A Prototype for an Incorrect or Defective Pill Detection Using a Dynamic Data-Driven Application System

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Outline of Talk

- Introduction and motivation.
- Common techniques to our applications.
- Handheld application to guarantee that pills prescribed are correctly delivered by a nurse or caregiver on time and in the right dosage.
- Manufacturing line application to ensure pill quality and correctness in packaging.

Why Does Anyone Care?

- Multi-million pill recalls happen every year.
- Administration of incorrect medications by professional caregivers is estimated to have killed more than 100,000 Americans after prescriptions were filled in 2007.
- These numbers are likely to be underestimates due to unreported deaths.
- The use of incorrect medication is the <u>eighth leading cause of death</u> in the United States and actually kills more people in a given year than traffic accidents, breast cancer, or AIDS.
- Other countries have a similar problem, too.
- This is a truly horrendous number of deaths that is preventable:
  - At least 50 people will die during a one hour version of this talk.
  - More than 1,000 people will die during a typical three day conference.

Common Techniques of the Two Applications

Physics

- All pills sold in the world are supposed to be unique in shape, size, and coloring.
- All pills have a unique audio spectra footprint.
- We play specific noise patterns at pills and measure the resulting spectra. We look for specific spectra to identify specific types of pills. We have to identify which spectra to look for given environmental factors that may change over time as short as a work shift.

Algorithms

- We use a particular algorithm to compare what we measure versus what we expect.
  - The Bootstrap Error-adjusted Single-sample Technique (BEST) is the analytical basis of our Acoustic Resonance Spectroscopy - Integrated Sensing and Processing (ARS-ISP) device, and the foundation for the pill chemical identification library.
  - The BEST metric is a clustering technique for exploring distributions of spectra in hyperspace.

Algorithms

- 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 very precise discrimination.
- 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.

Which Spectra?

- Choosing and identifying the useful spectra is a daunting process.
  - An infinite number of spectra are possible, so we choose the 5-10 most likely ones.
  - Have to make this work on an embedded system that has limited processing capabilities.
  - Not enough time to get a supercomputer to identify each pill as it is manufactured.
  - Temperature, humidity, and individual workers affect the pills.

Computing

- 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 on a supercomputer based on substances likely to be found in the target environment. This needs to be updated 2-3 times a day!
- When a substance unknown to the BEST library is found or is out of range (indicating a defect or foreign substance entirely), it has to be marked for special processing.

Choosing Wavelengths: Definitions

- We want a small set of N (out of a possible set of millions) wavelengths.
- Define
  - Frequencies $\nu^{(k)}$, $k=1,\ldots,N$
  - Concentrations c_i, $i=1,\ldots,m$
  - Intensities $F_i=\{f_i^{(k)}\}$, $k=1,\ldots,N$ (real N-vector)
  - Parametric curve $q(t)$ approximates the m sorted intensity points F_i

Choosing Wavelengths

- What we compute
  - Project points F_i onto the curve at parameter t_i
  - Determine arc length s_i from t_1 to t_i
  - $q(t)$ chosen so that $t_i < t_{i+1}$, for all $i=1,\ldots,m-1$
- The best curve $q(t)$ for our N-tuple of frequencies has the best linear correlation between the arc lengths $\{s_i\}$ and the measured concentrations $\{c_i\}$.
- The best suited frequency N-tuple will have the best linear correlation from all measured/possible N-tuples.

Choosing Wavelengths

- Determining the best curve means solving an optimization problem that can be expressed as a nonlinear equation that is solved using sequential quadratic programming methods.
- The gradient involved cannot be evaluated directly.
  - We use automatic differentiation methods (e.g., ADOL-C), not numerical differentiation methods.
  - We have a programming framework that is straightforward and completely parallel.

Petascale Computing Aspect

- The more *N*-tuples we consider, the more accurate the pill analysis.
- Regularly scheduled short runs on very large computers are necessary in order to keep the libraries for the embedded systems accurate for changing environmental and employee conditions.
- Output can be delivered and post processed on a local computer and then downloaded to ARS-ISP devices.

