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Data-Driven Pill Monitoring

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Abstract

We describe a viable dynamic system to guarantee that pills delivered to a patient are what were prescribed, of sufficient quality to be effective, and within the correct time frame. A handheld device that identifies pills is also described that is suitable for use by health care providers. Issues of patient privacy, network security, and interacting with multiple databases are inherent to the entire process.

Key words: dynamic data-driven application systems, cyber-physical systems, integrated sensing and processing, ISP, accoustic resonance spectroscopy

1. Introduction

In this paper, we describe a dynamic data-driven application system (DDDAS), or cyber-physical system (CPS), to improve the quality of care giving in medical environments. One of the major causes of death in the world is patients being given the wrong medication or the correct medication at the wrong time.

We describe a handheld device that can be used to monitor pills as they are dispensed, correctly identify the pills, and securely interact with multiple levels of databases to ensure the timely distribution of the pills.

In Section 2, we provide background material on why this topic of interest and the scope of the problem in the United States. In Section 3, we describe the handheld device. In Section 4, we describe the algorithms that need to be run on a regular basis in order to ensure high quality results of the pill identification. In Section 5, we make some conclusions.

2. Background material

Since the 1960s, pharmacists, pharmaceutical scientists, and clinicians have studied medication errors. In that time, the rate has not significantly decreased: 1 out of 10 of the medications given to patients in the hospital on average are incorrect [1]. This study found that the best way to find the errors was through having an independent observer compare what the doctor ordered to the medication actually observed being administered to the patient. The best estimate was that approximately one out of 100 of those errors harms or kills a patient, that an average 400-bed hospital harms approximately one patient per day due to medication errors, and each medication error costs the hospital an average of $4,000.

Several precipitating events have brought the medication error problem to national attention since the year 2000. A few years ago a health reporter for the Boston Globe, Betsy Lehman, died from an overdose during chemotherapy. Two large studies done by the Harvard Medical Group, one in Colorado and Utah and the other in New York, found

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that adverse events occurred in 2.9 and 3.7 percent of hospitalizations, respectively. In Colorado and Utah hospitals, 6.6 percent of adverse events led to death, compared with 13.6 percent in New York hospitals. In both of these studies, over half of these adverse events resulted from medication errors and could have been prevented. Two Harvard physicians, Dr. David Bates and Dr. Lucian Leape, contributed the most to the studies. Dr. Bates' recommendation: hospitals should invest heavily into computerized physician order entry (CPOE) systems that can be checked by other personnel carrying accoustic resonance spectroscopy combined with integrated sensing and processing (ARS-ISP) devices when they handle or deliver paper cups carrying the medications to the patients.

The National Institute of Medicine's first report on medication errors, "To Err is Human" [2], notes:

> "From 1983 to 1998, U.S. fatalities from medication errors increased by 243%, from 2,876 to 9,856. This percentage increase was greater than for almost any other cause of death, and was higher than the increase in the number of prescriptions."

When extrapolated to the over 33.6 million admissions to U.S. hospitals in 1997, the results of the study in Colorado and Utah imply that at least 44,000 Americans die each year as a result of medical errors. The results of the New York Study suggest the number of deaths may be as high as 98,000. Even when using the lower estimate, deaths due to medical errors exceed the number attributable to the 8th-leading cause of death. More people die in a given year as a result of medical errors than from motor vehicle accidents (43,458), breast cancer (42,297), or AIDS (16,516).

The report recommended improving the safety of hospital medical care by investing in high tech technology such as ARS-ISP CPS technology. An ARS-ISP CPS device provides a better bedside way for an independent observer holding a paper cup of plain white tablets to find the errors, by comparing what the doctor ordered in computerized physician order entry (CPOE) systems to the medication actually observed being administered to the patient.

