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SELF-LEARNING OPTIMIZING SYSTEMS[1]

Carlos Wm. Moreno, Ph.D.
Vice President, Research & Development
Ultramax Corporation
1313 E. Kemper Rd., Suite 300
Cincinnati, OH 45246

Advisory systems, including optimizing systems, typically depend upon an engineering staff developing models to simulate the behavior of existing production processes. In spite of its benefits, this is an impractical approach for very many processes.

New advances in statistical and numerical methods provide a reliable alternative which is quicker and independent of prior engineering models, and is an outstanding complement to largely automated facilities. Improving consistency, costs and production rates for operations, with existing equipment, often exceed expectations, and typically result in $100,000 to $1,000,000 per year gains.

The technology, called ULTRAMAX(tm)[2], is broadly applicable for repetitive pharmaceutical processes where important results are measurable on a timely basis. Among its unique features, it improves consistency by giving feed-forward advice to reset controlled inputs to compensate for known changes in external variables such as raw material and environmental conditions.

1. DESCRIPTION OF THE TECHNOLOGY

The ULTRAMAX computer system takes process input and output data as it is generated (either from batch or continuous processes); does "learning", or the continuing updating of models that represent the interrelationships between all the variables as it relates to the goals to be achieved; and does "synthesis", or providing direct advice as to where to set input variables next in order to maximize or minimize a measure of performance. Note that it does not require that process models be provided, even though it can accept them.

It is a Decision Support system, and some call it second-level control. Typically, it is used to find the best setpoints, such as temperatures, times, pressures for first-level control systems.

This technology exhibits COGNITION, where the "learning" is not only to know what is happening with the process, but what would happen under alternate conditions. It also exhibits VOLITION, where the "synthesis" selects setpoints based on the evaluation of consequences; and not on pre-established, reactive rules, as it is typical of first-level process control. Further, the synthesis guides the process to producing data which will improve learning in order to better achieve objectives in forthcoming runs. These aspects of Cognition and Volition are associated with the type of intelligence needed for goal-achievement, here taking place in a man-made or artificial entity, under limitations explained below.

Models are generated through goal-oriented regression, i.e., locally accurate in the region where we want to operate the system. This provides much more accurate prediction abilities for optimization than standard regression, but poorer predictions where results are not as good.

The computer transition from new data acquisition to a new advice generation is fully automatic, and thus it can be implemented in closed-loop computer-controlled systems. This advice is, of course, mindful of constraints on both input and output variables. It provides feed-forward compensation for known changes in external variables (raw materials and environmental conditions) and is ever-mindful of quality requirements. The priorities followed in generating each advice are:

1st: Certainty; be sure of the results to be obtained

2nd: Obey constraints

3rd: Achieve better measure of performance

These features fulfill main concerns of pharmaceutical production management and engineering.

This technology requires typically 1.25 mega-bytes of memory access (32 bit addressing), and fast processing -- i.e., a mini computer. It is written in Fortran 77.

1.1. Conditions and Limitations

The advanced features mentioned above can be automated because in fact we are resolving a problem of limited scope, even though it exists very frequently. The conditions are:

1) The variables can change gradually. That is, this excludes changes in kind, such as whether to use radiation or not (but this technology will solve the right amount or degree of radiation). This also excludes logistical problems such as scheduling.

2) Important variables are measurable. This includes subjective evaluations against a scale. The measurement must be sufficiently reproducible to detect important improvements.

3) The measurements are obtained on a timely basis so as to learn from them.

1.2. History

Box & Draper's factorial Evolutionary Operations (EVOP) methodology for continuing process improvement was an improvement over traditional design of experiments, whose implicit asumption is that you can run a large number of experiments at the same time, such as in agriculture. Production typically allows for one, or at most a few parallel runs, at the same time. In this environment deciding where to run experiments without using the data obtained in past runs is obviously a waste of very valuable information.

Starting in the early 70's, we developed ULTRAMAX as an attempt to resolve some practical difficulties with EVOP. We provided better protection against making off-quality product, and at the same time became more effective, i.e., faster or requiring fewer runs to approach practical optimization.

In addition, we developed well tested heuristics to eliminate the absolute need for user interpretation and judgement (but allowing for user judgement), which enables closed-loop optimization. Also, we added the features of feed-forward optimization, or immediate optimal compensation for known changes in external variables; and the ability to automatically take into account constraints on several input and output variables at the same time.

