLASH Titration is where a strong acid is determined. Up to the point where the end-point is reached, the process is almost entirely governed by the diffusion of free hydronium ions to the surface of the sensor chip and the end-point time therefore varies with the square of the acid concentration. The reaction product of the titration is in this case water, which has no influence on the evolution of the pH-change. When a weak acid is titrated, the process is somewhat more complex as it is determined by diffusion of the acid to the surface but at the same time also by diffusion of the reaction product, the conjugate base of the acid, into the solution.

In practice, for the titration of a weak acid the dependence of the end-point time on concentration is very close to linear as illustrated in Fig. 8. The method of choice for this type of titration is thus to use a constant current, the magnitude of which can be selected in relation to the expected acid concentration in order to assure a titration time in the range of 0.5–10 s. For the titration of a strong acid, the pH change is mainly determined by diffusion of hydronium ions and thus proportional to the square of the concentration. This non-linear calibration is inconvenient but also leads to a loss in sensitivity and range. When the generation current is varied with the square root of time, the resulting end-point times will depend linearly on concentration [13]. Practical experiments with the Orion FLASH Titrator have shown that the simple application of a linear current ramp is sufficient to bring linearity and range within acceptable limits.

5. *FLASH* Titration methods

In order to make *FLASH* Titration as easy as possible to apply to real samples without having to worry about "constant currents" or "current ramps", 30 specific methods have been pre-programmed at the factory into the *FLASH* Titration meter. Method numbers 1 through 12 are called *template* methods. These are generic and intended to be used as the first step in the development of a method for a specific application. Methods 13 through 30 are specific applications.

The 12 template methods are listed in Table 1 along with all of the specified parameters. The basic idea is for the user to select the template method that looks most appropriate for his or her sample. Any or all of the parameters can be changed by going into the set-up menu in the meter.

Table 1
Template methods and their parameters

Method number	Method name	Acid/base	Concentration range (mM)	Current	Stir time (s)	Wait time (s)	Titrate time (s)	Number of runs	End-point range (s)
1	Weak acid low range	HIBA	0.1–2	Cathodic constant 3 μA	10	15	5	3	2–6
2	Weak acid mid range	HIBA	2–20	Cathodic constant 20 μA	10	15	5	3	0.5–4
3	Weak acid high range	HIBA	10–100	Cathodic constant 100 μA	10	15	5	3	0.5–4
4	Strong acid low range	HCl	0.5–10	Cathodic ramp 4 μA/s	10	15	5	3	1.5–7
5	Strong acid mid range	HCl	2–20	Cathodic ramp 8 μA/s	10	15	5	3	2–7
6	Strong acid high range	HCl	10–50	Cathodic ramp 12 μA/s	10	15	5	3	3–9
7	Weak base low range	$NaHCO_3$	0.1–2	Anodic constant 3 μA	10	15	5	3	0.5–2.5
8	Weak base mid range	$NaHCO_3$	2–20	Anodic constant 20 μA	10	15	5	3	0.5–2.5
9	Weak Base High Range	$NaHCO_3$	10–100	Anodic constant 100 μA	10	15	5	3	0.5–2.5
10	Strong base low range	NaOH	0.5–10	Anodic ramp 4 μA/s	10	15	5	3	1–6
11	Strong base mid range	NaOH	2–20	Anodic ramp 8 μA/s	10	15	5	3	2–8
12	Strong base high range	NaOH	10–50	Anodic ramp 12 μA/s	10	15	5	3	2–8

Once a parameter has been changed, the user can save the method under a new number. This way, methods specific to a variety of samples can be stored in the meter and called up when needed.

In addition to the 12 template methods, 18 specific application methods for the food and beverage industry are pre-programmed into the meter. These methods are listed in Table 2.

Each method also has associated with it the default calibration constants and matrix factor. Even if a user does not change the operating parameters from the default values for a pre-programmed method, the meter will force the user to save the method under a new number if a calibration or matrix factor adjustment has been carried out. That way, the pre-programmed methods are never compromised.

In addition to developing his or her own specific application methods, a user has an option of downloading new methods from the *FLASH* Titration website [14].

5.1. High-throughput titration

Because *FLASH* Titration is so fast compared to conventional titration, users will be able to move more samples through their labs than ever before. The *FLASH* Titration meter is capable of interfacing to a versatile XY sample changer allowing unattended analysis of samples. Even allowing for the time it takes for the probe and stirrer to be transferred between solutions, over 60 samples/h can be titrated.

