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Design and implementation of a microchemistry analyzer

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Abstract

Advancements in the microfabrication methods of silicon chips make it possible to produce biosensor arrays coated with specific ionophores or enzymes, in large volumes, with a high degree of reliability, and at a low cost. The i-STAT System incorporates such micro-arrays in a disposable cartridge, 1x1.75x0.2 in. The cartridge performs analysis on 2-3 drops of whole blood and can within 2 minutes, measure Na^+, K^+, Cl^-, Ca^{++}, HCO_3^-, Glucose, Urea, pH, pO_2, pCO2, and Hct. In addition, the cartridge contains a fluid calibrant and is automatically calibrated before every patient's sample. The analyzer is fully automatic and specifically designed to assure reliable results in non-laboratory settings. The only steps required by the user are placing the blood, inserting the cartridge into the analyzer, and entering patient and operator identification numbers. Numerous automatic reliability tests are incorporated including detection of user induced errors. A unique quality control procedure is provided via an electronic simulator which tests the functionality of the analyzer at 2 levels beyond reportable ranges, and at narrow sensitivity limits.

Medical Needs and Opportunities

In the past decades the clinical chemistry laboratory had made significant technological advances focused on improvements in reliability and automation. Although quality improved dramatically, health care providers still desire faster turn around times and the availability of results at the patients' bed-side or at the point-of-care.

Designers of point-of-care systems face special challenges. Systems should be fast, small, and simple to use while maintaining state of the art performance features. Fast and simple imply a capability to analyze unprocessed whole blood in small sample volumes, and preferably finger stick capillary blood. Designers must also consider the intended user, i.e., a bed-side caregiver who may not have any training in laboratory practices. From that point of view, simplicity connotes a portable device which is small in size, light in weight, and battery operated. A system should always work, feature transparent and automatic calibration, its fluid motions should be controlled by the analyzer and it should have no need for volumetric sample additions, user intervention during the test cycle, mixing, reagent preparations, maintenance, adjustments, or checks. In addition, the system should have simple procedural quality checks and self monitoring capability at all times. Finally, as test results provide data, the information needs to be displayed, printed,

automatically managed, computerized, and easily interfaced with the various hospital information systems.

A Point-of-Care Microchemistry System

A system was recently developed to comply with the rigorous requirements of a point-of-care testing device. The i-STAT System (i-STAT Corporation, Princeton, NJ, USA) comprises of a hand-held device the size of a portable phone measuring 2.6x7.2x1.4inches (6.5x21.3x6.6cm) that operates on two 9 volt lithium batteries, small single-use cartridges 1x1.75x0.2inches (2.5x4.4x0.5cm), a small portable printer and a personal computer called the Central Data Station. To achieve the small dimensions desired, biosensors microfabricated on silicon chips were chosen as the preferred technology. This technology lends itself to a high volume production at a reasonable cost. It enables coating of sensors with sensitive biological molecules or enzymes as well as specific ionophores. Except for the micro size of the sensors, the electrochemical test methods shown in Table 1, are exactly the same as those employed by state of the art, large size laboratory analyzers.

The biosensors are configured in arrays of test combinations and are housed at the top of the plastic single-use cartridge. To date, tests available are sodium, potassium, chloride, ionized calcium, glucose, blood urea nitrogen, pO_2, pCO_2, pH, and hematocrit. Complying with design requirements, the cartridge takes 2-3 drops of fresh capillary, venous or arterial whole blood without dilution or pretreatment. The sample is introduced through a blood entry port on the cartridge which fills by capillary draw to a marked line, Fig.1. There is therefore no need to add a measured amount of sample. The disposable cartridge also includes a calibrant fluid pack which bursts at the start of the testing cycle and calibrates the sensors before each patient sample. The only steps required from the operator are filling the cartridge with blood, closing the cover over the entry port, inserting the cartridge into the analyzer, and then entering patient and user identification numbers. To assure accuracy of identification, each number is entered twice. Results are displayed digitally and graphically on the analyzers' screen within 2 minutes and can be printed at the bed-side.