Also, as compared to another approach to evolutionary optimization, the SIMPLEX method, ULTRAMAX is superior because its model building makes it much less sensitive to noise in the data, and requires fewer runs to reach a practical optimum.

Development and refinement of the technique took place through intensive application in consumer process industries. Pharmaceutical applications started two years ago.

2. APPLICATION

In production environments this technology is used most frequently to provide more consistency at lower unit cost, and to improve production rates. It is not unusual to obtain better results than optimistic estimates. The benefits typically fall between $100,000 to $1,000,000 per year gains.

To implement it there are two main issues to be resolved:

1. How to gather data and to implement the advice.

2. How to set up the computer to know what problem it is solving; i.e., the meaning of the variables and to goals to be achieved.

Eventually what limits reaching the absolute optimum is the amount of noise, or more precisely, the unexplained variability between the models and the results. Unexplained variability is often reduced by recognizing an external variable whose changes affect results. Longer term solutions are to measure results more accurately, and making changes in the process to reduce its inherent variability.

Understanding novel near-optimum operations sometimes makes the user aware of important cause-and-effect mechanisms which he/she would have neglected to include in engineering models. Yes, now it is practical to optimize a process first, and then write engineering models for better understanding and improved redesigns.

What-if and sensitivity analyses aid process and product management by evaluating the consequences of moving or removing constraints, and of controlling external variables. Global variables are used to represent changing economic conditions for both raw materials and energy, and to represent the demand for the product, so as to also include cost and profitability considerations.

Standard use of this technology as decribed here is typically applied to individual processes, or a sequence of few interactive processes for real-time ongoing optimization.

With unified data bases, each improved process performance data will provide the right information, for instance, for Scheduling and Forecasting. Further, ULTRAMAX can be used as an analytical tool (not real time), accessing the data of any combination of processes to do plant analysis and optimization taking into account interactions between far-away data.

2.1 Data Interphase

Here we shall emphasize batch process optimization, such as in the pharmaceutical industry. Continuous processes require a few other considerations.

The data consists of the values of the input and output variables in running a batch. The inputs might include decision variables, for instance, the threshold value of a dynamic variable at which a particular process step is completed (e.g., temperature as the batch is processed). The outputs are the results or consequences of the inputs with the existing equipment. These can include intermediate values within the batch process.

The data could be entered into the computer by hand through a CRT interactive terminal, and the return advice provided through a simple printed report. In fact, this constitutes a practical way to start implementing ULTRAMAX as prework for an automatic operation and as part of overall plant data unification. This exercise provides important insights as to the operation of the facilities and refines the definition of goals, i.e., the objectives and the constraints.

Usually there is computer control technology already in place to provide an easy link between the operator and the batch process, for instance, Fischer & Porter's DCI-5000 system. This system facilitates setting setpoints for the controlled variables, which is one type of input. There are typically many monitors for the control ware to know the value of external values (another type of input) and the results obtained. Frequently there are, also, results which come from laboratory tests which may or may not be automatically linked with the data highway.

Exhibit 1 illustrates a fully integrated, largely automated approach. Executive modules of the host computer accumulate the automatic input/output data until any other data for the batch is available, and then the complete batch data set is loaded into ULTRAMAX to update learning. In turn, every time an advice is desired, such as every so-many batches (for feed-back optimization) or when there is a known change in an external variable (for feed-forward optimization), the advice is requested and implemented, i.e., new set-points set for the control ware.

Until a sufficient data base is generated, a new advice and data point is generated for each batch. Especially at the beginning, the operator or engineer excercises continuing judgement to accept or modify the advice. Notable improvements are usually seen after four-times as many batches as there are input variables. Near optimal settings are typically achieved when there are as many data points (batches) as ten-times the number of input variables. The magnitude of most savings for most applications become evident by then.

This technology can detect when results are outside expected limits, such as in statistical control charts, to ring an alarm and call the attention of the operator.

2.2. Representing an Operation

Representing an operation is simply to define the role of each variable, as follows, with a TYPE number:

1 - Controlled variables, which will not change unless it is desired to change it. Note that insufficiently controlled intermediate variables always have more primitive, truly controlled variables, such as a valve position (primitive) which affects a flow (intermediate).

