Quarterly Progress Report Number 2

Transcutaneous Analyte Measuring Methods
(TAMM Phase II)

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Naval Medical Research and Development Command

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Abstract

The primary objectives of the second quarter of Phase II TAMM were the following:

1. The design of a near infrared (NIR)-800 photodiode array spectrometer, two of which would be used in clinical testing starting in June of 1992.

2. The development of data acquisition and advanced pattern recognition software for analyzing the data collected with the spectrometer.

3. Completion of an ongoing, internal test program with the BI-102 Infrared Analyzer.

4. The establishment of a clinical test plan and protocol with the Naval Medical Research and Development Command in Bethesda, Maryland, and with The Blood Center of Southeast Wisconsin.

The status of the major objectives outlined above is summarized below and detailed in the body of the report.

1. Delivery of the two instruments to be used in clinical testing has been delayed until June 1, 1992 due to difficulties in completing the experiments with the gallium arsenide (InGaAs) array, fiber-optic link and optrode. A revised schedule is included as Figure 1.

2. The development of the data acquisition and advanced pattern recognition software is proceeding on schedule. The data acquisition software has been completed. Many elements of the advanced pattern recognition software have been used experimentally in the analysis of the data collected with the BI-102.

3. The internal BI-102 preclinical trials have been completed. One hundred and twenty sets of d . were collected: 80 reflective and 40 transmissive. The data were only analyzed for glucose because this analyte is easily measured with home glucose testing instruments and reagents. In general, the results confirm the feasibility of noninvasive NIR blood analysis.

4. The test plan and protocol have been submitted for review to both the Naval Medical Research and Development Command of Bethesda, Maryland and The Blood Center of Southeast Wisconsin.

Instrumentation

Development efforts during the quarter were concentrated on working with the new Epitaxx InGaAs array (256 x 1). Bench system tests have demonstrated that adequate light can be received at all wavelengths from 1200 - 1800 nm in a reflective transcutaneous near infrared spectral environment. The reception of adequate light throughout this entire waveband is essential for success of the project. The remainder of the NIR-800 system is similar to previous Biotronics systems currently in the field that operate in the ultraviolet-visible spectral region.

A block diagram of the NIR-800 system with hardware details is provided in Figure 2. All major modules are indicated. A bifurcated fiber transmission link is used to transmit and receive light through a reflective optical probe. The geometry of the spectrograph also is delineated in Figure 2, including the concave grating and the 256 element array.

It should be strongly emphasized that the NIR-800 will function in a data acquisition mode during clinical tests conducted during the year 1992. Collected data will be processed at Biotronics to develop suitable algorithms for noninvasive field determination of blood analytes. These algorithms are developed in a portion of the data called a learning or training set that will then be used to estimate blood analyte concentrations in the remainder of the data called a test set. During the second year of the Phase II SBIR, near infrared field instruments developed at Biotronics will be used to determine on-site values of blood analyte concentrations based on the algorithms developed from NIR-800 clinical data.

Analytical Software

NETGEN

The new genetic neural network, NETGEN, was described in the previous report. NETGEN is expected to be the primary analytical technique used for the project. A secondary analytical technique, used in Phase I, is K-nearest neighbor analysis. Phase I test results comparisons strongly favored the NETGEN analytical approach. Both analytical techniques will be used throughout the Phase II clinical trials.

Preclinical Testing

The Biotronics BI-102 Infrared Analyzer was used to conduct four series of preclinical tests during the quarter. The BI-102 uses a monochromator, a chopper and a lock-in amplifier. Despite the use of old technology, the data collected provided highly useful information. The results of the BI-102 experimental testing of normal patients are summarized below. Four separate test sequences were performed:

- 40 normals (glucose) reflective

- 40 more normals (glucose) reflective

    1. reflective
    2. transmissive

- 25 measurements of a single local diabetic patient

Spectral standards were also run for comparisons with the patient data.

Analyses of the three sets of data collected from the 40 normal patients were conducted using 30 sets of data for the learning sets and 10 sets of data for the test sets. The analysis of the data for the diabetic patient was conducted using 20 sets of data for the learning set and 5 for the test set.

Test Results

GLU1 (40-patient reflective)

NETGEN

Average error	4.57 mg/dl (6.7%)
t-value	4.81

K-Nearest Neighbor

Average error	5.79 mg/dl (7.59%)
t-value	3.53

GLU2 (40-patient transmissive and reflective)

Transmissive

NETGEN

Average error	5.74 mg/dl (7.86%)
t-value	4.52

K-Nearest Neighbor

Average error	4.50 mg/dl (6.15%)
t-value	7.89

Reflective

NETGEN (Available in next report)

Average error	
t-value	

K-Nearest Neighbor

Average error	8.45 mg/dl (11.84%)
t-value	2.06

These results indicate that both the transmissive and reflective spectrometric techniques are effective, and that both NETGEN and K-nearest neighbor are possible analytical options.

