SEMIANNUAL REPORT NO. 1
NASA RESEARCH GRANT NGR 22-011-024

A STUDY OF MICROMINIATURIZED DEVICES FOR BIOASTRONAUTICAL MONITORING OR ANALYSIS

by

B. L. Cochrun
J.S. Rochefort

Electronics Research Laboratory
Northeastern University
Boston, Massachusetts
1 September 1967

The research reported here was sponsored by the National Aeronautics and Space Administration under Research Grant NGR 22-011-024. The research reported here covers the period from the receipt of the grant through August 31, 1967. This report is published for information purposes only and does not represent recommendations or conclusions of the sponsoring agency.

RESEARCH STAFF

Basil L. Cochrun, Co-principal Investigator
Associate Professor of Electrical Engineering

J. Spencer Rochefort, Co-principal Investigator
Professor of Electrical Engineering

K. Hergenrother
Research Associate

TABLE OF CONTENTS

I. INTRODUCTION

The original proposal for the work being carried out under NASA Grant NGR 22-011-024 suggested a starting time in January 1967. Uncertainty about the eventual acceptance of our proposal, as evidenced by a lack of communication until March 1967, and predating of the starting time to 1 February 1967 provided concern about the allotted time of a full year's effort. Subsequently we were informed that there would be sufficient flexibility to allow for an initial delay. For these reasons it was felt that this report covering a longer period of time would be satisfactory.

During this work period meetings have been held between key personnel of NASA ERC Cambridge and those of Northeastern University. Informal discussions regarding mutual problem areas have been of benefit to both parties. A greater familiarization with the projects and requirements of NASA ERC Cambridge has tended to polarize the projects at Northeastern University, NASA personnel have had the benefit of the specialized knowledge of Northeastern personnel in the area of electro-optical systems.

At Northeastern efforts have been devoted to three specific areas. These are a universal low-power electrode amplifier, systems for determining oxygenation of the blood and solid state light sources.

The universal amplifier is envisaged as being sufficiently flexible to be used as a buffer electrode amplifier for many applications. As such it would be able to replace the present day polygot configurations and thus standardize measurements. This modular buffer amplifier will be referred to as MEBA.

The second and third areas are intimately related in that the present approach to oximetry involves noninvasive electro-optical systems. One such system, to be discussed later, would be concerned with the use of several light sources of different wavelengths.

II. OXIMETRY

A brief survey of literature and instrumentation related to measurements of the percent oxyhemoglobin present in the blood circulating in the human ear indicates that much can be done to improve the performance and reduce the size of the instrumentation. However, aside from the prospect of realizing better instrumentation to process any measurement taken, there seems to be a question as to what, indeed, is measured. The blood in the ear is somewhat removed from the main arterial flow and consequently any measurements made upon it may only be representative of blood conditions elsewhere in the body during periods of high circulation of the type usually associated with heavy exercise. Consequently measurements of this type may be of value only under certain environmental conditions. There, of course, remains the possibility that measurements of the oxyhemoglobin in the ear may bear strong correlation to other physiological conditions. Certainly additional survey work along these lines seems warrented before any instrumentation program of the type which will be suggested in this chapter would be justified.

In the event that it is desireable to develop improved, lightweight apparatus for measuring the condition of the hemoglobin in the ear with non-invasive instruments, then the techniques employed in transmission and reflection spectrophotometers appear to be most promising. To date the survey has been concerned with the transmission type of instrument which certainly lends itself to convenient packaging since ear clips are readily feasible in which compact light sources are mounted on one side of the ear and photosensitive devices on the other side. However, the question as to exactly what is measured when light is passed through the ear once more becomes a concern because of the differences which necessarily exist between this method of measurement and those which are employed in transmission spectrophotometry in a laboratory when whole blood is isolated in a cuvette and a hemolyzing agent added. In any ear measurement there is the additional

problem that light scattering and absorption take place in the tissue and cartiledge and the hemoglobin itself is locked within the blood cell. This is not to imply that ear measurements are unfeasible. These other effects may well be slight. However, it is felt that all underlying assumptions should be carefully examined lest instrument design be undertaken solely on the basis of the challenge to build a better, more compact, device based upon the same approximations that others may employ.