In 2002, Flynn and Barker published a report "Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities" [3]. This study found that observers detected 300 of 457 pharmacist-verified errors made in 2556 doses (11.7%) compared to 17 errors detected by chart review and 1 error detected by incident report. The independent observation method remains the "gold standard" for detecting medication errors: very effective in comparison to self reporting (most common) or chart review, but independent observation is very expensive. To protect against the Hawthorne effect [4] (a form of reactivity whereby subjects improve an aspect of their behavior being experimentally measured simply in response to the fact that they are being studied, not in response to any particular experimental manipulation), the observers are unaware of the doctor's order at the time they observe the medication being administered. Unfortunately, this means that there is a 24-hour "gap" between the time the error occurs and the time it is detected. Thus, the method primarily provides feedback to nurses, who change their procedures to prevent medication errors. Over time, this method has been proven effective to reduce the rate of medication errors. However, only 300 of 457 pharmacist-verified errors would be detected. Part of the remaining problem is that most tablets simply do not have enough distinguishing features to make an error easily detectable by an independent observer. ARS-ISP CPS is the best way to reduce the cost of checking medications because it enables many different people in the health care loop with different kinds of training to easily identify the tablets with a handheld device and to compare the analysis instantly with the CPOE.

The medication error problem remains significant and has gained national attention. There are two distinct problems: measuring error rates and decreasing error rates. Most technology has been focused on addressing the second need (CPOE, bar coding, etc.) without addressing the first. Thus, hospitals implement the technology, but have no way to measure its success. The independent observation method is currently the most accurate method to measure the rate of medication errors in the field, but doesn't directly detect medication errors and is too expensive for hospitals to adopt without a federal mandate. An ARS-ISP CPS system provides instant detection of errors, thereby also decreasing medication error rates. It will be safer from a patient standpoint because the independent observer is really a CPS that can catch the error before it actually occurs, and more cost effective because it does not require separate trained, independent observers.

3. A handheld device

The CPS device uses integrated sensing and processing acoustic resonance spectroscopy, which is a novel approach to acoustic spectroscopy that can be implemented using instruments as simple as an MP3 player or far more complex depending on the environment that ARS-ISP will be used in.

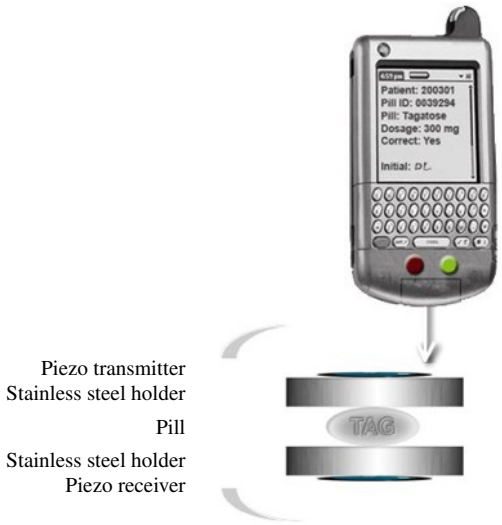

Figure 1: PDA and pill detection

The ARS-ISP CPS device needs to be small enough to be carried easily by a medical caregiver yet have enough capabilities to identify pills, patients, and communicate wirelessly with databases on potentially remote computers. In Figure 1 is a view of the basic components assuming the device communicates using a personal desktop accessory (PDA). Many smart phones are candidates as a replacement for the PDA.

Initially, we are targeting one pill detection at a time. Obviously this will need to change over time to identify the contents of a paper cup full of pills, as is the usual delivery container for pills at medical facilities and nursing homes.

The databases that need to be communicated with include the following:

- The patient's medical history, including possibly allergies and bad reactions to medications so that a patient is not accidentally given medications that are harmful.
- The pharmacy or pharmacies that issues the medication(s) and that have the original prescription(s) so that the medications can be verified each time.
- Compare drugs to the patient's medical history to determine if the drugs are indicated for the conditions observed.
- Generate a warning if the prescribed dose falls into a range identified as an overdose in the package insert.
- The time frame that the medications can be given safely and the complete history of when the medications were given in the past.

The information is quite sensitive and numerous laws now exist to ensure privacy for the patient. Significant computer security issues have to be addressed. Further, at this point, the set of databases that we need to access are, in general, not available under any circumstances. The U.S. governement is currently pursuing research programs to make online medicine records a reality.