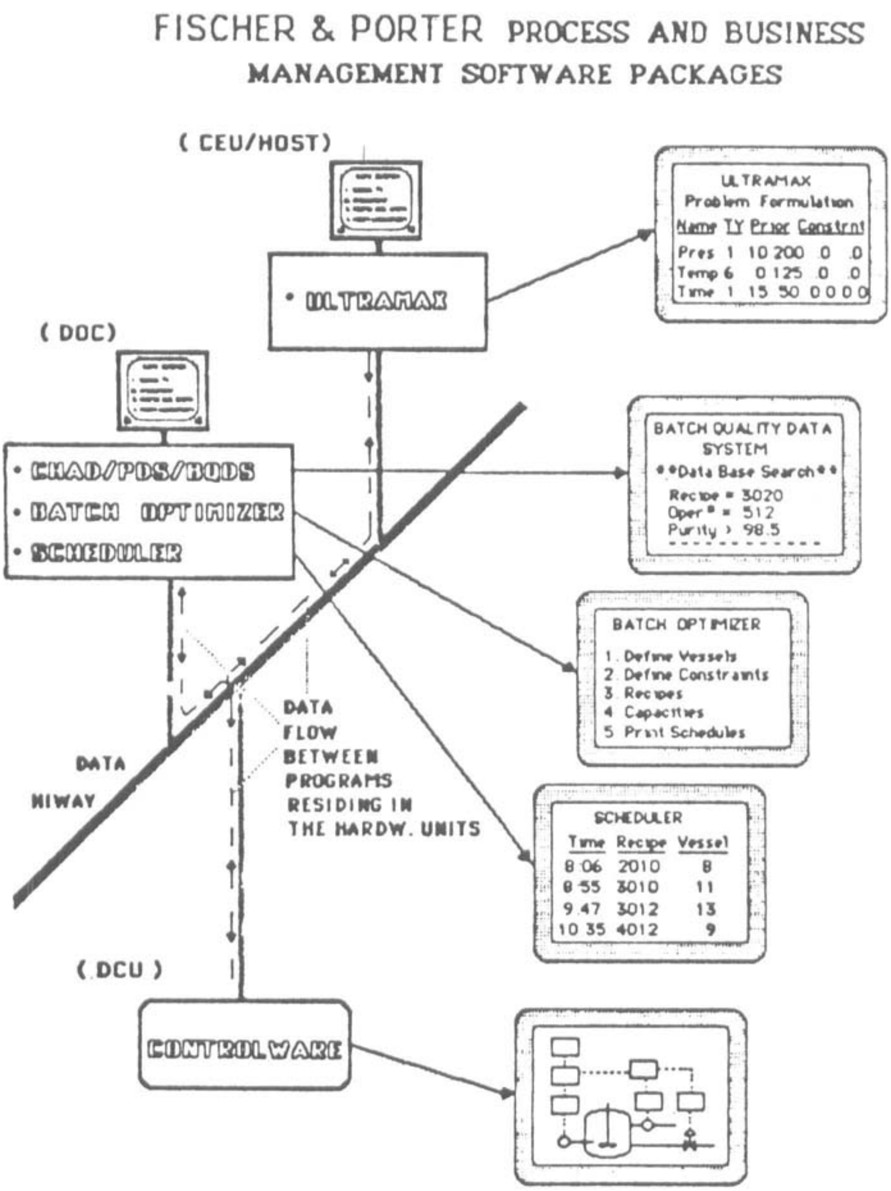

Exhibit 1, An Integrated Plant Control and Optimization System

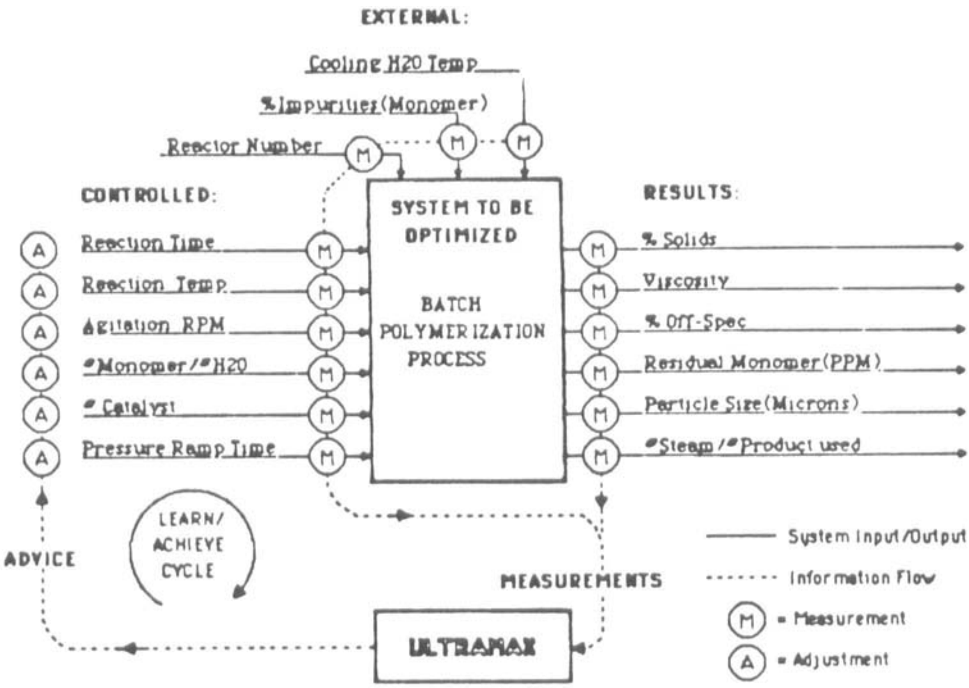

Exhibit 2, An Input-output Diagram

2 - External variables, which are set elsewhere, and the process itself does not change.

5 - Results variables, which are the consequence of the Controlled and External variables. This includes all intermediate variables, even though they are also an input to the next operating step.

6 - The Measure of Performance, the objective which you wish to maximize or minimize.

Exhibit 2 shows a typical way to portray the relative role of the different variables for a particular problem.

The Goal includes, in addition to the objectives, any constraints within which you must operate, such as specification or the intermediate or final product(s), capacity or safety limitations, etc.

In addition, to start up, you must determine a prior region of the values of the variables so that the performance of the process and the interaction between the variables can be explored without affecting the quality or productivity of the operation.
Following is a pharmaceutical example:

COATING GRANULES:

The process consists of spraying a coating on granules in a rotating drum through which hot air flows. The objective is to provide maximum consistency of active coating weight per granule, which in turn results in reduced losses due to screening processes downstream.
The problem is formulated for ULTRAMAX as follows:

ULTRAMAX PROBLEM FORMULATION

GRANULES Coating Maximum Consistency 16:44 TUE, 04 JUN 1985

VAR #	NAME	UNITS	TYPE	MODE	TRSF	PRIOR REGION LO	PRIOR REGION HI	CONSTRAINTS LO	CONSTRAINTS HI
1	Granules	#/Ba.	1	H	0	100.0	150.0	90.00	175.0
3	Coating	#/Ba	1	H	0	23.00	35.00		
2	Cycle Time	Hr/Ba.	1	H	0	1.500	2.200		
4	Rotation	Amps	1	H	0	10.00	12.00		
5	Air Flow	CF/M	1	H	0	5.500	7.500		10.00
6	Air Temp	Deg C	1	H	0	55.00	75.00		75.00
8	Abs.Humid.	%	2	H	0	0.10	2.00		