5.2. Outlook

Integrated coulometric sensor–actuator devices have been around for close to 20 years but it is only through a considerable product development effort that these systems are now coming to commercial bloom. The *FLASH* Titration instrument described in this article is the first of its kind and only scratches the surface of what the technology is

Table 2
Pre-programmed, specific application methods

Method number	Species	Sample (ml (g)) per 100 ml of solution	Species type	Template method number	Standards	Standard concentration used (mM)
13	Orange drink	10	Weak acid	2	HIBA	5, 10, 20
14	Apple juice	20	Weak acid	2	HIBA	5, 10, 20
15	Red wine	20	Weak acid	2	HIBA	5, 10, 20
16	Clear soft drink	50	Weak acid	2	HIBA	5, 10, 20
17	Cola	90	Weak acid	2	Phosphoric acid	8, 10, 15
18	Sports drink	25	Weak acid	2	HIBA	5, 10, 20
19	Tomato juice	25	Weak acid	2	HIBA	5, 10, 20
20	White grape juice	20	Weak acid	2	HIBA	2, 10, 20
21	Red grape juice	10	Weak acid	2	HIBA	5, 10, 20
22	Cranberry juice	10	Weak acid	2	HIBA	2, 10, 20
23	Iced tea	50	Weak acid	2	HIBA	5, 10, 20
24	Ginger ale	50	Weak acid	2	HIBA	5, 10, 20
25	Orange soda	50	Weak acid	2	HIBA	5, 10, 20
26	Ketchup	4 (g)	Weak acid	2	HIBA	5, 10, 20
27	Cider vinegar	1	Weak acid	2	Acetic acid	2, 10, 20
28	Milk	75	Weak acid	2	HIBA	5, 10, 20
29	White wine	20	Weak acid	2	HIBA	5, 10, 20
30	Mayonnaise	10 (g)	Weak acid	2	HIBA	5, 10, 20

ultimately capable of. The present system is limited to total acidity/total alkalinity, equivalence-point (first derivative) titrations. In the future look for multiple equivalence-point and fixed end-point acid–base, as well as redox, argentometric, and conductimetric *FLASH* Titrations. Applications will move out of the laboratory as well. The absence of liquid titrant makes *FLASH* Titration ideal for on-line process and on-site field applications. In flow-through configurations or with specialized sample handling equipment titrations can be made even faster. Adventurous users will find they can titrate a single drop of liquid or the surface of a gel. Rapid, non-destructive titrations in microtiter plates will become possible. Clearly, microfabricated sensor structures combined with electrochemical titrant generation can bring titration to new levels.

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Biographies

Bart van der Schoot is co-founder and vice-president R&D of Seyonic SA in Neuchâtel, Switzerland. The company specializes in sensor-controlled liquid handling of sub-microliter volumes in laboratory automation instrumentation. He obtained an MSc in pharmaceutical sciences from the University of Groningen (NL) and a PhD in technical sciences from the University of Twente (NL). He worked for 10 years at the Institute of Microtechnology at the University of Neuchâtel (CH), as project leader in the area of miniaturized chemical analysis systems, micro-fabricated fluid handling devices and micro-instrumentation, including their industrial application.

Peter van der Wal received an engineering degree in chemical technology in 1985 and his PhD natural sciences in 1991, both from the University of Twente, The Netherlands. During the years 1991–1992 he participated in a project entitled “ionsensors for horticulture,” a collaboration between Priva B.V., Twente Technology Transfer and the Organic Chemistry group of the University of Twente. After a practical training at Microsens S.A., Neuchâtel, Switzerland in 1992, he joined the Sensors, Actuators and Microsystems Laboratory (SAMLAB) at the Institute of Microtechnology, Neuchâtel, Switzerland in 1993. Since then he is working as a scientific co-worker at the SAMLAB in the field of chemical sensors.

Nicolaas F. de Rooij received a PhD degree from Twente University of Technology, The Netherlands, in 1978. From 1978 to 1982, he worked at the Research and Development Department of Cordis Europa N.V., The Netherlands. In 1982, he joined the Institute of Microtechnology of the University of Neuchâtel, Switzerland (IMT UNI-NE), as professor and head of the Sensors, Actuators and Microsystems Laboratory. From October 1990 till October 1996, he was acting as director of the IMT UNI-NE, since October 2002, he is back at the direction of the institute. Since 1987, he has been a lecturer at the Swiss Federal Institute of Technology, Zurich (ETHZ), and since 1989, he has also been a professor at the Swiss Federal Institute of Technology, Lausanne (EPFL). His research activities include microfabricated sensors, actuators, and microsystems.

Steve West studied chemistry at Bates College in Lewiston, Maine and Northeastern University in Boston, Massachusetts and did a 2-year internship in the Department of Organic Chemistry under Professor Wilhelm Simon at the ETH, Zurich, Switzerland. In a career spanning almost 30 years with Thermo Electron Corporation (Environmental Instruments Division, Water Analysis formerly Orion Research), he has held various positions in Research and Engineering and is currently Vice President of Research, Development, Engineering, and Quality Assurance.