We can deliver an infinite number of acoustic spectra, but that defeats the creation of a small, embedded CPS device that is useful in itself. Instead we choose a small number of spectra, which changes slightly over time based on environmental and personnel factors.

Once the spectrum of a sample has been collected, it will be classified to determine the substance present. The Bootstrap Error-adjusted Single-sample Technique (BEST) [5] is the analytical basis of our ARS-ISP CPS device, and

the foundation for the pill chemical identification library. The BEST metric is a clustering technique for exploring distributions of spectra in hyperspace.

A sample spectrum will be compared to each substance in a biogeochemical and industrial library based on its direction and distance, measured in standard deviation units, from the known substances. BEST handles asymmetric standard deviations surrounding each substance nonparametrically, allowing more precise discrimination than other metrics, e.g., a Mahalanobis distance [6]. A sample within 3 standard deviation units of a substance will be considered to be composed of the matching substance while others will be classified as unknown substances.

For a given library entry, the BEST algorithm will be suitably approximated using multiple linear regression to substantially reduce computational requirements. In this implementation, BEST standard deviation units will be precalculated before the ARS-ISP CPS device is deployed in a large number of directions from the population means, and multiple linear regression will be used to fit the standard deviation contours as a function of direction.

The BEST classification algorithm will be performed in situ, allowing a sensor to classify many samples, only notifying the simulation when an interesting substance is found. An initial library will be computed based on substances likely to be found in the target environment. When a substance unknown to the BEST library is found or is out of range (indicating a defect or foreign substance entirely), the CPS will reject the pill with the appropriate reason given.

The data-driven application is comprised of distributed processes that execute on different ARS-ISP CPS devices and cooperate by exchanging messages with a server to achieve a common objective. An application requirement is that the processes must accomplish these tasks by specific deadlines, which are nearly immediate in time. The algorithms need to negotiate their requirements with the communication services in advance. The success of the system in supporting distributed CPS applications therefore depends crucially on the ability of the hosts and network to manage the communication to guarantee a pre-specified quality of service, such as deadlines, latency, and bandwidth, with a given probability over existing network protocols.

The basic requirements associated with end-to-end delay guarantee mechanisms are as follows:

- Scalable: This means that the overhead of schedulability testing (i.e., delay verification) should be independent of the number of CPS device flows in the system.
- Effective: Our schedulability testing intends to maximize system resource utilization to the greatest extent possible. This means that it is highly accurate even though it does not rely on per-flow information.
- Adaptive: Resource allocation has to be cognizant of the dynamic fluctuations in resource availability. This will lead to a better quality of services and better utilization of system resources.
- Compatible: For practical purposes, our system must be compatible with current industrial practice.

Clearly there are extremely low probability circumstances such that no guarantees can be met, but then if the guarantee fails, it is a fact with a high information content.

The applications in the proposal require real time services, which is a term whose definition has been debated for decades. One definition uses scheduling/priority assignment: manipulate the service order in accordance to real time requirements. In this case, the issues are as follows:

- How to manipulate the queues.
- What can be expected (some kind of evaluation and/or assessment).

However, studies have shown that just manipulating queues is not necessarily sufficient to actually deliver real time services.

The challenge is how to develop and use a reservation system in the current IP based distributed system. The key here is to produce a schedulability test that can testify if a request can make its end-to-end deadline. The test must be scalable since our system is both very large and complex. This turns out to be an extremely difficult (and hence interesting) problem.

Schedulability testing is the key to the delay guarantee approach. We have several advantages using this approach:

- If a request is guaranteed at request time, the requestor gains immediate confidence that the system can successfully guarantee the request.

- If the request is denied by the testing algorithm, the requestor can then quickly find several alternatives.
- Testability can be applied directly to any adaptation scheme.

4. Algorithmic approaches

Identification of pills is somewhat sensitive to the temperature and humidity conditions. The chemical library that the ARS-ISP CPS device needs must be re-calibrated from time to time. The process requires recomputing the correct acoustic waves and downloading a new library to the devices. The computational time is nontrivial for a large number of pills and is well suited to cluster computing on any scale from a traditional or GP-GPU cluster to a Petascale system.

