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Incorrect or Defective Pill Detection

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Abstract

Identification of defective tablets at the time of creation is currently infeasible. Medications are dispensed to patients in health care locations without a final check to see if a patient is receiving the correct medications. A prototype of a practical embedded, network based sensor system to solve both problems is described in this paper.

1. Introduction

Administration of incorrect medications by professional caregivers is estimated in 1997 to have killed as many as 44,000 to 98,000 Americans after prescriptions were filled [1]. These numbers are likely to be underestimates due to unreported deaths. To put this number in perspective, use of incorrect medication is the eighth leading cause of death in the United States and actually kills more people in a given year than traffic accidents, breast cancer, or AIDS. The situation is no better in 2007.

A secondary issue is defective tablets coming off a pharmaceutical production line or mistaken packaging. Many errors are readily visible and are caught immediately. However, not all are detected and the defective or mislabeled tablets reach the marketplace.

In Section 2, we discuss the advantages of using a real-time dynamic approach instead of using static data.

In Section 3, we discuss why catching errors at the pharmaceutical production and packaging areas is essential to reducing recalls and should be part of process analytical technologies.

In Section 4, we describe an integrated acoustic sensing and processing device. A handheld version can also be used to identify medications before a caregiver delivers them to individuals. We also describe a cyber physical system (CPS) to detect incorrect or defective tablets.

In Section 5, we provide simple results based on a prototype system that has been built and tested in a limited manner.

In Section 6, we provide conclusions and briefly describe what needs to done next.

2. Dynamic versus static data

A data driven system allows for the implementation of real-time data to model or predict a measurement or event. By incorporating data dynamically rather than statically, the predictions and measurements become more reliable.

Consider weather forecasting. If predictions are made based on static data collected from sparsely distributed sensors, then rapidly changing conditions often make a prediction obsolete shortly after it is made. A more reliable forecasting system continuously incorporates real-time changes from many sensors into its predictions so that the forecast is always built around current conditions. As the conditions change, so does the forecast, in real-time.

Data driven applications have the ability to guide their measurement processes and refocus their resources, much as forecasts guide US Air Force 53rd Weather Reconnaissance Squadron aircraft away from calm seas and into the eyes of hurricanes to concentrate their data collection. The information collected makes possible advance warning of hurricanes and increases the accuracy of hurricane predictions and warnings by as much as 30 percent [2].

3. Catching mistakes at the source

Numerous large pharmaceutical manufacturers outsource their small-scale manufacturing needs as a

way of reducing cost or meeting their production deadlines. A contract manufacturer may make several kinds of pills that are similar in appearance at almost the same time, e.g., testing various dosages and placebos for clinical trials. A contract manufacturer may also produce pills for multiple companies. One way to reduce the possibility that pills may inadvertently become confused or contaminated is to employ a rapid and nondestructive means of verifying tablet identity. Such systems for identifying contaminated or mislabeled products must be strategically placed to prevent problems with pills before they are shipped. Process analytical technologies (PAT) on the production line should have the ability to work in real-time. Currently there are no foolproof methods to eliminate mislabeling or contamination. As a result, millions of pills are recalled in some years.

For example, in November 2006, 11 million bottles of contaminated acetaminophen were voluntarily recalled by the Perrigo Company of Allegan, Michigan due to contamination of the tablets with metal wire **3** The FDA admits that current good manufacturing processes (cGMP) have reached their limits and better "science-based" approaches are needed to insure product safety [3]. PATs are designed to prevent large recalls by detecting problems before they occur.

4. An integrated sensing and processing approach

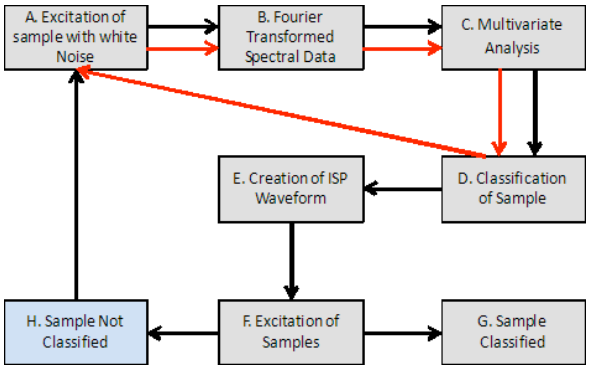
Integrated sensing and processing acoustic resonance spectroscopy (ISP-ARS) is a novel approach to conventional acoustic spectroscopic techniques. In ISP-ARS, an ISP acoustic waveform is created such that it comprises only the distinguishing spectral details associated with an analyte in question. Fourier transform acoustic resonance spectroscopy (FTARS) is used to develop ISP acoustic waveforms employed in differentiating different drugs.

