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A GENERIC SIMULATION MODEL THAT REFLECTS THE FLEXIBILITY OF AN AUTOMATED SYSTEM FOR PHARMACEUTICAL AND CHEMICAL LABORATORY TESTING

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ABSTRACT

Merck & Co., Inc. has developed a laboratory automation system that is targeted towards low volume pharmaceutical and chemical testing. The nature of laboratory testing requires this system to adapt to changes in assays and testing procedures, as well as a variety of laboratory and material handling device characteristics and configurations. This adaptability is essential to keeping the laboratory from becoming obsolete. While low volume efforts are not generally viewed as opportunities for automation, this system's design, incorporating modular laboratory equipment cells and robotic material handling devices under a common controller, provides the requisite flexibility necessary for laboratory adaptation while retaining the advantages offered by automation.

Inherent to this system's flexibility is the recurring problem of identifying the desired or optimal laboratory configuration for a given implementation instance when faced with several choices. While discrete-event simulation has proven to be quite beneficial for solving problems of this nature, parochial design philosophy has tended to result in models that are brittle in structure. The focus of this paper is a discussion of a single generic simulation model written in the SIMAN IV simulation language that emulates the adaptability of the flexible automation system it represents. Like the automated system, the model allows for convenient changes in nearly all aspects of the process being studied. Equipment and operations within the model may be easily included (or excluded) from the scope of a given simulation run. Included within this discussion is a description of the Merck Flexible Laboratory Automation System as well as a case study applying the flexible simulation model to an actual laboratory instance.

1 INTRODUCTION

Automation has typically been reserved only for processes that are repetitive and that change relatively infrequently. Merck & Co., Inc., in an effort to automate their pharmaceutical and chemical laboratories, has taken a different approach towards automation. This approach targets low volume testing and relies on the reconfigurability of the automated system to adapt to the changing needs of each laboratory. The Merck Flexible Laboratory Automation (FLA) system was developed to meet these needs. This system is intended to be installed in numerous laboratories throughout Merck, each of which processes hundreds of different products, and expects their testing processes to change in order to accommodate different products.

A simulation of the FLA system requires that the simulation model be able to adapt to changes in the products and in the configuration of the laboratory. In fact, one of the most important aspects of a simulation of the FLA system is the ability to compare several different FLA configurations prior to deciding upon which of the configurations to implement. These configurations may be vastly different from each other with changes representing differences in the layout of the laboratory, the number and speed of the robots, the capacity of each of the functional work cells within this system, and the products that are to be tested. The simulation model that was developed for FLA mimics this flexibility; with relative ease a new product or system configuration may be simulated.

This paper presents a description of the FLA system and its associated simulation model. The process of building a flexible simulation model will be discussed in some detail. The simulation model has been used to aid in the evaluation of installing FLA systems in several laboratories at Merck. This paper will conclude with a discussion of the simulation of one laboratory and its corresponding results.

2 BACKGROUND

Merck & Co., Inc. is a global pharmaceutical company with research and manufacturing operations worldwide. For the past several years Merck has been developing a flexible automation system that aids chemists in performing their laboratory testing. Traditionally, the pitfalls in automating the laboratory environment have been three fold. First, the cost to automate a laboratory is prohibitive unless the majority of the low volume testing done in a laboratory may be performed on the automated system. Second, the type of testing that is performed is constantly changing as new products and techniques are developed. Third, the automated system must be able to incorporate new technology in order to prevent the system from becoming obsolete. Despite these hurdles, laboratory automation presents several significant advantages over its manual counterpart. An automated system improves testing consistency and repeatability, reduces testing costs, allows laboratory personnel to focus on analysis as opposed to testing, requires less laboratory space, and typically generates a higher sample throughput rate. In addition, the risk of employee exposure to hazardous chemicals during testing is substantially reduced.