In the following subsections, we describe a computational methodology to choose a small number of "good enough" accoustic waves in order to identify pills within a fixed standard deviation in an N dimensional space of waves.

4.1. A general algorithm for the best curve fitting in the pill identification problem

The identification of pills by using acoustic waves is a challenging problem in technical pharmacy. Different ingredients of the pills can be identified by their absorption of certain frequencies. Practical pill testing has to be done with a very low number (N) of frequencies instead the million frequencies in the frequency range. This requires determining the N-tuple of frequencies suited best for identification.

The frequencies $\nu^{(k)}$, $k = 1, \cdots, N$ from each N-tuple are tested for m concentrations c_i, $i = 1, \cdots, m$, resulting in intensities $\underline{f}_i = \left\{f_i^{(k)}\right\}_{k=1}^{N} \in \mathfrak{R}^N$ for these frequencies $\nu^{(k)}$ in test i. The data points are sorted with respect to strictly increasing concentration, i.e., $c_i < c_{i+1}$, $\forall i = 1, \cdots, m-1$.

Let us assume that a parametric curve $q(t) \in \mathfrak{R}^N$ approximates the m sorted intensity points $\left\{\underline{f}_i\right\}_{k=1}^{N} \in \mathfrak{R}^N$. Then we project the points $\underline{f}_i$ onto the curve at parameter t_i and determine the arc length s_i along the curve from t_1 to t_i. The curve $q(t)$ must be chosen such that these parameters increase according to the concentration, i.e., $t_i < t_{i+1}$, $\forall i = 1, \cdots, m-1$. The best curve $q(t)$ for our N-tuple of frequencies will be the one with the best linear correlation between the computed arc lengths $\{s_i\}$ and the measured concentrations $\{c_i\}$. The best suited frequency N-tuple will be the one with the best linear correlation from above for all possible N-tuples.

4.2. A general algorithm for determining the quality of one curve

We have the given intensities $\underline{f}_i \in \mathfrak{R}^N$ and the given concentrations c_i, $i = 1, \cdots, m$ and let us assume first a given spline curve [7] $q(t) \in \mathfrak{R}^1 \to \mathfrak{R}^N$ which is parameterized via t_i. The spline functions are chosen such that $q(t)$ is a C^1–function. Then we have to perform the following algorithm in order to calculate the quality of this curve.

1. $\forall i = 1, \ldots, m$: Projection of $\underline{f}_i$ onto $q(t)$.
   Determine t_i sucht that $q(t_i) = \{q^{(k)}(t_i)\}_{k=1}^{N} \in \mathfrak{R}^N$ is the closest point to $\underline{f}_i \in \mathfrak{R}^N$.
2. $\forall i = 2, \ldots, m$:
   Calculate the arc length s_i along the curve $q(t)$ for t from t_1 to t_i.
3. Determine the parameters a, b in the regression line

$$g(s) = a \cdot s + b \tag{1}$$

   from the given data pairs $\{(s_i, c_i)\}_{i=1}^{m} \subset \mathfrak{R}^2$.
4. Calculate the functional

$$F := \sum_{i=1}^{m} (g(s_i) - c_i)^2 \tag{2}$$

4.3. Projection

Since $q(t) \in C^1(\mathfrak{R}^N)$ the tangential vector of $q(t)$ at parameter t^* is $q'(t^*) = \left(q^{(1)'}(t^*), \ldots, q^{(N)'}(t^*)\right)^T$ wherein $q^{(k)'}$ denotes the first derivative of $q^{(k)}$ with respect to t. Therefore the projection of the point $\underline{f} \in \mathfrak{R}^N$ onto the curve $q(t)$ can be expressed in terms of the inner product $\langle \cdot, \cdot \rangle$ in the Hilbert space $\mathfrak{R}^N$:

$$\text{find } t^* \in \mathfrak{R} \text{ such that } p(t) := \left\langle q'(t^*),\ \underline{f} - q(t^*) \right\rangle = 0. \tag{3}$$