In what follows laboratory techniques for transmission measurement of blood parameters are discussed and analytic expressions developed. The additional complications associated with actual measurements made on the human ear are next treated. Finally suggestions are made for the development of a more compact and accurate instrument capable of measuring the relative percents of the total hemoglobin concentration in the form of either oxyhemoglobin or carboxyhemoglobin, or both.

2 A. Laboratory Techniques

Two commercial instruments for the laboratory measurement of the percent oxyhemoglobin present in whole blood have been considered to date. The operation of each instrument is based upon the applicability of the Beer-Lambert equation to the ensuing absorption which occurs when light energy at different wavelengths is passed through a cuvette containing whole blood.

Lambert's law merely states that the proportion of incident radiation absorbed in a medium is independent of the intensity of the radiation. Beer's law extends this concept by stating that in a given medium the optical density of a specimen depends only upon the number of absorbing molecules through which the radiation passes and is independent of their mutual proximity. When both laws are combined the resulting equation is

$$I = I_o \exp [ECx]$$

where

I_o = incident light intensity
I = intensity of transmitted light
E = extinction coefficient for a unit concentration
C = concentration of the medium
x = path length of light in the medium

In the event that N different absorbing species are present in a medium, then the equation can be rewritten as

$$\log (I_o/I) = \sum_{i=1}^{N} E_i C_i x_i$$

where E_i, C_i and x_i are the appropriate parameters for the i-th species present in the medium.

The Instrumentation Laboratory, Inc., of Watertown, Mass., manufactures the Model 182 CO-Oximeter. This instrument is essentially an absorption spectrophotometer coupled to an analog computer. Whole blood is mixed with a hemolyzing agent and inserted in a cuvette. Since the three major light absorbing species are reduced, oxygenated and carbon-monoxide bound hemoglobin, the absorbancy of the sample is determined at three wavelengths in the visible spectrum. Interference filters in front of three phototubes are used to detect the transmitted light at three wavelengths in the visible spectrum. After passing the output signals from the phototubes through logarithmic amplifiers the data is in the form of

$$A_i = x E_{ri} C_r + x E_{oi} C_c + x E_{ci} C_c$$

where the index i = 1, 2, 3 is in keeping with the three wavelengths employed. The extinction coefficients E_r, E_o and E_c respectively apply to reduced, oxygenated and carbon-monoxide bound hemoglobin. The concentrations C_r, C_o and C_c apply in similar fashion with the total concentration of hemoglobin, C, given by the sum of the three. Since a cuvette is used the optical path length, x, is common to all. The absorbance, A_i, at any

wavelength, λ_i, is proportional to

$$\ln (I_o/I_i)$$

The three expressions for the absorbance are solved on an analog computer for the unknowns C_r, C_o and C_c, and the percents of C_o and C_c present in C displayed along with C.

Telephone conversations with company personnel revealed that the hemolyzing agent was necessary to break down the red cell since in certain deseases it is abnormally large. Thus by breaking down the cells in all samples the same conditions are encountered. This factor may not be important when blood is analyzed from healthy individuals (as would be encountered in man-space programs) as the red cells would probably not differ substantially in size from one individual to the next.

It was further brought out in the telephone conversation that the percent carboxyhemoglobin is often overlooked in measurements made on hemoglobin with resulting errors. The percentage appears to run from about 2% in the case of a city dweller to as high as 10% in the case of a heavy smoker. This parameter, again, may be insignificant in the case of astronauts living in a controlled environment on a space mission. On the other hand, it certainly could be used as a monitor on the working efficiency of the air system of a space capsule and the condition of the subjects respiratory system.

The Waters Company of Rochester, Minn., manufacture the X-350 Oximeter. This instrument utilizes solid state circuitry and two photosensitive resistors to measure the absorbancy at two specifically chosen wavelengths. The photoelectric pickup is in two forms. One is used in conjunction with a cuvette and is discussed in this section. The other is in the form of an earpiece and is discussed in the next section.