The pharmaceutical and chemical laboratories that the Merck FLA system targets process large numbers of low volume assays. A single laboratory may process more than a hundred different products, and each product may undergo five to ten different tests. Individually these assays are not performed often enough to consider automating, but taken together as a whole, these assays share many common procedures. For example, a laboratory may process several products that are in powder form. In order to test any one of these products, a small amount of powder is dispensed into a bottle and then brought into solution. Once in solution, this product may be used as a reagent with other products or may be analyzed itself by processing it through a variety of laboratory test equipment. The technique for testing this powder is similar for most powders. Each assay will differ according to the amount and type of solution that the powder is dissolved in, the time it takes for the powder to be brought into solution, and which of the laboratory testing devices will be used for analysis. These differences are simply represented as data parameters at common functional devices.

Despite these commonalties, new products and techniques constantly change each laboratory's testing needs. The scope of products that are currently being tested may change dramatically within a few years. Additionally, laboratory test equipment changes as new technologies are introduced. These changes make it difficult to predict the future laboratory requirements as they pertain to product type, analytical methods, and throughput requirements. As a result, change threatens to make existing laboratory automation obsolete. Certainly an automated system that handles powders and bottles is not expected to convert into a system that controls jells and Petri dishes, but it must adapt to changes that occur regularly within a laboratory and be poised to incorporate the resulting new devices and product types with a minimal amount of setup time.

A laboratory automated system designed to adapt to these changes benefits significantly from a simulation model that is equally as flexible. Changes in the assays, devices, and layout of both proposed and existing laboratories must be easily incorporated in the simulation model to prevent obsolescence.

3 DESCRIPTION OF THE FLEXIBLE LABORATORY AUTOMATION SYSTEM

FLA was Merck's response to the goal of automating its pharmaceutical and chemical laboratory testing. The FLA approach recognizes the common functions within a laboratory and tries to automate the laboratory environment as opposed to any individual assay. In addition, FLA is modular in design to allow reconfiguration as the needs of the laboratory change. This flexibility is achieved by breaking down the laboratory environment into basic functional devices. These devices perform operations such as dispensing powders, injecting solutions, and shaking bottles, etc. Virtually any combination of devices may be controlled by the FLA system controller. This flexibility allows FLA configurations to vary in the number of material handling devices, the number and type of laboratory devices, and the tests and products that are used.

The FLA system, like its simulation model, is event driven; in order to run, an operator enters one or more *methods* that contain a list of *unit operations* that must be sequentially performed on an *entity*. Each unit operation specifies a laboratory device and parameters that affect it's processing. Position numbers are not specified in these operations since the FLA will transport entities to the devices as positions become available. For instance, a shaking device can shake several bottles at the same time and allow these bottles to move as their individual processing delay completes. Each unit operation for this device specifies the entity to be shaken and the amount of time that it needs to shake.

In addition to the methods that an operator will run, the FLA system keeps track of an inventory of various supplies, solutions, and other operator supplied inputs. These inventory items may be consumed during the running of a method and, as in the case of bottles,

automatically restocked when the inventory item is no longer needed. Some methods will also create inventory themselves so that they may in turn be used by other methods in the system. This scenario allows for inventory contention. A holding pen where methods-in-process may wait for inventory items to become available is necessary in order to prevent system deadlock.

Each of these aspects of FLA are simulated by the SIMAN simulation model developed for this system.

4 MODEL DEVELOPMENT

Simulation model development began with a joint kickoff meeting between Merck & Co. and Systems Modeling Corporation (SMC) personnel at Merck facilities in Rahway, NJ. Critical model design requirements and issues were discussed and agreed to at this time. Following this meeting, a functional specification for the FLA simulation project was developed by SMC. This specification served three purposes. First, it described the FLA. This description included entity process flow, equipment functionality, operating procedures and rules, system interactions, modeling assumptions, and scheduling and logical issues. Since the simulation model was to be generic or flexible in design, a thorough description of the range of differences between facilities was included. This description was necessary in order to fully recognize and accommodate model needs and design requirements early in its development life cycle.

Second, the user input required to perform a simulation analysis was defined. This description included the method for defining equipment or device configurations, laboratory operating characteristics, and entity processing specifics.

Third, the output requirements for the simulation model were defined. Output statistics included such things as product throughput, cycle time, and equipment utilization.

Upon completion of the functional specification and acceptance by Merck, model code development began. Since considerable effort had been expended in developing a detailed functional specification, code development was a relatively straight forward process and was completed in less than one man-month. Upon completion of code verification, several validation runs were performed using Merck supplied experimental data. During this process, minor adjustments in model structure were made to account for any inaccuracies and/or assumptions that proved incorrect.

