ABSTRACT
The application of computer simulation has been proposed and implemented to optimize an integrated manufacturing system using lean manufacturing principles.
A simulation model only acts as a tool in examining performance. It is essentially a trial and error methodology, and does not directly provide explanations for observed system behaviors. Therefore, in this paper the use of design of experiment in simulation is studied to solve decision-making problems in integrated manufacturing systems. In order to achieve the objectives described above, the authors have developed a simulation model for a manufacturing process in the packaging area.
In particular, the authors have been modeling the automatic material handling and storage system served by automatic guided vehicles (AGV) versus packaging lines in a pharmaceutical plant. The lean manufacturing principles have been used to simulate different settings of the process as bottleneck removal, buffer removal and kitting operation introduction. The design of experiment 2^5 factorial design has been used to optimize the scenario.

Keywords: Simulation, Design of experiments, Factorial experiment, AGV, Pharmaceutical Plant

1. INTRODUCTION
The modeling and analysis of integrated manufacturing systems have become more and more important since the wide acceptance of factory automation. However, in many integrated manufacturing systems, production processes are complicated by many interactions between these processes such as deadlock, conflict, as well as uncertainties in the manufacturing environment such as machine failures, tool changes or variability in production requirements. As a result, technologies based on specific management objectives are necessary to model and analyze this class of systems (Tsai 2002).
An approach that can assist engineers and managers is the application of computer simulation (Law 1991). Since the early development of models and languages, simulation has evolved into a technique, which is extremely useful as a facility to test on the model rather than the real-world system, and also to analyze the relationships between the parameters and output behavior. Moreover, there is flexibility in the use of simulation languages, the model can be built as close to reality as we need and taken as a decision-making support tool. Thus, it is very helpful to analyze, schedule or plan manufacturing systems using simulation instead of using complicated mathematical model equations (Galbraith 1994).
Significant work has been performed over the past 25 years in the areas of simulation language development, simulation model design, and model/memory optimization (Tsai 1997). Less attention has been focused, however, on the issues associated with the use of the simulation model as a design and analysis tool. Often, once a simulation model has been verified and validated, the modeler will initiate a series of tests in a random fashion in order to determine the effect of these changes on the model’s output, or response. It is essentially a trial and error methodology, and does not directly provide explanations for observed system behaviors. This approach to scenario creation often results in a “good” solution to the design problem, but does not always result in an optimal solution (Callahan 2006).
Many existing manufacturing system design procedures attempt to minimize a static measure of material handling time or cost, but the performance of a manufacturing system can also depend on other factors such as the batch sizes of parts, scheduling rules, downtimes and setup times on machines, and demand. So, basically there is a need to determine the combination and level of these factors so that a measure of performance is optimized (Ekren and Ornek 2008).
A simulation model only acts as a tool in examining performance. The activities involved in simulation models are to predict results from operational parameters and to select the best solution from a variety of possible options. Combining simulation modeling with design of experiments analysis can be a powerful tool in developing near optimal solutions in a short period of time.
This paper describes a systematic methodology for the use of DOE methods in conjunction with a system simulation study. An application of this methodology is
also presented that analyzes a specific manufacturing system of pharmaceutical plant. In this paper, the use of Factorial experiment in the activities of simulation is proposed to achieve the objectives above.

The experimental design is carried out by simulating the system using the ARENA 10.0 (Hammann 1995) simulation software and analyzing outputs using Minitab statistical package.

2. USE OF DESIGN OF EXPERIMENT

Experimental design is a strategy to gather empirical knowledge, i.e. knowledge based on the analysis of experimental data and not on theoretical models. It can be applied whenever you intend to investigate a phenomenon in order to gain understanding or improve performance.

Building a design means carefully choosing a small number of experiments that have to be performed under controlled conditions. There are four interrelated steps in building a design (Montgomery 2005):

- Define an objective to the investigation, e.g. better understand or sort out important variables or find optimum.
- Define the variables that will be checked during the experiment (design variables), and their levels or ranges of variation.
- Define the variables that will be measured to describe the outcome of the experimental runs (response variables), and examine their precision.

Among the available standard designs, the modeler choose the more compatible with the aims, number of design variables and precision of measurements, and reasonable cost.

Standard designs are well-known classes of experimental designs. They can be generated automatically as soon as you have decided on the objective, the number and nature of design variables, the nature of the responses and the number of experimental runs you can afford. Generating such a design will provide you with a list of all experiments you must perform, to gather enough information for your purposes.

Design of Experiments (DoE) is widely used in research and development, where a large proportion of the resources go towards solving optimization problems. The key to minimizing optimization costs is to conduct as few experiments as possible. DoE requires only a small set of experiments and thus helps to reduce costs.

