Modular Design of Automated Biochemistry Analyzer

Swati Kapoor
CDAC, Mohali

Vikas Goel
CDAC, Mohali

ABSTRACT

Fully automatic biochemistry analyzer (FABCA) is a high performance micro-controller based Photometric biochemistry analyzer used to measure various blood biochemical parameters such as blood glucose, urea, protein, and bilirubin etc. that are associated with various disorders such as diabetes, kidney diseases, liver malfunctions and other metabolic derangement's. The quantization of these parameters is helpful in diagnosing health disorder. In the proposed project work, it is planned to automate the filter selection, sample aspiration, auto-calibration and other related parameters to be controlled through micro-controller based hardware and software system. It is proposed to automate the sample handling system to cope up with the large no. of blood sample at a time. The modular design of automatic biochemistry analyzer (ABC) analyzer facilitate to be controlled via laptop or PC by using the interfacing/front end software or as standalone unit.

Keywords

Bio-chemistry analyzer, Lamberts & Beer law, Autosampler, Optical assembly for analyzer, OD→ Optical Density, FABCA→ Fully automatic biochemistry analyzer, SCU→Signal Conditioning Unit

1. INTRODUCTION

An automated analyzer is a pathological lab instrument designed to analyze blood bio-chemistry parameters like glucose, amylase, urea, triglycerides etc. with minimal human assistance. Blood samples are placed in a rack of test tubes. This rack is rotated through a stepper motor for positioning of blood sample through the measurement chamber of the analyzer. The purpose of the fully automated bio-chemistry analyzer is intended for labs where heavy load of blood samples is estimated. Selection of filters for a respective test, sample aspiration, check of water level, different reagents and standard levels, washing of flow through cell, QC level, auto-calibration of peristaltic pump and many other checks are automated. This automation provides a lot of convenience to lab operator to concentrate on sample preparation and reporting/documentation part. Biochemical analyzer (BCA) is a kind of instrument based on the principal of Lambert-Beer. It is often used to measure the clinical and chemistry indexes of blood, such as, the glucose, bilirubin, albumin, uric-acid, cholesterol, HGB, etc. Because it can truly and rapidly offer test data for doctor or chemistry identifier, it plays an important role in clinic diagnose and chemistry inspection. An automated analyzer is a medical laboratory instrument designed to measure different chemicals and other characteristics in a number of blood samples quickly, with minimal human assistance. Blood samples are placed in a rack of test tubes and then this rack is rotated through a stepper motor for positioning of blood sample through the measurement chamber of the analyzer. The purpose of the fully automated bio-chemistry analyzer is intended for the labs where heavy load of blood samples is estimated. Presently, in the market, bio-chemistry analyzers are in different variants like colorimeter, semi-automatic bio-chemistry analyzer, fully automatic bio-chemistry analyzer, photometer, spectrometer etc. A biochemistry analyzer and a biology analyzer is a term that could refer to a variety of different instruments that are intended to perform various functions like analyze and measure the actual characteristics of samples. The most typical use of the biochemistry analyzer is to look for the structure and functions associated with biomolecules such as fats, proteins, enzymes as well as nucleic acid. Automation in the biochemistry analyzer brought change in the manner in which numerous laboratory functions are completed and allows a lot of time insensitive tasks to be streamlined which in turn provides good throughput. These automatic biochemistry analyzer products can calculate the focus and/or figure out the features of particular substances inside a sample quickly and with minimal operator treatment.