Acceptance of the completed simulation model consisted of on-site delivery of the final validation run results, model source code and related documentation, and a user's manual to Merck personnel in Rahway, NJ. In addition, training in use of the simulation model was provided by SMC.

4.1 Model Description

The FLA simulation model was written in the SIMAN IV simulation language. The model consist of a single "model" (*.MOD) and "experiment" (*.EXP) file. No external event routines (i.e., FORTRAN or C subroutines) were required. Although developed under the DOS environment, the model is fully transportable to both OS/2 PC and UNIX-based workstation environments without further modification.

FLA simulation model configuration changes are easily accomplished through programmable software switches centrally located within the experimental (*.EXP) file, no modification of the model itself is required. Over two thousand seven hundred variables are provided for this purpose. These variables are identified with full symbolic names for self-documentation. The flexibility offered by the model allows up to a maximum of fifty unique laboratory equipment cells, five material handling robots, and a nearly unlimited number of test procedures or assays to be defined for a given laboratory configuration and trial instance.

To further aid in configuring the model, the types of devices used within a laboratory are divided into five classes of *stations*. These classes are defined be their processing time and inventory requirements. They are:

1. Single Delay Stations
2. Two Delay Stations
3. Batching Stations
4. Inventory Add Stations
5. Inventory Consumption Stations

Laboratory devices that process an entity for a single period of time may be modeled as a Single Delay Station. This class of stations retain the entity for a single processing time. A shaking device is an example of this class.

Two Delay Stations are devices that retain an entity for the first time period and then release the entity and continue processing for a second time period. The entity is free to leave the station during the second time delay. This class represents most of the analytical instruments which first withdraw liquid from a bottle, and then perform analysis internally.

The third class, Batching Stations, are devices that allow multiple entities to arrive before the device begins processing. Once a batch processing station has started

its processing delay, no other entities may arrive until the device has finished. A vacuum oven is an example of this class of stations since it cannot be opened while it is running.

The fourth class of stations, Inventory Add Stations, create inventory items or methods that are subsequently used by other methods within the system. A solution preparation device is an example of this type of station.

The fifth and final class of stations, Inventory Consumption Stations, are stations that consume inventory in order to perform their individual processes. Each of these stations is modeled explicitly because their consumption requirements vary significantly from station to station. An example of this type of station is the powder dispensing device since it requires two inventory items to perform its process - a powder and a clean bottle. Individual method device parameters such as processing times, batch size, and inventory requirements are specified in the unit operations of the FLA method's process plan, discussed below.

Each laboratory test procedure defined within the model is represented by its own unique entity which flows through the model according to a process plan. To provide maximum flexibility in defining the number or types of products that are to be tested, the number and sequence of test that are to be performed, and the processing time associated with each test within a given FLA configuration and trial, the model has been designed to allow convenient method definition via the SIMAN "Sequence" construct located within the experimental file. Using this construct, the analyst simply enters the station or equipment visit sequence, processing delay time or distribution, and related processing media requirements (e.g., glassware, filters, chemicals, etc.) prior to model execution. The analyst may define as many methods and steps as are required, no predefined restriction in their number, beyond the memory addressing capabilities of the hosting operating system, exist.

All inter-station material handling of methods is accomplished via robotic movement. The number of robots available, feasible station moves by robot, and initial robot startup positions are defined via the experimental file variables described above. Delay times for robot inter-station moves are defined via a 50x50 data matrix. These times represent standard robot travel times between all stations defined for the laboratory configuration being studied. To allow for known variation in individual robot movement speeds, a second 1x5 data array is provided which allows adjustment in robot speed via a rate multiplier. Because input of the 50x50 matrix is a tedious and error prone process, the model has been designed to interface with Lotus 1-2-3 generated "worksheet" (*.WKS) files on startup for automatic input of this information. This technique not only reduces data entry errors, but also facilitates rapid configuration changes by the analyst by allowing data definition within the Lotus environment.

