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System Theory in Medical Diagnostic Devices: An Overview

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Abstract— **Medical Diagnostics refers to testing conducted either *in vitro* or *in vivo* to provide critical health care information for risk assessment, early diagnosis, treatment, or disease management. Typical *in vivo* diagnostic tests include the computed tomography scan, magnetic resonance imaging, and blood pressure screening. Typical *in vitro* diagnostic tests include cholesterol, Papanicolaou smear, and conventional glucose monitoring tests. Historically, devices associated with both types of diagnostics have used heuristic curve fitting during signal analysis. However, since the early 1990s, a few enterprising engineers and physicians have used system theory to improve their core processing for feature detection and system identification. Current applications include automated Pap smear screening for detection of cervical cancer and diagnosis of Alzheimer's Disease. Future applications, such as disease prediction before symptom onset and drug treatment customization, have been catalyzed by the Human Genome Project.**

I. Introduction

MEDICAL diagnostics refers to testing conducted to provide critical health care information for risk assessment, early diagnosis, treatment, or disease management. In the 17th century, clinicians diagnosed diabetes through the level of sweetness in urine samples. By the end of the 18th century, when the first hospital laboratory was established in Britain, diagnostics started to become recognized as a standard and indispensable part of health care. Current *in vivo*, or within the body, diagnostic tests include the computed tomography scan, magnetic resonance imaging, and blood pressure screening. Current *in vitro,* or from an external body specimen, diagnostic tests include cholesterol, Papanicolaou (Pap) smear, and conventional glucose monitoring tests.

Certainly, *in vivo* diagnostics are considered medical devices. The basic components of an *in vivo* diagnostic are shown in Figure 1. Here, data are acquired from a patient, using a sensor technology that outputs an analog electrical signal. The signal is digitized, and subjected to signal processing. The signal processing may be heuristic in nature, or could include digital signal processing or imaging. Manual (human) or automated detection then occurs to produce a diagnostic result.

Per Food and Drug Administration (FDA) classification, *in vitro* diagnostics (IVDs) are also considered devices. IVDs are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions. The basic components of an IVD are shown in Figure 2.

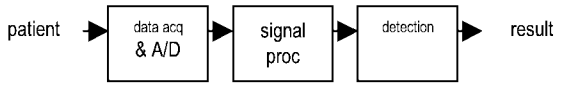

Fig. 1. *in vivo* diagnostic components.

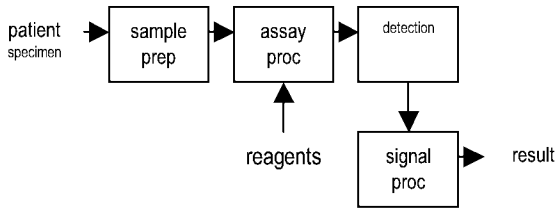

Fig. 2. *in vitro* diagnostic components.

Here, a patient specimen is subjected to sample preparation, such as dilution or thermal cycling. In many cases, reagents are added; assay processing then proceeds. Five types of applications are enabled during assay processing. General chemistry is based on quantitative measurement of base compounds, while immunochemistry is based on the antibody-antigen response. Hematology/cytology is based on the blood and cells; microbiology/infectious disease is based on detection of disease-causing agents. Finally, molecular tests study DNA and RNA to detect specific genetic sequences [1]. Detection occurs using mass spectroscopy, optics, or another technique. Signal processing is then conducted to produce a result.

II. Historical Uses Of System Theory

A. System Theory Definition

Signal processing may be system theory-based. System theory is the transdisciplinary study of the synthesis and design of systems and the analysis of their performance. Many of the problems present in diagnostic devices can be solved efficiently with standard digital signal processing and control techniques, which are subsets of system theory [2]. For example, in the 1990s, Aspect Medical Systems and Neopath utilized digital signal processing to increase

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detection sensitivity, without sacrificing specificity.

B. *In Vivo Example*

In 1987, Nassib Chamoun founded Aspect Medical Systems to investigate depth of anesthesia monitoring, based on the processing of electroencephalograms (EEG). Eventually, using more than 5000 patient training data sets, Aspect developed the bispectral index (BIS), a parameter between 0 to 100 that corresponds to the range of brain activity between flatline EEG and wakefulness. BIS was developed by using multivariate statistical models to derive the optimum combination of EEG variables calculated in the frequency domain [3]. In a randomized, double-blind, multicenter trial of 2463 patients, BIS-guided anesthesia reduced the risk of awareness in at-risk adult surgical patients undergoing relaxant general anesthesia by 82% ($p=0.022$) [4]. This platform is now being investigated for diagnosis of preclinical stages of Alzheimer's disease and antidepressant efficacy [5].