The system is planned in a way that it can be operated either from its own control unit or directly attached to a PC or laptop for its operation. Individual control cards for each module are planned. This will help in troubleshooting of the system and easy replacement of the defective card.
With a good automated analyzer, there are often dedicated auto samplers being used combined with the instrument or oftentimes, even a built-in auto sampler. These additional features simplify the job of biochemistry and biology analysis and because the safety associated with laboratory personnel whenever using biological samples is usually a concern, also make the current, automated biochemistry and biology analyzer easier and safer to make use of. In bigger medical laboratories, for example those from hospitals, we can find dedicated biochemistry analyzer systems being used, often used to perform various common assessments needed from healthcare amenities. These include assessments for amounts of albumin, sugar, enzymes as well as creatine levels within the blood or even serum. These tests can be performed through measuring colorimetry, turbidity conductivity, and a variety of other techniques. The automatic analyzer mainly includes:

- Sample handling system
- Sample aspiration
- Reagent handling system
- Washing of the flow cell
- Incubation of the sample at the selected system
- Automatic filter selection and gain according to the requirement of the test
- Automatic printed test result

The main components analyzer includes:

- CPU
- Signal Conditioning Unit (SCU) and ADC
- Display Unit
- Motor Control Unit

- PC Interface Unit
- Printer Control Unit
- Power Supply
- Optical Module
- Temp. Control Assembly
- Keyboard Control Unit
- Flow Cell Chamber
- Samples Holding and Control Unit
- Reagents Holding and Control Unit
- Water Holding and Control Unit
- Control Serum Handling System for QC Test

2. PRINCIPLE OF OPERATION

The principal of operation of a bio-chemistry analyzer is based on LAMBERTS AND BEER'S Law of photo-chemistry. This law relates absorption of the light to the properties of the medium through which it travels. The amount of light penetrating into the solution is termed as transmittance and is expressed as the ratio of the intensity of the transmitted light I_t and intensity of the incident light beam I_i. According to the Lamberts law absorbance is directly proportional to thickness of the sample. According to the Beers law absorbance is proportional to concentration of the sample. Lamberts and Beers law combines these two laws and correlates the absorbance to both concentration as well as to the thickness.

Thus according to the Lamberts and Beers law, the transmitted light coming out of a liquid contained in a transparent glass depends upon the concentration (C), path length (T) and intensity of the incident light. If path length T and intensity of the incident light are kept constant, the transmitted light intensity will be proportional to the concentration of the liquid contained in glass chamber.

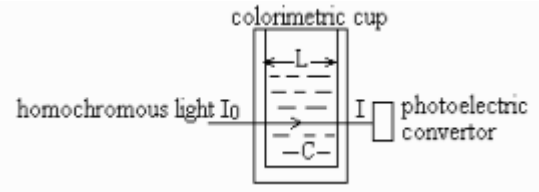

Figure 1: Schematic diagram of the sample absorbing monochromatic light

A bundle of monochromatic light with intensity I_o transmits through the sample solution with concentration C, and arrives at the photoelectric converter. Suppose the transmitted light intensity is I, the distance that the light goes across or the light pathway is L, then

$$I_o/I = e^{KLC}$$, where K is absorbency

Thus we can conclude that sample concentration can be measured based on relative change of the transmitted & incident light intensity provided if the light pathway is fixed. According to Lambert and Beer's law, when monochromatic light passes through colored solution, the intensity of the transmitted light decreases exponentially with the increase in concentration of the absorbing substance. The amount of the light energy absorbed depends on the number of molecules present in absorbing material and the thickness of the medium. Thus, intensity of light energy leaving the absorbing substance is used to provide an indication of concentration of that particular substance. In this system, the basic requirement is to measure optical density/absorbance and the concentration of the test parameter under run accurately.

3. COMPARISION WITH RELATED WORKS

In the case of existing analyzers all the filters were placed in a linear array and each filter had a corresponding photodiode of its own placed right below the filter. Once the light generated from the halogen lamp passes through the sample placed in the flow cell it will fall on each filter, i.e. everytime each filter is exposed to the light due to which the lifetime of each filter decreases. On the other hand in the case of FABCA, we have a circular filter wheel assembly in which each filter is placed and only a filter for a particular test is brought in front of the flow cell and only the lifetime of that filter reduces.