Control of robot assignments for the servicing of material handling request is accomplished within the model via a SIMAN robot selection and move *submodel* process. Upon receipt of a move request by the *primary* model, a search is conducted by the submodel for the first idle robot which is "feasible" for the move requested. Since not all robots defined for a particular FLA configuration instance may service every move request, a set of five 1x50 data arrays have been provided for the analyst to allow definition of each robot's feasible moves. If a robot is not immediately available for assignment to the requesting entity (method), the entity will be queued in a SIMAN first-in, first-out (FIFO) disciplined queue until an *idle robot* SIMAN signal is received from the primary model. Upon receipt of this signal, the entity in queue rank position one (oldest) is released to again check for move feasibility. If the idle robot proves to be infeasible, the entity is again returned to the queue and the next most senior entity is released to check the feasibility of its move. This process is repeated until either a feasible robot move has been identified or until all methods in queue have proven the infeasibility of the idle robot for their respective moves. Infeasible entities which were removed from the queue during this process are returned to queue in their original order of arrival, preserving the FIFO queue ranking. Statistics are automatically maintained by SIMAN on this queue in order to determine robot material handling service rates for the defined FLA configuration and methods trial.

Three categories of inventory are provided within the model. The first category, "glassware," is inventory that is consumed during the normal operation process of the FLA. To manage this inventory, the model is designed to allow the analyst to define an initial glassware startup or preload inventory level for up to five different types of glassware. In addition, the analyst may define automatic reorder points and restocking quantities for each. Statistics on glassware stock levels and the number of inventory reorders are maintained by the model.

The second category of inventory, "infinite inventory," is inventory that is assumed to always be available or in stock. While this category of inventory may require material handling delays for movement to the requesting method's processing station, no delay resulting from an out of stock situation is possible. However, delays for a temporary "not in stock" situation due to concurrent demands by multiple methods for the

same item may be realized. Examples of this inventory category include most powders, filters, and test media.

The third category of inventory, "methods inventory," is inventory that must first be produced by the laboratory before it is available for consumption by secondary methods. This inventory is introduced as a preload method at simulation time zero. Once this method has completed its required processes for preparation, it is then moved to an Inventory Add Station were the method's inventory identification attribute (NS) is added to an inventory array. Because this inventory may be required by other methods at inventory consumption stations (e.g., a dispense solution station), a SIMAN signal is sent indicating the availability of this new inventory item. All methods waiting for this signal will, upon its receipt, interrogate the inventory array for their respective inventory requirement. If the necessary inventory is now in stock, the inventory is dispensed and the method resumes processing.

4.2 Model Statistical Outputs

A wide variety of statistics are automatically collected during each replicate and displayed via the standard SIMAN Summary Report format at its conclusions. This report consist of three categories of output: Discrete-Change Variables for time-persistent statistics, Tally Variables for observational-related statistics, and Counters for simple enumeration of event occurrences. All statistics collected are tailored specifically to the FLA environment and are labeled on the summary report with full descriptive titles for ease of analysis. In addition, any statistic may be easily excluded from a simulation replicate via minor changes to the experimental file prior to the models execution if no longer desired.

Discrete-Change Variables are used to provided average, coefficient of variation, maximum and minimum observation recorded, and last value recorded statistics for all laboratory equipment wait queues (machine is busy), inventory wait queues (out of stock), robot wait queue (robots are busy and/or infeasible), laboratory equipment utilization, robot utilization, and glassware inventory queues (stock levels). Note that Discrete-Change Variable average and coefficient of variation statistics are weighted by time for which each value that exist (e.g., number in queue) during the simulation replicate.

Tally Variables are used to provide the average, coefficient of variation, maximum and minimum observation recorded, and number of observations recorded (sample size) for each method's time-in-system or flow time, as well as an overall flow time for all methods processed. Unlike Discrete-Change variables, Tally Variable average and coefficient of variation statistics are not time-weighted; rather, they are simply averages of the total number of recorded observations for a given simulation replicate.

The third category of statistics, Counters, are used to provide a simple count of the number of glassware restocks that are required during the simulation replicate. Counters are provided for each glassware type defined in the system.