9	Coatg %H2O	% wt	2	H	0	65.00	75.00		
11	Avg Coatg	mg/gr	5	H	0	1.200	1.800	1.46	1.54
12	Out Specs	%	6	H	0	15.000	25.000		

PARAMETER(50) : -1 MINIMIZING result variable of type 6

Exhibit 3, A Problem Formulation

This means that before a batch we will know the values of the external variables (type 2): Absolute Air Humidity and Water Concentration in the Coating fluid.

Giving these values to ULTRAMAX, it returns a set of setpoints for the controlled variables (type 1): lbs. Granules per batch, lbs. Coating fluid per batch, Cycle Time, amount of Rotation, Air Flow and Air Flow Temperature. Spraying parameters are held constant.

The results of importance are: (type 5) average milligrams of active coating per gram of finished product, and (type 6) percent granules outside specified weight limits, which are measured in the laboratory from a well-drawn sample from the whole batch.

The goal is to reduce the (type 6) percent of granules outside specs, while the average weight of the coating is within specs.

An alternate goal might be to minimize standard deviation of the particle weight while the average active weight is as consistently close to target as possible.

In other processes the concern might be to reduce the costs of expensive ingredients or processing steps to achieve desired product performance. Still other objectives might include production rate and its influence on revenues, for direct profitability optimization, even if at the expense of higher unit costs.

3. SUMMARY

Reliable, self-learning, optimizing technology is now available to serve as advisory control systems in pharmaceutical batch operations, particularly for largely or entirely automated plants. Improved consistency, reduced losses, reduced costs and improved production rates are typical benefits to be obtained.

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[2] ULTRAMAX is a Registered Trade Mark of Ultramax Corporation, Cincinnati, Ohio