GLUCH (25 measurements of a single diabetic patient)

Transmissive

NETGEN (Available in next report)

Average error	
t-value	

K-Nearest Neighbor

Average error	21.81 mg/dl (9.71%)
t-value	2.42

Reflective

NETGEN (Available in next report)

Average error	
t-value	

K-Nearest Neighbor

Average error	46.42 mg/dl (17.53%)
t-value	3.56

Clinical Test Plan and Procedures

Proposed clinical test protocols have been submitted to the Naval Medical Research and Development Command in Bethesda, Maryland, and The Blood Center of Southeast Wisconsin in Milwaukee, Wisconsin. The clinical test contacts at Navy-Bethesda are Dr. Randy Frost and LCDR Lisa Hildebrand. Plans originally called for the completion of and agreement on both clinical test protocols prior to June 1, 1992. Actual completion should be sometime in April, 1992 for The Blood Center (Wisconsin), but the Navy does not expect full approval until the middle of July. A copy of the test protocol and volunteer consent form submitted to The Blood Center of Southeast Wisconsin are included with this report.

NAVY TAMM NIR-800 DEVELOPMENT SCHEDULE

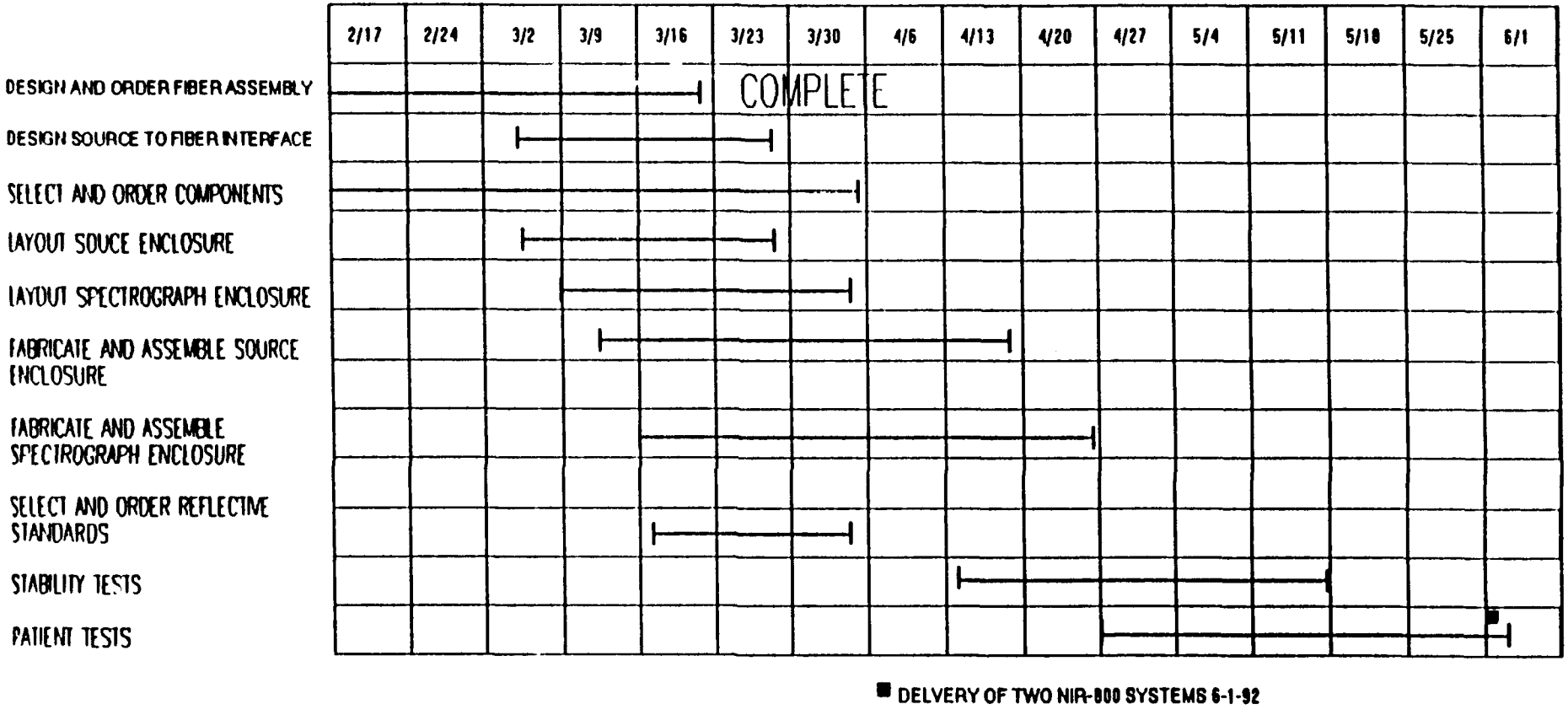

Figure 1.