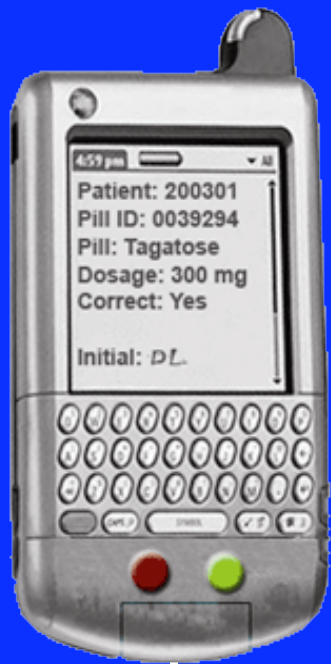
Integrated Sensing and Processing

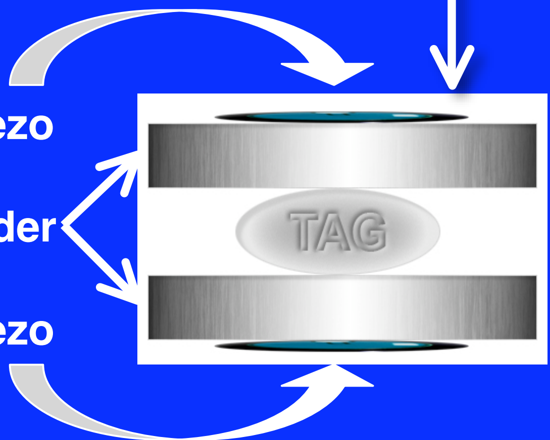
- The embedded system must perform an optimization of a functional that is equivalent to solving a complicated nonlinear equation.
  - We use automatic differentiation techniques to simplify the entire process to something that can be put into an embedded system.
  - Numerical approximations are used to further simplify the computing tasks to something practical for the embedded system.
  - The system is fast enough for the task.

The Handheld Device System

Sensors

- Acoustic resonance spectroscopy (ARS) sensors:
  - Tablet holder containing piezoelectric transducers connected to a PDA.
- Integrated sensing and processing (ISP-ARS) mp3s's are downloaded when a patient barcode is scanned.





The Manufacturing Line System

Goals

- Identify all defective pills during the manufacturing process.
- Remove defective pills before packaging.
- Guarantee that all pills in a package are what is on the label.

Why is this a Challenge?

- We are using audio techniques to identify compounds.
  - Manufacturing lines are extremely noisy environments.
- We typically have 5-10 milliseconds to identify and qualify each pill.
  - We have to remove defective or incorrect pills from the manufacturing line.
  - We have to do this process correctly every single time.
  - Too many exceptions in a short time $\Rightarrow$ signal an alert.

Manufacturing Modification Issues

- In the U.S., a pilot line is created, tested, and eventually approved by the Food and Drug Agency (FDA).
- Once approved, it becomes a production line and cannot be modified in any significant way.
- Any significant modification to a production line makes it a pilot line again with all of the testing and approvals required again. Further, the FDA has to approve to conversion back to a pilot line, which it may not do.