Design models are very different among authors, particularly in the names of activities and in the level of whom tasks are defined. But the models consistently identify similar types of activities as central to design: problem identification and definition, ideation, evaluation and analysis, and iteration as quintessential examples. Furthermore, most models recognize that design projects transition pass through phases, or alternatively, that designers operate at different cognitive levels of abstraction over the course of a design project. Again, the phases, cognitive levels and labels can differ widely, but most models start with an early conceptual phase, end with a detail design phase, and connect the two with one or more intermediate phases.

Factorial design are widely used in experiments involving several factors whose it is necessary to study the joint effect of the factors in a response.

It is very often required to investigate the effect of several different sets of treatments, or more generally several different explanatory factors, on a response of interest.

Factorial designs allow for the simultaneous study of the effects that several factors may have on a process. Tester make an experiment, varying the levels of the factors simultaneously rather than one at a time is efficient in terms of time and cost, and also allows for the study of interactions between the factors. Interactions are the driving force in many processes. Without the use of factorial experiments, important interactions may remain undetected.

The different aspects defining treatments are conventionally called factors, and there is typically a specified, usually small, number of levels for each factor.

A single treatment is a particular combination of levels of the factors.

A complete factorial experiment consists of an equal number of replicates of all possible combinations of the levels of the factors.

There are several reasons for designing complete factorial experiments, rather than, for example, using a series of experiments investigating one factor at a time. The first is that factorial experiments are much more efficient to estimate main effects, which are the averaged effects of a single factor over all units. The second, and very important, reason is that interaction among factors can be assessed in a factorial experiment but not from series of one-at-a-time experiments.

Interaction effects are important in determining how the conclusions of the experiment might be applied more generally.

Experiments with large numbers of factors are often used as a screening device to assess quickly important effects and interaction. For this reason it is only common to set each factor at two levels, with the aim to keep the size of the experiment manageable. The levels of each factor are conventionally called low and high, or absent and present.

Very often experimenters do not have adequate time, resources and budget to carry out full factorial experiments. If the testers can reasonably assume that some higher-order interactions can be obtained by running only a fraction of the full factorial experiment. A type of orthogonal array design which allows experimenters to study main effects and desired interaction effects in a minimum number of trials is called a fractional factorial design. These fractional
factorial designs are generally represented in the form $2^{(k-p)}$ where $k$ is the number of factors and $1/2^p$ represents the fraction of the full factorial $2^k$.

This paper takes full advantages of factorial experimental design and simulation to identify and to weight the importance of different factors in the operation of integrated manufacturing system (Antony 2005).

The following methodology is proposed as a technique for quickly and effectively gaining information from a simulation model.

1. Develop a simulation model that addresses the impact of the more important factors in the system on output.
2. Perform verification and validation on the simulation model.
3. Determine the experimental design for a 2k factorial using the inputs and outputs from the simulation model.
4. Adjust inputs to the simulation model in various combinations, as specified by the factorial design, and collect data from the simulation output.
5. Use DOE techniques (and software) to conduct a factorial analysis using the inputs of the simulation as factors and the output of the simulation as the response or responses.
6. Interpret the data and determine the best combination of input factor settings using the ANOVA, effects graphs, and interaction graphs.
7. Repeat the process, if necessary, to further refine significant factor levels.

3. A CASE STUDY OF PHARMACEUTICAL PLANT

This case study is about a pharmaceutical plant and in particular its automated guided vehicles (AGV) system.

The aim was the optimization of AGV’s flow between packaging area (called white area) and warehouse.

The layout is shown in figure 1. In particular this case study refers to packaging and warehouse areas in order to optimize the AGV flow.

- Warehouse: it has been automated by 5 automated storage and retrieval machines (ASRS) that transport units on 5 roller conveyors. It had a capacity of 15000 cells. Shelving cells are structured for euro-pallets dimension. At the end of the warehouse there were 5 roller conveyors that canalized units versus corridor and packaging area.
- Shape Control: it was an activity to control the shape of the pallets and assigned the cell before storing in the warehouse. There were 3 stations for shape control.
- Buffers: two buffers were present in the layout. The first one was at the end of warehouse in which units are cumulate holding AGV. The second one was before white area, at the end of the corridor, in which units holds to be loading in the packaging lines.
- AGV: two type of AGV were in the considered area. The AGV called “White” had the function to transport the pallets through the black corridor. The white AGV were 4 with capacity of 1200 kg each one. The AGV called “Blue” had the function to transport as pallets as bins through White Area that was the packaging area of medicinal drugs. The blue AGV were 2 with a capacity of 2200 kg each one. Pallets dimensions were 1.160 mm x 1.200 mm x 2.300 mm for both AGV types. Moreover both types was endowed with bumpers and sensors for automatic stopping in case of obstacles presence.