Whole blood is circulated through the cuvette and suitable measurements made while the blood is in motion with a minimum flow in excess of 5cc/min. A lamp is used as a light source and filters are employed in the two photoelectric pickups used to accept light energy at wavelengths of 800 and 640 millimicrons respectively. The pickups are

followed by a linear differential amplifier whose output is proportional to the ratio of the light transmitted at the two wavelengths. The output meter itself is calibrated in terms of the percent oxygenated blood present in the blood in the optical pathway.

At 800 millimicrons the molecular extinction coefficients are identical for oxygemoglobin and reduced hemoglobin. At 640 millimicrons the coefficient for reduced hemoglobin is approximately 9 times larger# than for oxyhemoglobin. Since the blood is not hemolyzed, it is known that the analytical expression differs somewhat from Beer's law. Deviations result from the scatter of light by the cellular suspension and seem to be dependent upon the nature of the incident light, the depth of the sample, the particle concentration and the rate of flow of the concentration. The resulting relationship is not unique and is dependent upon the equipment used and can only be properly evaluated by experiment. It appears that the Waters company makes use of the usual approximation that Beer's law applies and under these conditions the voltage outputs of the two photoconductors are given by

$$\ln (V_1/V_0) = m \times E_1 \, C = m \times E_1 \, (C_r + C_o)$$

and

$$\ln (V_2/V_0) = m \times (E_{r2} C_r + E_{o2} C_o)$$

where V_1 and V_2 are the respective phototube output voltages at 800 and 640 millimicrons; V_0 is the output voltage of either phototube in the absence of light attenuation, m is a system constant, E_1 is the extinction coefficient for hemoglobin at the infrared wavelength of 800 millimicrons, and E_{r2} and E_{o2} are the respective extinction coefficients at 640 millimicrons for reduced hemoglobin and oxyhemoglobin. Under these conditions the relative oxygen saturation, S, given by the expression

$$S = C_o/C = \frac{E_{r2}}{E_{r2} - E_{o2}} - \frac{E_1}{E_{r2} - E_{o2}} \left[\frac{\ln V_2 - \ln V_0}{\ln V_1 - \ln V_0} \right]$$

Tait, G.R., et al, "A Theoretical Analysis of Some Errors in Oximetry", IEEE transcations on Bio-Medical Engineering, Vol. BME-13, No. 4, October, 1966.

In the event that the linear approximation to the logarithm can be employed the bracketed quantity in the previous expression can be replaced by

$$\left[\frac{V_2 - V_0}{V_1 - V_0}\right]$$

The Waters Company makes use of the linear approximation to the logarithm and further appears to use the approximation that at about 640 millimicrons $E_1 \approx E_{o2}$. Under these conditions the previous expression can be manipulated to give

$$1 - S = \frac{E_1}{E_{r2} - E_1} \left[\frac{V_2 - V_1}{V_1 - V_0}\right]$$

or

$$(V_2 - V_1) = \frac{(1-S)(E_{r2} - E_1)(V_1 - V_0)}{E_1}$$

This latter quantity, $(V_2 - V_1)$, is the input to the differential amplifier. The output, V, of the amplifier is related to the input by the differential gain, A. The quantities V_1 and A are adjusted by the calibration proceedure so that

$$\frac{A(E_{r2} - E_1)(V_1 - V_0)}{E_1} = 1$$

and then $V = A(V_2 - V_1) = 1 - S$

so that $S = 1 - V$

The indicated subtraction is carried out by applying V across a voltmeter and labeling the reading in terms of $(1 - V)$.

In view of the above it appears that errors are encountered because of the departure from Beer's law and the linearizing approximation for the logarithmic expression. The validity of the subtractive process introduced by the differential amplifier is completely dependent upon the accuracy of the assumption, $E_1 \approx E_{o2}$. If this latter assumption could not be made elaborate circuitry would have to be used to evaluate

the expression for S.