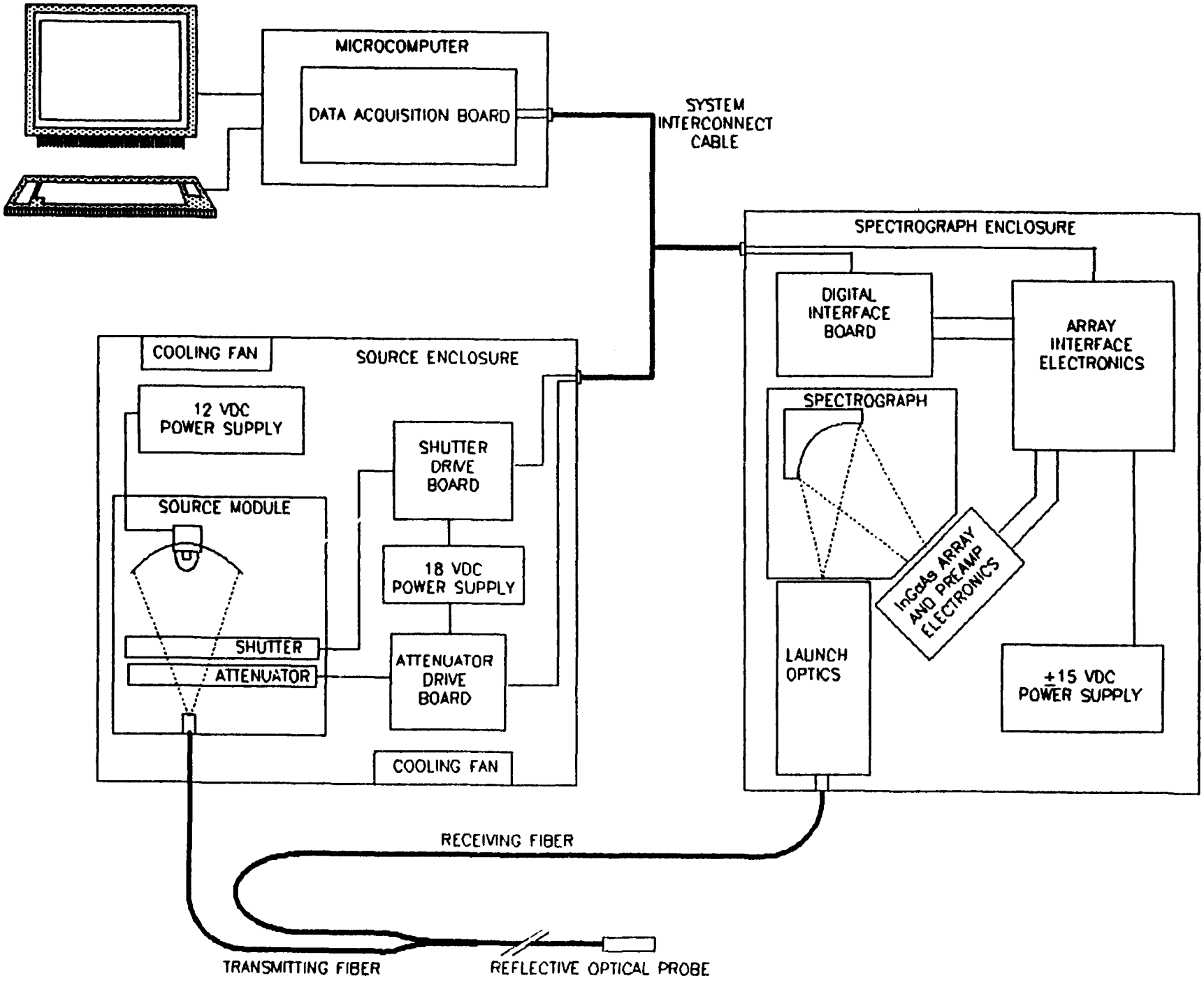

Figure 2. NIR-800 Array Spectrometer Block Diagram

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