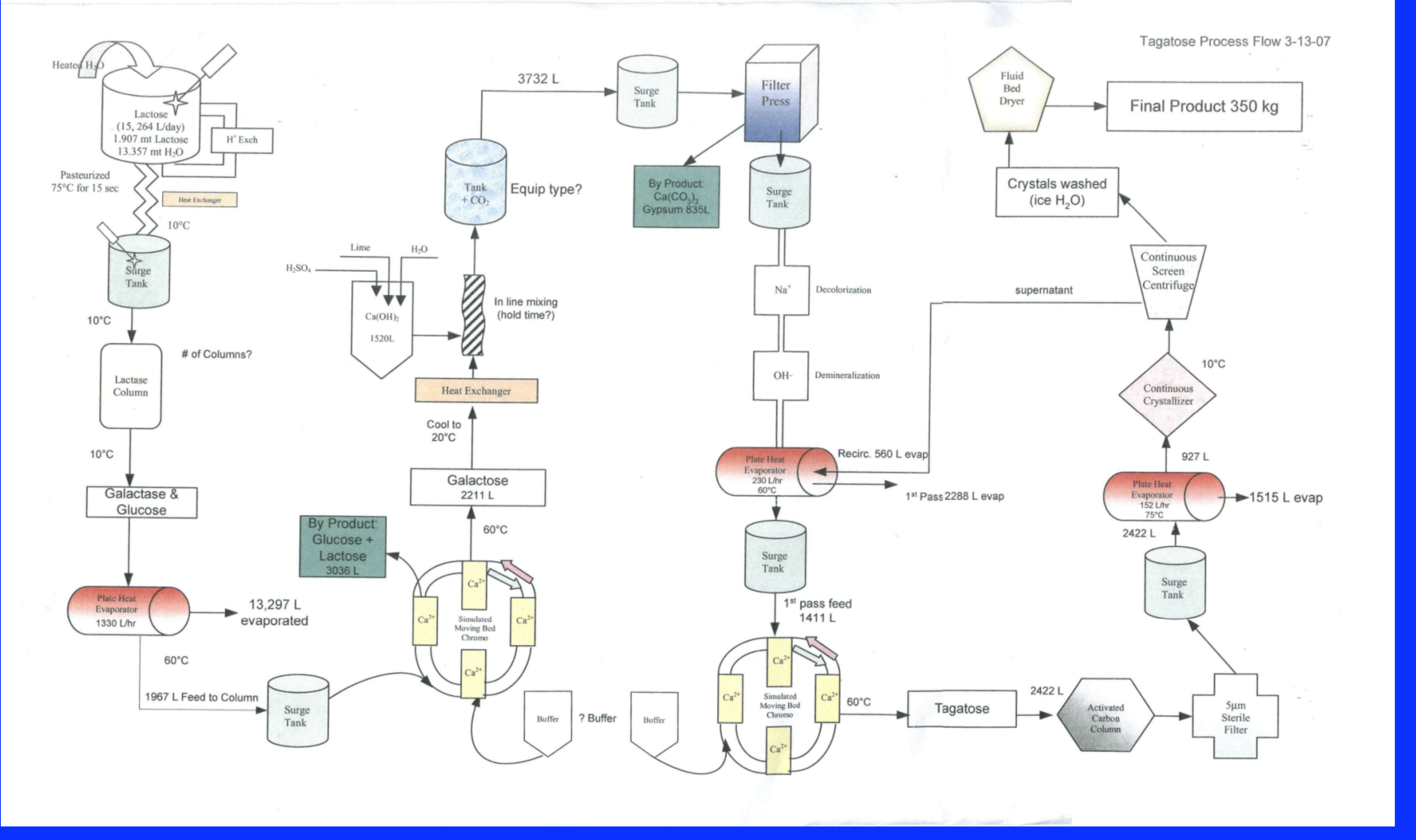
Prototype System

- The pills pass through a box that is added to manufacturing line in an open space. Inside the box is quiet enough to use our ISP-ARS devices and provide a spraying device to mark defective pills.
- The box is connected through a standard network to an external computer of sufficient power to generate the library (and updates) needed by the ISP-ARS devices.

How Will We Test Our Ideas?

- We have a partner in Italy (who does not need FDA approval) who makes pills willing to put our system on a production line.
- The company cannot reliably make a new drug that will be useful for diabetes patients and does not understand where the process is failing.
- Our devices will isolate where they are failing and hopefully lead to a change in the manufacturing process of the drug.

Test Production Schematic



Packaging Identification

- There are many small pharmaceutical companies that make pills for larger companies in a highly economical manner. This is similar to offshoring jobs.
- Multiple drugs are made on the same production line including placebos for testing effectiveness in trials.
- Every year, pill recalls occur due to the wrong pills being put into packaging at the end of the manufacturing process. 2,000,000 pill recalls happen every year.
- Our devices can guarantee the pills in the package are what is on the label using the ISP-ARS devices.

Conclusions

- We have a system that works in a laboratory setting.
- It can be used to
  - Reduce errors in pill dispensation and usage.
  - Identify defective pills in the manufacturing process in real-time.
  - Identify pills in the wrong packaging at end of manufacturing.
- We have a willing test partner for the manufacturing application.
- We need a test partner for the dispensation application and government approval for human testing.