C. *In Vitro Example*

In 1998, Neopath's AutoPap cervical cancer screener became the first primary (unassisted) screener approved by FDA. Now part of Tripath Imaging, AutoPap is still the only primary screener with FDA approval. A key technology that enabled unassisted screening was the use of fuzzy models.

The fuzzy model was developed by Dr. Stanley Cohen, a noted cytologist whose 1969 monograph became the basis for the Bethesda System of Pap smear classification. With the assistance of Dr. James Lee and his Neopath engineers, Cohen learned fuzzy model theory, and converted his personal classification system into a linguistic fuzzy model. Based on 4,174 slides of training data, the resulting model had 6 inputs and 24 cell sub-classification outputs [6].

In a primary screening validation study of abnormal Pap smear categories, the classifications of 25,124 slides at five commercial laboratories were compared between AutoPap and cytotechnologists. In all four categories (ASCUS+, LSIL, LSI+, HSIL), the AutoPap sensitivities were statistically equivalent, and showed numeric superiority to the cytotechnologist sensitivities [7].

III. Emerging Medical Diagnostic Devices

A. *The Effect of the Human Genome Project*

New molecular IVDs are expected to emerge in the near future, catalyzed by identification of the human genome sequence. The complete sequence of the entire human genome was published in 2003. Within the new field of proteomics, which is the study of protein expression patterns, protein interactions, and protein pathways, scientists and engineers are searching for biomarker molecules. Biomarkers indicate an alteration of the physiologic state of an individual, in relation to health or disease state, drug treatment, toxins, or other environmental challenges [8].

B. *Disease Prediction Before Symptom Onset*

Using screening biomarkers with acceptable specificity and sensitivity, new IVDs will predict individual disease susceptibility before disease onset. For example, genetic testing for BRCA I and II mutations can indicate individual risk for developing breast or ovarian cancer. This knowledge will enable patients and their health providers to take steps to minimize risks and avert future adverse health outcomes [1].

C. *Drug Treatment Customization*

Further, using prognostic, stratification, and efficacy biomarkers, new IVDs will enable clinicians to customize patient drug treatment. Once disease status is established, prognostic markers will predict the likely disease course and influence the aggressiveness of therapy. Stratification markers will predict the likely response of a drug, predetermining if a patient is a "responder" or "nonresponder". Efficacy markers will monitor the efficacy of drug treatment. For example, in rheumatoid arthritis, it is important to discriminate slow from fast progressors, and treat them with appropriate drugs. The collagen turnover of a set of markers can be used to monitor efficacy [8].

IV. Future Uses Of System Theory

A. *Detection Algorithms*

With emerging new tests comes the opportunity for further utilization of system theory. An informal rule in diagnostic systems development is the 30-30-30 ratio: 30% of the development process is chemistry, 30% is detection instrumentation technology, 30% is software, and 10% is luck [9]. In recent years, IVD innovations have been based on increased chemistry and detection sophistication. As signal-to-noise ratios decrease but the demand for diagnostic specificity remains constant, detection algorithm development may finally shift from heuristic to system theory-based implementation.

B. *Bioinformatics*

During biomarker discovery, bioinformatics platforms will be used to identify true markers from groups of marker candidates. Bioinformatics applies system theory to make life sciences data more understandable and useful. As in classic system identification, potential markers are identified from training data, and tested in validation data.

As an example, the Proteome Quest software application from Correlogic Systems uses a genetic algorithm and cluster analysis to determine a marker candidate's ability to distinguish between disease and non-disease. This application analyzed 15,500 possible mass-to-charge ratios

present in collected human serum for identification of an ovarian cancer biomarker. During validation of the identified biomarker, all 18 patients with stage I cancer and patients with later-stage disease were correctly identified; 63 of 66 subjects without cancer were also correctly identified. This resulted in a sensitivity and specificity of 100% and 95%, respectively. Other system theory approaches for biomarker identification include hierarchical-clustering algorithms and neural networks [10].

V. Conclusion

To date, system theory has been underutilized within *in vivo* and *in vitro* diagnostic tests. Using system theory in detection algorithms may increase the specificity of some new IVDs. Its use, through bioinformatics, is crucial in biomarker identification for molecular IVDs.

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