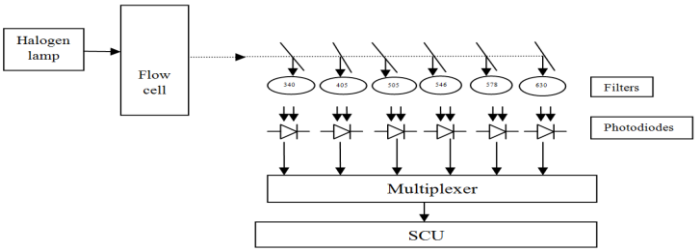

Figure 2: Existing Analyzers

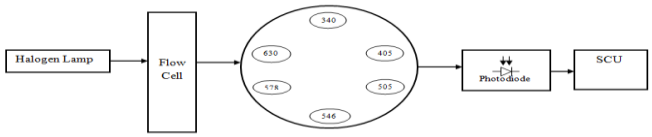

Figure 3: FABCA

4. SYSTEM DESCRIPTION

It consists of light source, homochromy device, colorimetric cup, temperature sensor, sampling device, photoelectric converter and microcomputer system and so on. The light source is a 30W/12V halogen lamp and gives off the steady white light. The homochromy device is composed of the rotating wheel, interferential filter and step motor and so on. The step motor drives the rotating wheel where there are 8 interferential filters distributed proportionally, one of them is a standby and the others are employed for the measurement. Their wavelengths are 340nm, 405nm, 510nm, 546nm, 578nm, 620nm and 670nm separately. The basic block diagram of the fully automatic biochemistry analyzer (FABCA) is shown in figure 3 below. The system mainly constitutes a light source, an optical assembly, a flow cell (where the sample is placed) shown in figure 3, a peltier device (to maintain the desired temperature for the performing the particular test on the sample in the flow cell) a filter wheel assembly, a photodiode, a signal conditioning unit (SCU), analog to digital (ADC), a processing unit which can be interfaced with a display device like LCD, or with a printer or keyboard.. The components are discussed in brief below.

Keeping in view the low response of photo detector in UV (340nm), all the optical components have been provided with enhanced antireflection coating in the UV region. In the opto-mechanical assembly, special care has been taken in the design so that each component is properly aligned with respect to optical axis. To get the required wavelength of light to be passed, 6 interference filters of different wavelengths

such as 340nm, 405nm, 505nm, 546nm, 578nm, and 630nm, from UV region to visible region spectrum (300nm to 700nm), have been mounted on the filter wheel

Figure 4: Filters

Figure 5: Flow cell in which sample is placed

These filters are selected automatically depending on the test performed. When the filter of required wavelength is selected, the corresponding gain is selected automatically. The filter wheel is driven by a stepper motor, which is interfaced with the port of microcontroller through driver circuit. Pulses are generated according to required sequence to rotate the motor at required angle, which brings the filter in front of photo detector.

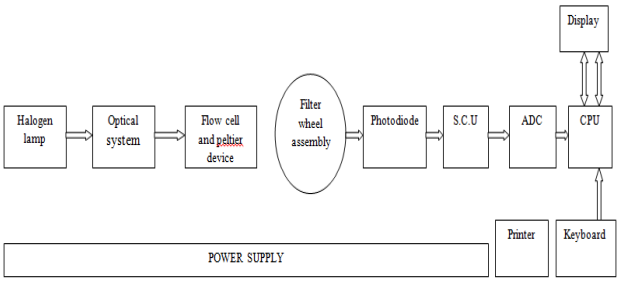

Figure 6: Block Diagram

4.1 Optical Assembly of the Analyzer

The operation of this optical system can be best understood by classifying it into three parts. Firstly, that it transforms the duplicate colored light into the monochromatic light. Secondly is transforms the light signal of the monochromatic, which have the information of the measured sample, as the electric signal by use the photoelectric detector The optical assembly of the analyzer includes a halogen lamp, a flow cell, a pair of plano convex lenses, the filter wheel assembly attached to the stepper motor that controls its movement, and a photodiode. The motion of the stepper motor is controlled by the AT89C51RE2 microcontroller. Initially a filter is selected for the test to be carried out on the sample, and then the filter is brought in the front of the flow cell in which the sample is placed. Whenever a desired filter for a specific test is selected, the filter wheel moves from its home position to the desired position. In this way the desired filter is selected. The movement of the filter wheel and the placement of the corresponding filter in front of the flow cell are controlled by a stepper motor which is programmed through the controller. The light generated from the halogen lamp then passes through the sample placed in the flow cell and further passes through the filter. We have a module that is fitted with the pair of lenses so as to provide proper pathway to the light. The light then falls on the photodiode which converts the light into an output voltage.