Literature study[#] indicates that approximations of this type together with light sources which are not monochromatic can lead to errors of the order of several percent. Additional errors will be introduced if carbon-monoxide bound hemoglobin is present. Finally, any instrument employing direct-coupled circuitry is bound to suffer from drift and other stability problems which become a factor in space applications. When non-hemolyzed whole blood must be employed error reduction requires the employment of stable and accurate data processing circuitry, close approximations to monochromatic light sources, and the use of a modified Beer's law in analysis. One cannot help but feel that more suitable light systems are available than the tungsten bulb and filter combinations used in the Waters instrument. Furthermore, pulsed light sources and digital techniques would enable the drift and stability problems to be virtually eliminated.

2 B. Ear Oximeters

The only commercial ear oximeter surveyed to date has been the Water's X-350 with earpiece input in place of cuvette. The earpiece is somewhat bulky and brings a tungsten bulb light source against one side of the pinna and two pickups consisting of filters and photoconductors against the other side of the pinna. A pressure capsule is also included so that the blood may be squeezed out of the optical path by increasing pressure as part of the calibration proceedure. Several adjustments are made on each subject before the final reading is taken.

This device seems typical of others mentioned in the literature since its geometry produces different optical paths for each light source. This factor taken together with the nonhemogenity of the bloodless tissue in each path and the varying depth of blood vessels causes additional errors in the Beer's law assumption.

As in the case of the cuvette, Beer's law is assumed to apply. Light attenuation is obviously assumed identical by the tissue in each optical

Ibid

pathway and at each wavelength. This assumption allows the common mode rejection of the differential amplifier to dispose of the tissue attenuation term. The input to the differential amplifier then becomes

$$V_2 - V_1 \approx V_0 \, m \, x \, (E_{r2} - E_1) \, C_r$$

where all symbols are the same as before except that x is the unknown average thickness of the blood in the optical path. The voltage, V_1, is adjusted to its previous value during the cuvette measurement by adjusting V_0 for each subject. The gain of the amplifier is then cleverly adjusted with the pressure capsule inflated and an artificial voltage inserted for V_2 which is equal to the known voltage V_1. Under this artificial condition the amplifier output becomes

$$V_a = A \, V_0 \, m \, x \, E_1 \, C$$

If A is adjusted to realized

$$V_a = \frac{E_1}{E_{r2} - E_1}$$

then the output voltage, V, under actual conditions of measurement becomes

$$V = \frac{C_r}{C} = 1 - S$$

and the oxygen saturation, S, is displayed on the same meter face as in the cuvette measurement.

The errors associated with this ear oximeter should be greater than those encountered with the cuvette version because of the different optical paths, the somewhat poorly understood effects of the ear tissue, and the dependence upon the common mode rejection of the differential amplifier to reject all undesired quantities.

III. SOLID STATE LIGHT SOURCES

Many of the present day systems utilizing light sources involve the use of incandescent sources. Some of the drawbacks of such sources are excess heat and bulkiness which is of primary importance as far as the comfort of the subject being instrumented is concerned. From a circuit implementation viewpoint further drawbacks are the broad spectral output and the difficulty of obtaining light modulation. The latter difficulty is of importance since modulation systems offer an opportunity to obtain higher rejection of unwanted background signals than that afforded with unmodulated or d-c systems.

Solid state light sources with their increased efficiency will operate with far less heat and power consumption. This in conjunction with their small size makes them particularly attractive where intimate contact with the monitored subject is required. The relative narrow bandwidths of the spectral output of semiconductor sources enhances the possibility of the use of multiple source-detector units. One such application, for example, would be in an ear oximetry system where the use of multiple wavelengths could increase the accuracy by additional data.

A most important advantage of solid state sources over incandescent sources is the case by which light modulation of the former can be obtained. Intensity modulation by variation of bias current can be obtained readily by means of semiconductor switches using minimal power.