3.1. Modeling Issue

Following the lean manufacturing principles (Melton, 2005), a simulation model was developed to assess:

- removal of the two buffers in order to serve the packaging lines just in time. Resource wastes existed in drop & pick of AGVs in the different buffers. Buffers removal aimed to decrease AGVs cycle time and delay of the packaging lines starting production process due to the absence of processing batch conveyed by AGVs.
- removal of roller conveyors at the end of the warehouse that were a structural bond in the system and bottleneck. The model simulates the absence of roller conveyors and the presence of a pick and drop station at the end of each automated storage and retrieval machines (ASRS) that could be served directly by AGVs.
- optimization tool; this tool was add-on to the model because the AGVs were inclined to come back to the battery charger points after a mission failed according to logic that assigns the missions near the drop stations. The
optimization tool has the task to find the path with the less times for the mission in the whole possible paths. The impact of the time necessary to elaborate the path solution has been assessed with simulation model.

- kitting activity: to avoid the presence of different types of material in a pallet a kitting activity was design at the end of the warehouse. In the pharmaceutical sector laws forbid the presence of incompatible materials in the same pallet. The impact of the presence of kitting activity on the system has been assessed with simulation model.

The simulation model has been validated under different setting conditions. Simulation model design is shown in figure 2.

Figure 2: Simulation model design (Arena elaboration)

3.2. Design of Experiment
In the following the steps for the analysis are shown.

3.2.1. Factors and levels
In the design of experiment, process variables include both factors and responses. The selection of these variables is best done as a team effort. The team should:

- include all important factors;
- check the factor settings for impracticable or impossible combinations;
- include all relevant responses;
- avoid using only responses that combine two or more measurements of the process.

From this point of view the project team has identified the variables and their levels for the simulation experiment. As shown in the previous paragraph, simulation model deals with 5 variables critical for the system:

- number of white AGV.

The response is the delay of the packaging lines starting production process due to the absence of processing batch conveyed by AGV.

Each variable has been analyzed in order to determine the number of levels in 2\(^{5}\) DOE design:

- number of blu AGV: this factor, called A, is set in the real system in 2 AGV; in the simulation we are interested to assess the effect of 2 (+) or 1 (-) AGV in action;
- number of white AGV: this factor, called B, is set in the real system in 4 AGV; in the simulation we are interested to asses the effect of 4 (+) or 3 (-) AGV in action;
- kitting activity: this factor, called C, may influence the number of AGV cycles in the system; the levels are relating to the presence (+) or not (-) of this activity;
- optimization tool: this factor, called D, may influence the AGV cycle time in the system; the levels are relating to the presence (+) or not (-) of this tool;
- contemporaneous packaging lines: this factor, called E, influences the cycle time of system; the levels have been fixed to 3 (-) or 4 (+) contemporaneous lines after simulation runs.

3.2.2. DOE: first step analysis
The objectives for the experiments have been determined by a team discussion. First of all it was necessary to identify which factors/effects were important. Factorial design are widely used in experiments involving several factors whose it is necessary to study the joint effect in a response. In this case the number of parameters (5) yields number of experiments equal to 32 (2\(^{5}\)). Referring to the objectives of this experiment is useful to use an half reduction design of 16 (2\(^{5-1}\)) experiments.

The experimental design and the alias structure obtained by Minitab software are shown in figure 3.

A confounding design is one where some treatment effects (main or interactions) are estimated by the same linear combination of the experimental observations as some blocking effects. In this case, the treatment effect and the blocking effect are said to be confounded. Confounding is also used as a general term to indicate that the value of a main effect estimate comes from both the main effect itself and also contamination or bias from higher order interactions. They also occur whenever a fractional factorial design is chosen instead of a full factorial design.

In the case it was V resolution design with ABCED = I; no main effect or two-factor interaction is aliased with any other main effect or two-factor interaction, but two-factor interactions are aliased with three-factor interaction.

The higher the resolution, the less restrictive the assumptions that are required regarding which
interactions are negligible to obtain a unique interpretation of the data.

Figure 3: First step DOE (Minitab elaboration)

The result could be discussed after the simulation that takes one hour each one.

Before the conclusions from the first step of DOE, the adequacy of the model should be checked. Factorial design makes assumptions about the errors:

- the errors are normally distributed with mean zero;
- the error variance does not change for different levels of a factor or according to the values of the predicted response;
- each error is independent of all other errors. In a designed experiment, the best way to obtain independent errors is to randomize the run order of the experimental trials.

The diagnostic tool, used in the case study, is residual analysis shown in figure 4.

The probability plot is used for the standardized residuals to check whether:

- the distribution assumption is appropriate;
- the assumption of equal shape (Weibull or exponential) or scale parameter (other distributions) is appropriate.