Although analysis of FLA simulation results begins with examination of the summary statistics provided by the SIMAN Summary Report described above, it is not intended to be the primary mechanism for decision making since it represents only one of many possible outcomes. In order to more accurately perform output analysis on a statistic of interest (e.g., queue utilization), the analyst simply modifies the Discrete-Change, Tally, or Counter variable to include an output file name for each variable. This file will contain all the observations of changes in the statistic for the simulation replicate. These files are then used with SIMAN's Output Processor after the replicates completion to perform plots, histograms, confidence interval calculations, etc. on the statistic.

5 USING SIMULATION TO ANALYZE FLA ENVIRONMENTS

The simulation model developed is used both as an aid in evaluating new FLA configurations as well as existing ones. When analyzing proposed configurations for a new laboratory, several different simulation model summary reports may be compared. These simulations are used to identify optimal laboratory configurations and provide information relating to throughput, glassware requirements, and bottlenecks. These quantities are very difficult to calculate using other methods because of the event driven nature of the FLA system, system stochastics, and because the FLA processes multiple methods in parallel. Merck has found that the use of simulation analysis in the early stages of an automated laboratory design provides invaluable information and feedback about the systems overall performance level. Examples of this feedback include identification of system bottlenecks, estimating system throughput for alternative capital equipment justifications, providing estimates of inventory requirements for inventory capacity planning, etc. In addition, the modeling process itself provides a vehicle for describing a systematic view of the proposed laboratory.

While existing FLA systems benefit from the simulation model in a manner similar to new systems, three primary advantages are especially exploited.