At present, the major difficulty of semiconductor light sources is their lack of availability with specific spectral output. Consideration of this problem leads us to believe that this is not the result of inability in so far as the present state of the art of semiconductor technology is concerned. Rather, it appears to be that current demand for such sources does not warrant commercial exploitation.

This situation has led us to the consideration of designing and assembling an epitaxial crystal growing system for the purpose of fabricating light sources here at Northeastern in the laboratory. This capability would be enhanced by the university's integrated circuit facilities. Eventually it should be possible to extend our capabilities to the fabrication of compact efficient optical readout devices.

IV. MODULAR ELECTRODE BUFFER AMPLIFIER - (MEBA)

Two students have been conducting a literature survey of electrode measurement technology. The initial results of this search and discussions with members of the medical profession reveals that the required characteristics of a general purpose electrode amplifier are varied and contradictory in terms of the state of the art of solid state devices. Contradictions are exemplified by the specifications given by those individuals associated with both the medical and the engineering professions. The requirement that the signal output power exceed the total power consumption is one rather obvious discrepancy. The viability of data obtained by present day systems is limited since medical men in certain instances have not been inclined to investigate data other than that which correlates with symptoms obtained by more primitive methods. Bandwidth restrictions, for example, are in some cases tied to the reduction of unknown signals referred to as noise. In general, however, the overall characteristics appear to be high input impedance, low noise linearity and minimal power consumption. Bandwidth fortunately does not appear to be a major problem.

There are two approaches to be taken which can be differentiated as d-c and a-c systems. Both have their advantages and disadvantages. A d-c system affords the greatest simplicity since it represents basically an operational amplifier approach. An a-c system, such as a parametric amplifier, is fundamentally more complex due to the needs of modulation and detection.

Operational amplifiers are attractive from the viewpoint of their versatility. In addition to their capability of performing various computing functions they can also compare, regulate and detect linear as well as nonlinear signals. With open loop gains and input impedances of the order of 5×10^3 and 10^5 ohms repectively, the use of negative feedback simplifies signal processing to a function of the ratio of the source and feedback impedances.

Our first consideration has been directed toward the d-c operational amplifier approach using discrete commercially available

components. Aside from its size and versatility it offers an excellent possibility of operation using minimal power consumption. Minimization of over all size would dictate the use of mercury cells for power. Their low potential, about 1.3 volts, places a severe restriction on the use of active semiconductor devices to obtain stable operation with high input impedance, however, this does not appear to be insurmountable.

Field-effect-transistors, FET's, are available which are capable of providing input impedances greater than 10^9 ohms. In practice those impedances are generally not realizable because of thermal drift and noise limitations, but a target input resistance of 10^7 ohms appears feasable.

Of the two types of FET's currently available commercially only the junction FET appears to be useful because of the limitation of the small potential of the mercury cell. The desirable impedance of FET's requires that the device be operated above the pinch-off voltage, V_p. From the viewpoint of the operating point this would require a device with a V_p of less than about 0.6 volts. Thermal drift considerations add to this requirement since it is known that FET's have a minimum temperature coefficient near this value of V_p. For these reasons a search was made for such a junction FET. Having found a type whose V_p was of the order of 0.26 volts the design of a prototype amplifier was initiated.

In addition to a stable input resistance the following target characteristics appear to be feasable; an output voltage swing of $\pm$ 1 volt with a maximum current drain of less than $\pm$ 3 ma, an open loop gain of 5×10^3 with rated load, a 2000 hz 3-db point for full output, a broadband noise voltage less than 2 μ volts and an operating temperature range from 10°C to 40°C. In view of the much lower frequency range of many medical signals the target bandwidth of 2000 hz may need to be revised downwards to reduce output noise.

A survey of the available operational amplifiers has found only two which were capable of operation from mercury cells at 1.3 volts. One of these did not have either the temperature stability or the input impedance

desired. The other came the closest to matching the previously listed characteristics, however, it was found that this amplifier had been withdrawn from the market because of thermal difficulty.

It is possible to obtain the specified amplifior characteristics using an a-c approach. These considerations will be taken up in Section V.