Using the first derivative of $p(t)$,

$$p'(t) = \left\langle \underline{f} - q(t),\ q''(t) \right\rangle - \left\langle q'(t),\ q'(t) \right\rangle, \tag{4}$$

allows us to solve the nonlinear equation $p(t) = 0$ via the Newton iteration,

$$t^{(l+1)} := t^{(l)} - \frac{p(t)}{p'(t)}, \tag{5}$$

with an appropriate initial guess $t^{(0)}$. We have to be aware that (3) may have non-unique solutions. Therefore this initial guess for the nonlinear solution procedure is of great importance.

Solving (3) for all $\underline{f}_i$ will determine the t_i, $i = 1, \ldots m$ from step 1 in the algorithm from Section 4.2.

4.4. Arc length

The formula for the arc length is simply

$$s(t^*) \ := \ \int_{t_1}^{t^*} \left(\sum_{k=1}^{N} [q^{(k)'}(t)]^2 \right)^{1/2} dt. \tag{6}$$

A arc–length parameterized curve, i.e., using s instead of t as parameter, is rather hard to achieve and can be done only numerically for the general case. An approach for classical spline curves is described in [8]. Using circular splines simplifies the arc length computation [9].

4.5. Regression line

Determining the a, b in the regression line (1) from the given data pairs $\{(s_i, c_i)\}_{i=1}^m \in \mathfrak{R}^2$ is equivalent to minimizing the functional

$$\widetilde{F}(a, b) \ := \ \sum_{i=1}^{m} (g(s_i) - c_i)^2 \ \overset{(1)}{=} \ \sum_{i=1}^{m} (a \cdot s_i + b - c_i)^2 \tag{7}$$

with respect to the parameters a, b. Note that the linear functional $\widetilde{F}$ in (7) is similar, but not identical, to the nonlinear functional F in (2).

Some simple numerical analysis solves (7) as

$$\begin{pmatrix} a \\ b \end{pmatrix} \ = \ \frac{1}{m \sum\limits_{i=1}^{m} s_i^2 - \left(\sum\limits_{i=1}^{m} s_i \right)^2} \begin{pmatrix} m \sum\limits_{i=1}^{m} s_i c_i & -\left(\sum\limits_{i=1}^{m} s_i \right) \left(\sum\limits_{i=1}^{m} c_i \right) \\ \left(\sum\limits_{i=1}^{m} s_i^2 \right) \left(\sum\limits_{i=1}^{m} c_i \right) & -\left(\sum\limits_{i=1}^{m} s_i c_i \right) \left(\sum\limits_{i=1}^{m} s_i \right) \end{pmatrix} \tag{8}$$

4.6. Parameterization of the curve

Let us assume that the functions $q^{(k)}(t)$ are global polynomial functions of order ℓ, i.e.,

$$q^{(k)}(t) := \sum_{j=0}^{\ell} a_{kj} \cdot t^j, \quad \forall k = 1, \ldots, N. \tag{9}$$

The parameter ℓ must be optimized during the process.

If we use piecewise polynomial function, e.g., cubic or circulant splines, then we take into account a similar representation of the curve in which the coefficients a_{kj} will characterize the curve $q(t) \in \Re^N$. These coefficients are functions of the given intensities $\underline{f}_i \in \Re^N$. The coefficients a_{kj} are unique under the presupposition $q(t = 0) \equiv \underline{f}_1$.