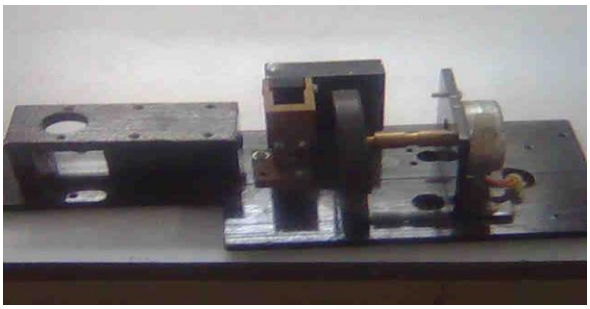

Figure 7: Optical Assembly of the analyzer

4.2 Photodiode (S13368BQ)

It is also termed as UV enhanced photodiode. The photodiode is placed in between the signal conditioning unit and the controller. The monochromatic beam of the light that passes from the filter falls on the photodiode where it is converted into a corresponding output voltage to drive the further circuitry. The main features of this photodiode include:

- High sensitivity
- Low capacitance
- High reliability

This photodiode is primarily used in applications like in analytical instruments and optical measurement systems

4.3 Signal Conditioning Unit (SCU)

The voltage generated from the photodiode is of order few millivolts and is not sufficient to operate the further circuitry therefore we employ a signal conditioning unit. The signal conditioning unit mainly constitutes an amplifier, a second order low pass butterworth filter and a buffer. The amplifier is mainly used to boost up the amplitude of the signal output from the photodiode. The second order butterworth filter is designed with cut off frequency of about 5-6 KHz. The main aim of designing this second order low pass butterworth filter is to remove the noise, which is done by increasing signal to noise ratio (which in turn reduces noise). The main aim of the buffer is to make the output impedance minimum.

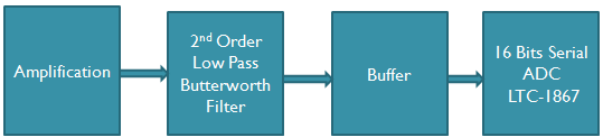

Figure 8: Signal conditioning unit

4.4 Analog to digital converter (ADC) LTC1867

The LTC1867 is a pin compatible, 8 channel, 12/16 bit A/D converter with an internal reference and serial I/O. The ADC's typically draw 1.3mA from single 5V supply. The main features of this ADC are:

- Sample Rate- 200mbps
- Automatic nap mode between conversions
- 8 channel multiplexer with :
  Single ended or differential inputs and unipolar and bipolar conversion modes
- Single 5V operation
- Signal to noise ratio-89dB
- SPI/serial I/O

The main applications where this ADC is used include:

- Industrial process control
- High speed data acquisition
- Battery operated system
- Multiplexed data acquisition systems
- Imaging systems

As this ADC is housed in narrow and a compact 16 pin- SSOP package, therefore LTC1867 ADC can be also used in space sensitive as well as low power applications. The automatic nap mode between conversions also benefits power sensitive applications.

5. AUTOSAMPLER

An auto-sampler used in fully automatic bio-chemistry analyzer is an integral part of this instrument. It is an electro-mechanical device fitted with different probes to aspirate water, reagents and samples from the test placed in different holes provided in the sampler tray. Each test tube has its unique position and is programmed through the software section of the unit. The entire sampler unit is attached to stepper motor shaft and the position of each test tube is controlled via the commands from software section in synchronization with different probes. The probes are also attached to a separate stepper motor shaft. Once a particular test is selected the respective test tube comes under the probe.