V. PROJECTIONS

5 A. A Speculative Ear Oximeter

It is felt that many of the errors encountered in ear oximetry can be reduced by the employment of compact light sources with low spectral spread which are capable of pulsed operation. Compact light sources could be clustered on one side of the ear to the extent that a common optical pathway could be employed. If each light source were then pulsed on in time sequence a single photodetector could be employed and operated in a synchronous mode. The dwell time for each light source would have to be long enough to allow a meaningful reading to be taken at each light wavelength. The sample rate, on the other hand, would have to be much higher than the blood pulse-rate to guarantee that the same conditions would apply during each wavelength reading in a given frame (i.e. the time required to cycle through all light sources in the cluster). The pulsed mode of operation would eliminate the usual problems associated with direct-coupled circuitry. If it developed that the light sources themselves were sufficiently monochromatic and the pulsed rate not adverse, then the filtering problem usually associated with tungsten light sources would be eliminated. Furthermore, a pressure capsule in the earpiece can be eliminated by using an additional light source if the effects of tissue are the same over the common optical path at each of the wavelengths employed. Under these conditions the absorbance at any wavelength, i, would be given by

$$A_i = x\left[E_{ri}C_r + E_{oi}C_o + E_{ci}C_c \right] + yT_i$$

In this expression the symbolism is the same as that employed in Section 2 A with the addition that x is the depth of the blood, y the tissue depth, and T_i the extinction coefficient for the tissue. If four light sources were employed and T_i were constant for each, then simultaneous solution of the four resulting equations would allow the ratios C_r/C, C_o/C and C_c/C to be obtained.

The speculative ear oximeter described above is only feasible if more factual information is obtained in connection with the many assumptions. Accordingly, a student is currently engaged in a literature search of ear oximeters. Staff effort currently is being given to the feasibility of designing and assembling an epitaxial crystal growing system for the purpose of fabricating compact light sources which are suitable to this application.

5 B. Electrode Amplifiers

Work on the present MEBA should be continued to prove the feasibility of using discrete components. The next logical step is the use of integrated circuitry. This opinion is based upon the fact that sixty percent of the monolithic linear integrated circuits (IC) used in systems over the past two years have been operational amplifiers. IC op-amplifiers are generally more complex than their discrete counterparts, but they can be made much smaller while offering some other fundamental advantages. The close proximity of the active devices, for example, allows for some radical biasing techniques which result in superior tracking at reduced current levels.*

Consideration should be given to a-c systems for achieving the desired amplifier characteristics. The basic approach is to convert the d-c or low frequency signal to a higher frequency, amplify using a-c amplifiers and demodulate to obtain the original signal. The shifting of the frequency of operation has several advantages. One is to remove the operating point from the range of frequencies for which semiconductors are particularly noise prone. Another is that an a-c amplifier is less subject to drift and is simpler to design at the higher frequencies.

One method of achieving frequency conversion is the classical method of the chopper stabilized d-c amplifier. The advent of FET's with zero off-set voltage makes possible an all solid state chopper stabilized

* Widlar, R.J., "Some Circuit Design Techniques for Linear Integrated Circuits", IEE Trans. on Circuit Theory, December 1965 pp 586-590.

system thus eliminating the mechanical aspects of the earlier versions and realization of a substantial reduction in size.

A second method of frequency conversion is the use of varactor diodes in the input stage whose change of capacity with input signal results in a change of frequency of a reference oscillator. Noise and bias currents for the varactor diodes should be considerably smaller than those encountered with present day FET amplifiers. Input impedances of the order of 10^{13} ohms should be possible. Such an amplifier should be able to replace electrometer tubes which traditionally have been used and whose superior performance in the measurements of minute currents below 10^{-9} amperes has not been challenged as yet by the new semiconductor devices.

In the past the use of varactor diodes has been limited to UHF amplifiers. Their use as noted in the previous paragraph has only recently been suggested as a new approach to operational amplifiers. Of the few available commercially none can operate at the desired low levels. Thermal stability and drift are factors which are not well known at present and which require study.