ISP-ARS is fast and non-destructive. Acoustic methods are able to deeply penetrate many types of opaque packaging, in contrast to near-infrared and other optical methods. The ability to penetrate many types of packaging can be a distinct advantage in preparation of clinical trial lots, where drugs and placebos must be blinded from users. As a PAT, a series of ISP-ARS sensors could potentially scan every pill produced by a manufacturer, enabling the removal of only those pills that did not meet quality standards. A dynamic system should control a manufacturer's product line based on measurements from a series of ISP-ARS sensors, adjusting process conditions and ingredients in real time based on actual process measurements [4-5].

ISP-ARS reduces the time required for processing that is normally observed with full spectrum FTARS. An ISP acoustic waveform is the result of chemometric analysis of the FTARS spectrum. By weighting the frequency changes according to their individual component scores, an acoustic waveform can be made that excites only those frequencies important to the analyte under observation.

The ISP output is a voltage that can be read immediately and corresponds to only the analyte under investigation.

Creation of the ISP acoustic wave begins with the chemometric analysis of the initial FTARS data. Therefore, FTARS itself makes a prediction about what will work as an ISP acoustic waveform for a given set of samples. This training process can be viewed as a cyber physical system when the performance of the ISP waveform is continuously monitored and the ISP waveform is continuously adjusted through retraining.



The red arrows indicate the traditional FTARS cycle. In traditional FTARS, samples are scanned and classified according to their inter-cluster distances found via multivariate analysis (A-D). This process is repeated for each sample or groups scanned. With ISP-ARS the FTARS data is used as a predictor and an ISP acoustic waveform is constructed from the prediction (E). Once the ISP waveform is constructed the traditional FTARS cycle is not needed. Samples scanned with the ISP waveform are classified according to their voltages (F-G). If a sample cannot be classified (H) then FTARS is employed and a new ISP acoustic waveform is constructed chemometrically with a training set that it includes the new unknown. As samples change the ISP waveform can adapt to the new data.

FTARS is well established and has been shown to differentiate drugs, powders, liquids, as well as predict dissolution rate in otherwise identical samples.

FTARS is nondestructive and complete scans can be made in seconds, therefore it should be a prime candidate for use as a PAT.

Unfortunately, FTARS relies on intensive computer processing following data collection due to the amount of information gained in each scan. An ARS spectrum recorded over the interval of 20 Hz to 20 kHz with a sample rate of 44.1 kHz for one second generates a substantial amount of data (44100 data points). Chemometric analysis of multiple FTARS data sets computationally demanding and limits the production rate of tablets, especially if 100% tablet inspection is considered.

ISP-ARS reduces the computational burden of FTARS because it directly produces the analyte identity as an output. ISP-ARS is fast enough to not limit production rates.

5. Preliminary results

ISP acoustic waveforms composed of 10, 100, and 1000 frequencies were used to identify several toll-manufactured drugs. The pills used in this study were aspirin, acetaminophen, D-tagatose, ibuprofen, vitamin C, and vitamin B. It was found that only the top 10 frequencies were required to properly classify each pill used in this study. Intra-cluster distances were calculated to be less than 3 multidimensional standard deviations (MSD) for each pill type. The average accuracy of prediction was 98.47, 97.45 and 95.41 percent for the 10, 100 and 1000 frequency component acoustic waveforms respectively.

6. Conclusions

We have described a prototype cyber physical system for use in identifying defective or mislabeled pills. Integrated sensing processing acoustic resonance spectroscopy has the ability to differentiate between different types of pills in contract manufacturing and bedside applications.

The results are preliminary and much more research and development will be necessary in order to produce systems that can be deployed on pharmaceutical manufacturing lines. A handheld version that can be networked needs to be refined so that caregivers can correctly identify all pills before giving them to patients.

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