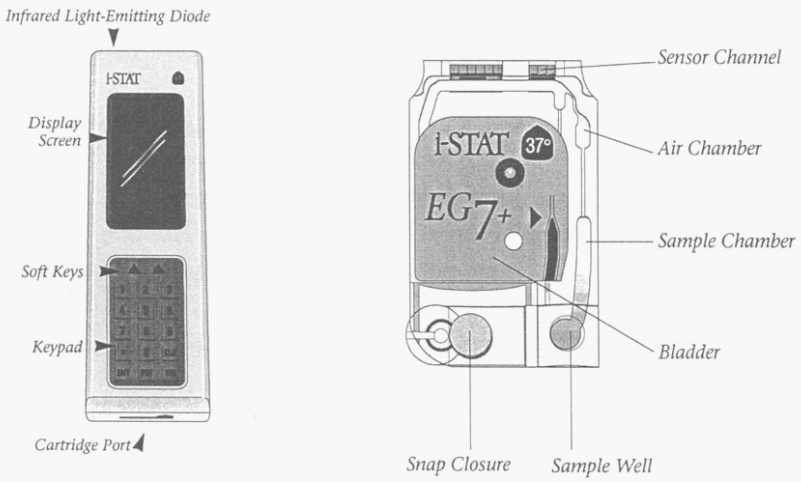

Fig. 1 The i-STAT cartridge and analyzer

TABLE 1: The i-STAT tests

Chemistry	Temp.	Principle of Measurement	Measurement	Range
Sodium	RT or 37°C	Thin film sodium selective electrode.	Potentiometric	100-180 mmol/L
Potassium	RT or 37°C	Thin film potassium selective electrode.	Potentiometric	2.0-9.0 mmol/L
Chloride	RT or 37°C	Thin film chloride selective electrode.	Potentiometric	65-140 mmol/L
Ionized Calcium	RT or 37°C	Thin film calcium ion selective electrode.	Potentiometric	0.25-2.5 mmol/L
Glucose	RT	Glucose is oxidized in the presence of glucose oxidase which is immobilized over an electrode. The oxidation of the resulting hydrogen peroxide is electro-chemically measured.	Amperometric	20-450 mg/dL
BUN	RT	Urea is hydrolyzed in the presence of urease. The production of ammonium is measured by a micro-fabricated ammonium selective electrode coated with the immobilized enzyme.	Potentiometric	3-140 mg/dL
PO_2	37°C	Clark type electrode, where oxygen permeates through a gas permeable membrane to a thin film oxygen reducing electrode.	Amperometric	0-800 mm Hg
PCO_2	RT or 37°C	Severinghaus type electrode, where CO_2 permeates through a gas permeable membrane to a bicarbonate solution. It dissolves and dissociates to create a pH change which is measured at a thin film pH electrode.	Potentiometric	10-100 mm Hg
pH	RT or 37°C	Thin film hydrogen ion selective electrode.	Potentiometric	6.8-8.0
Hematocrit	RT or 37°C	A two terminal, noble metal electrodes, alternating current resistivity cell.	Conductivity	15-75 %

The system can store up to 50 patient records that can be down-loaded at a later time. A record consists of the patient's results, date, time, patient identification number, user identification number, and appropriate patient specific parameters. The information,

along with the analyzer identification number and results of electronic simulators tests, is transmitted via an infra-red link to a Central Data Station. Consequently, operation of the system at different locations can be monitored centrally and provides a convenient way of transferring patient information to the hospital system.

In the analyzer, the testing process is automatic and fully controlled. First, electrical contact is made with the sensors on the cartridge. Next, the calibrant pack is burst and the fluid is moved over the sensors. After a very short wetting time period afforded by the thinness of the sensors, the electrochemical signals are read and recorded. Then, separated by an air bubble, the blood sample is moved over the sensors and the calibrant fluid is displaced to a waste chamber. The concentration of each analyte is calculated by comparing the blood sample signals to those of the calibrant fluid. Performance features of the system were studied extensively and were proven to meet the high standards required of comparable laboratory analyzers (1-4). A sample of imprecision data is presented in Table 2.

TABLE 2: Imprecision of the i-STAT tests

Chemistry	Mean	SD	CV
Sodium, mmol/L	113.5	0.61	0.5
	141.7	0.71	0.5
Potassium, mmol/L	5.61	0.064	1.1
	2.76	0.047	1.7
Chloride, mmol/L	78.7	0.76	1.0
	105.8	0.80	0.8
Ionized Calcium, mmol/L	1.56	0.018	1.1
	0.76	0.012	1.6
Glucose, mg/dL	214.5	6.7	3.1
	55.3	1.4	2.6
BUN, mg/dL	4.3	0.4	9.4
	66.5	2.2	3.2
PO_2, mm Hg	65.1	2.6	3.9
	130.1	2.7	2.1
PCO_2, mm Hg	63.8	0.83	1.3
	20.2	0.60	3.0
pH	7.190	0.003	0.04
	7.675	0.004	0.05
Hematocrit, %	29.9	0.68	2.3
	49.8	1.00	2.0

The Approach to Quality Assurance

To assure high quality of results, the system incorporates numerous quality checks which are specifically designed with the point-of-care, non-laboratory user in mind. During each testing cycle the system performs continuous on-line measurements to monitor the reliability of the sensors, fluidics and instrumentation. The readings of the calibrant are compared to predetermined narrow ranges set in the software. In addition, the analyzer detects user induced errors such as incorrect filling of the cartridge, clots, and bubbles in the sample path. Failure of any such checks leads to suppression of patient results and a displayed code alerts the user to the error or appropriate corrective action. As intended by design goals the system is not dependent on technique or training of the operator. The user has no impact on the testing cycle and cannot impinge on the quality of the results.

Another feature incorporated into the system tests the quality of the analyzer. An independent device the size and shape of a cartridge is inserted into the analyzer daily and simulates the characteristics of the sensors. It emits two signals consistent with both very low and very high concentrations of each of the analytes and stresses the performance of the system beyond what is encountered in blood samples. The signals read by the analyzer are checked against predetermined thresholds and acceptance is communicated via a pass/fail message. There is no need to look up control charts or to interpret test results.

Being single-use and cartridge based, the i-STAT System is not prone to persistent errors stemming from electrode drifts or repeated use of the same sensors and sample channels. In addition, each unitized i-STAT cartridge, sealed in its own separate foil pouch and having its own individual history, can not be susceptible to events that may affect an entire reagent batch on other systems. Traditional quality control regimens such as testing a cartridge with a liquid control solution offer no benefit to this system as they can not predict the quality of other cartridges. As a result, quality control materials although provided, are only intended to check proper storage of newly arrived shipments or assure integrity when storage conditions are questioned.

Summary

New technologies make it possible to develop a microchemistry diagnostic system that meets design goals required from a point-of-care testing device and features high quality performance characteristics equal to what is found in large and sophisticated laboratory analyzers.

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