The first derivative of $q^{(k)}(t)$ is

$$q^{(k)'}(t) := \sum_{j=0}^{\ell-1} a_{k,j+1}(j+1) \cdot t^j, \quad \forall k = 1, \ldots, N. \tag{10}$$

4.7. Determining the best curve

Formally, determining the best curve is equivalent to minimizing functional F from (2). The functional F is a function of the regression parameters a, b which are functions of all s_i, c_i. The s_i are determined from $q^{(k)}, t_i$ and the latter is a function of curve $q^{(k)}$ and intensities $\underline{f}_i$. The paramerization of $q^{(k)}$ involves finally the curve parameters a_{kj}.

$$\begin{aligned}
F &:= \sum_{i=1}^{m} (g(s_i) - c_i)^2 \\
&\qquad \text{regression line} \\
&= F(a(\{s_i\}, \{c_i\}),\ b(\{s_i\}, \{c_i\})) \\
&\qquad \text{arc length} \\
&= F(a\left(\left\{s_i\left[\{q^{(k)}\},\ t_i\right]\right\},\ \{c_i\}\right), b(\cdots)) \\
&\qquad \text{projection} \\
&= F(a\left(\left\{s_i\left[\{q^{(k)}\},\ t_i\left(\{q^{(k)}\},\ \underline{f}_i\right)\right]\right\},\ \{c_i\}\right), b(\cdots)) \\
&\qquad \text{parameterization} \\
F(\{a_{kj}\}, \{f_i^{(k)}\}, \{c_i\}) &= F(a\left(\left\{s_i\left[\{a_{kj}\},\ t_i\left(\{a_{kj}\},\ \underline{f}_i\right)\right]\right\},\ \{c_i\}\right), b(\cdots))
\end{aligned}$$

Determining the best curve means solving the optimization problem

$$\min_{a_{kj}} F(\{a_{kj}\}, \{\underline{f}_i\}, \{c_i\}), \quad \forall i = 1, \ldots, m,\ \forall k = 1, \ldots, N,\ \forall j = 0, \ldots, \ell, \tag{11}$$

which can be expressed as nonlinear equation

$$\nabla_{a_{kj}} F(\{a_{kj}\}, \{\underline{f}_i\}, \{c_i\}) = 0 \tag{12}$$

with respect to the design variables a_{kj}, $k = 1, \ldots, N$, $j = 0, \ldots, \ell$.

Solving (12) directly cannot be done analytically because of the nonlinear equation (3) the gradient cannot be provided analytically. Instead, we tackle the optimization problem (11) with standard sequential quadratic programming (SQP) methods [10, 11]. The optimizer is based on a Quasi-Newton approximation of the Hessian using a modified Broyden-Fletcher-Goldfarb-Shanno (BFGS) update formula following [12] in order to avoid the need for Hessian information of the objective. The gradient $\nabla_{a_{kj}} F$ is needed in SQP and instead of its numerical approximation we use an automatic differentiation procedure, ADOL–C [13, 14], for calculating ∇F. Automatic differentiation derives a new code for the first (and higher) derivatives from a given code for calculating the functional F (see the description of ADOL–C for details).

The SQP requires an initial guess for the design parameters $\{a_{kj}\}$. A natural choice is determining them from the regression line of the intensities $\{\underline{f}_i\}$. As a consequence we get $a_{kj} = 0$, $j > 2$, $k = 1, \ldots, N$.

Algorithm 1 double functional($\{a_{kj}\}$, $\{s_i\}$, $\{c_i\}$)

$\{t_i\} \longleftarrow$ projection($\{a_{kj}\}$, $\{\underline{f}_i\}$)
$\{s_i\} \longleftarrow$ arc($\{a_{kj}\}$, $\{t_i\}$)
$a, b \longleftarrow$ regression($\{s_i\}$, $\{c_i\}$)
$F \longleftarrow \sum_{i=1}^{m} (a \cdot s_i + b - c_i)^2$
return F

4.8. Determining the best curve for one N-tuple of frequencies

Finally, we summarize what has to be programmed as a flow chart in Algorithm 1. While Algorithm 1 appears quite simple, it is best used where a time limit is placed on the overall computation, no matter how many processors are in use, and to take the optimal acoustic waves at the time limit. This algorithm does not need to be run often, but needs to be run on a substantial computational resource. The end redult is a pill library that is quite suitable for the embedded computation on the ARS-ISP CPS device.

5. Conclusions

We have described a viable dynamic system to guarantee that pills delivered to a patient are what were prescribed, of sufficient quality to be effective, and within the correct time frame. Issues of privacy, network security, and interacting with multiple databases are inherent to the entire process.

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