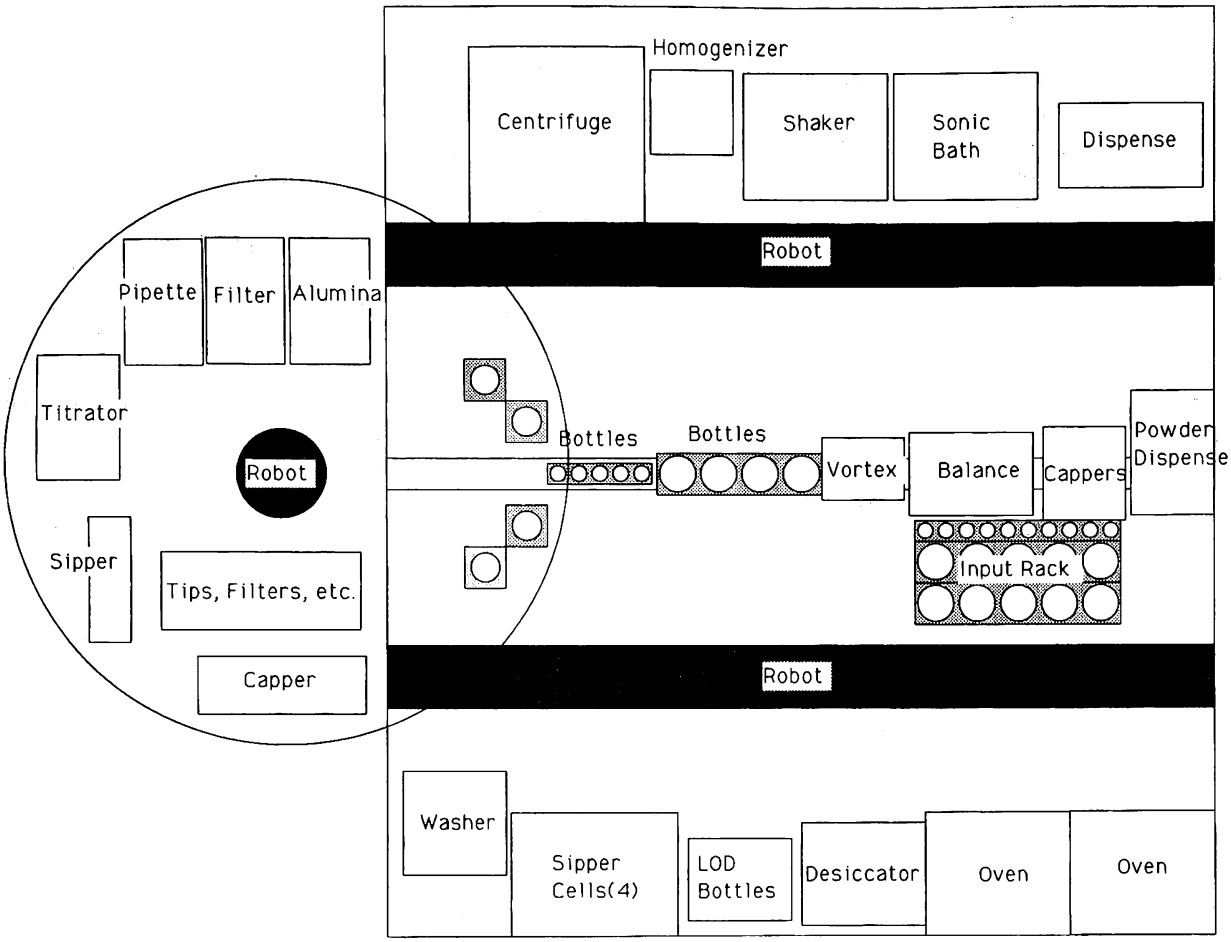

Figure 1. Merck Automated Pharmaceutical Laboratory Configuration Layout

First, a simulation study will give time estimates for completing a method or set of methods that are to be run on the existing FLA system. Second, whenever the configuration of the existing FLA system is examined for potential improvements, the simulation model provides feedback as to the benefits of this configuration change. This type of feedback provides evidence that may be used to justify the purchase of new laboratory devices, faster robots, or an expanded system. And third, when a laboratory needs to optimize its FLA system to efficiently run a particular assay, the simulation model can assist in identifying the advantages to be gained by the proposed configuration before any changes are implemented.

6 EXAMPLE SIMULATION OF AN FLA LABORATORY

The simulation model described has been used successfully in the design of an FLA system for one of Merck's pharmaceutical laboratories. This laboratory consisted of three robots, two of which move along separate seven foot tracks, and the third stationary, but capable of pivoting about its hip. This system included twenty-one device or equipment stations with representatives from each of the five station classes described above in section 4.1. Each of these stations performed unique operations and several were capable of processing multiple methods concurrently (batching). A diagram of this system is shown above in Figure 1.

The methods that where simulated represented fifteen different assays that corresponded to a total of 260 laboratory tests or steps. These assays represented the base level functionality for the proposed system and establish a standard or control for the measuring performance characteristics of the system. Against these performance characteristics, other simulation experiments were run. Each experiment attempted to isolate a different element or set of elements that had the potential to improve various measures of system performance.

One objective of the simulation study was to determine the impact of a particular group of assays on system throughput performance. Comparisons made between the base level assays and the results of the secondary experiments revealed several performance considerations impacting the proposed system design. As a result, it was determined that better system performance for these additional assays could be achieved by altering the positions of the laboratory devices involved. These subsequent changes resulted in reduced robot utilization with no adverse effect upon base level assay throughput performance.

Laboratory layout is an issue that must be extensively simulated. During laboratory design, it is important to position devices so that the frequency of entity transfer is kept to a minimum (each additional transfer operation results in both reduced method throughput rate and increased robot utilization). In addition, robot utilization must be balanced between all robots defined. The simulation model provided a valuable tool in quantifying this utilization as well as for the identification of device bottlenecks.

During the analysis of this laboratory configuration, the washing device that is used to clean bottles for recirculation was determined to be a bottleneck operation in the system originally specified. The optimal number of additional washing positions needed to resolve this problem was easily determined through additional simulation experiments. Removal of this bottleneck resulted in a 2% increase in system throughput.

7 SUMMARY

Because of the complex interactions involved with the design of flexible automated laboratory environments, the variety of testing equipment utilized, and the frequency of change necessary in order to adapt to changing demands, the generic simulation model has proven valuable for the purposes of designing, operating, and promoting the use of automated systems that have proven to be safer, cheaper, faster, and more consistent than their manual counterpart. And yet, the benefits of this technology are, in many ways, unrealized. As new pharmaceuticals and chemicals find their way into society as solutions to problems yet unsolved, only then will a true understanding of the impact of this application begins to be fully understood.

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