Figure 9: Reagent sampler

The probe is moved down into the test tube to aspirate the water/sample or reagent. The sampler may have number of test tube positions depending upon its application and requirement. The placement of test tube should be accurate and precise enough so that each test tube is at an equal angular distance from one another. This ensures the proper dipping of the probe into the selected test tube.

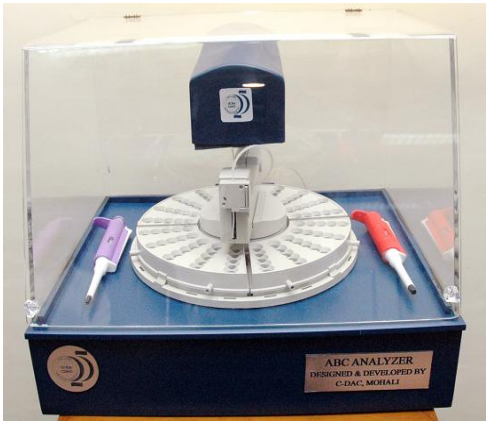

Figure 10: Automatic biochemistry Analyzer

5. COMPUTATION OF OD

The optical density of the sample is given by:

Optical Density (OD) = $2 - \log_{10}(T)$,

and T is Transmittance given by:

$$T = I_t / I_0$$

Where, I_t is intensity of transmitted light, and Io is the intensity of the incident light

T is also computed by the following equations:

Say, V_w and V_{sample} are the voltages with water and sample respectively.

Then T is given by:

$$T = (100 \times V_{sample} / V_w)$$

RESULTS & CONCLUSION

The system is designed using the modular approach. This enables the system to be used as standalone unit or as an optical assembly along with sampler system and can be interfaced with PC or laptop. In that case, the PC/laptop resources are used in terms of memory, display, keyboard etc. Further, the limitation on account of memory for result storage, test storage and sorting of results becomes easier as the same can be analyzed by using different s/w installed in the system (PC). However, the PC or laptop needs to be communicated over a communication channel, serial protocol is being used in the present case. USB/four wire interface may also be employed with necessary modifications in the software of the same.

REFERENCES

[1] Xiafu Lv and Yingqiong Luo Mingxi Deng and Yong Chen, "The Design of the Semi-Automated Biochemistry Analyzer", 0-7803-8629-9/04/$20.00 © 2004 IEEE

[2] Wang Xu Huang Kaizheng and Xu Bin, "Design of step motor control of Automatic Biochemistry Analyzer" ,ICEMI'2007

[3] R. WYLD, F.S.E.R.T., C.Eng., M.I.E.R.E.R.,"An Automatic Biochemical Analyzer", U.D.C. 545.81: 577.1:620-52

[4] S. R. Taneja, R. C. Gupta, Jagdish Kumar, K. K. Thariyan, and Sanjeev Verma "Design and Development of Microcontroller-Based Clinical Chemistry Analyser for Measurement of Various Blood Biochemistry Parameters", Journal of Automated Methods & Management in Chemistry, 2005 (2005), no. 4, 223–229

[5] Ze-xin Xiao and Kuan Chen "Research and design of an optical system of biochemical analyzer based on the narrow-band pass filter", Proc. SPIE 6834, Optical Design and Testing III, 68343P (November 28, 2007); doi:10.1117/12.758069;

[6] Saetchnikov, V.A.; Tcheriavskaia, E.A.; Schweiger, G., "Point of care fiber optical sensor for non-invasive multi parameter monitoring of blood and human tissue biochemistry," *Advanced Optoelectronics and Lasers (CAOL), 2010 International Conference on* , vol., no., pp.242,243,10-14Sept.2010doi: 10.1109/CAOL.2010.5634197

[7] Swati Kapoor, Vikas Goel, "Design and Interfacing of the Optical Assembly for Automated Analyzer", International Journal of Science and Research (IJSR), India Online ISSN: 2319-7064, Volume 2 Issue 5, May 2013