The probability plot for standardized residuals combines the data to calculate one fitted line, thereby making it easier to determine if the plot points hug the fitted line. If the plot points hug the fitted line then the assumptions are appropriate. The assumptions can be violated when the line does not adequately fit the points. In the case study the plot points hug the fitted line adequately and therefore provide evidence that the assumptions are validated.

A histogram of the residuals shows the distribution of the residuals for all observations. Testers use the histogram as an exploratory tool to learn about the following characteristics of the data:

- typical values, spread or variation, and shape;
- unusual values in the data.

The histogram of the residuals should be bell-shaped.

In the case study the residuals didn’t appear to indicate the presence of an outlier confirming the normal distribution.

Residuals versus fits plots the residuals versus the fitted values. The residuals should be scattered randomly about zero. This plot points out nonconstant variance an outlier.

In the case study the residuals appear to be randomly scattered about zero.

Residual versus error graph plots the residuals in the order of the corresponding observations. The plot is useful when the order of the observations may influence the results, which can occur when data are collected in a time sequence or in some other sequence, such as geographic area. This plot can be particularly helpful in a designed experiment in which the runs are not randomized. The residuals in the plot should fluctuate in a random pattern around the center line. Testers examine the plot to see if any correlation exists among error terms that are near each other. Correlation among residuals may be signified by:

- an ascending or descending trend in the residuals
- rapid changes in signs of adjacent residuals

For the case study data, the residuals appeared to be randomly scattered about zero. No evidence seemed to exist that the error terms were correlated each other.

Therefore the validity of these assumptions in analysis was confirmed.

The Pareto Chart, shown in figure 5, pointed out the importance on response (with significant level $\alpha=0.01$) of all factors except for optimization tool. Moreover the effect of kitting activity, number of blu AGV, number of white AGV was influenced by alias structure. Therefore, the factor optimization tool was set the level of (-), the factor contemporaneous lines was set the level (-) as discussed in the results paragraph.

3.2.1. DOE: second step analysis

A complete factorial design $2^3$ has been performed including the remaining variables.

The experimental design obtained by Minitab software is shown in figure 6. All terms are free from aliasing.

The results have confirmed the important effect (with significant level $\alpha=0.01$) of factors number of AGV blu and white as shown in figure 7. On the other hand, no influence of kitting activity has been foreseen.
The main effects plot, as shown in figure 8, shows the effect of the factors on the response and compare the relative strength of the effects.

The factor number of blue AGV has been set the level of (+) and the factor number of white AGV has been set the level (+) as discussed in the results paragraph.

The factor kitting activities has been set (+1) to evaluating the third combination factors by cube plot as shown in figure 9.

Figure 7: Pareto chart second step DOE (Minitab elaboration)

Figure 8: Main effect plot second step DOE (Minitab elaboration)

Figure 9: Cube plot second step DOE (Minitab elaboration)

### 3.2.2. DOE Results

Summarizing, the optimal configuration was:

- Blue AGV set at the number of 2 AGV; it’s the most important factor for the response in the system with 1500 s of impact on performance as shown in figure 7; this is due also to the functionality of this type of AGV in the system
that may transfer both BIN missions and pallets as shown in the previous paragraph;

- White AGV set at the number of 4 AGV; the running operation of white AGV has an important impact of 500 s on the response;
- Kitting activity set at level (+1) because its presence is requested in the system; but as shown in figure 7, the absolute value doesn’t have an important effect; but considering the combined effect with numbers of AGV, fig.7, factor we could conclude that the presence of kitting activity improve (435 s) the impact on final performance;
- Optimization tool set at level (-) because its presence is not requested in the system; optimization tool improves the AGV flow in the system but slows down the whole performance due to the time for mission allocation;
- Contemporaneous lines set at number of 3. Increasing of contemporaneous lines increases the traffic in the system with an important impact on the final response as shown in figure 9.

The design of experiment has not only allowed to define the optimal configuration with the delay of the packaging lines starting production process equal to 0 s but also to quantify the results of the impact in the system. The optimal configuration allows to reduce the delay of 435 s.

4. CONCLUSIONS
In this paper the application of computer simulation and design of experiment has been proposed and implemented to optimize AGV’s flow between packaging area (called white area) and warehouse of a pharmaceutical plant and in particular its automated guided vehicles (AGV) system.

Manufacturing systems can be very complex with numerous paths of material flow and varying capabilities of equipment. Simulation modeling is well suited to represent these systems and can be enhanced by including design of experiments techniques as shown in the case study.

Simulation modeling is well established and can be very useful in analyzing the performance of a manufacturing system. These models can become very complex as the number of factors and system outputs increase. In this article, a study was done to investigate the usefulness of combining DOE techniques with simulation modeling. The DOE techniques were used to determine the number of experiments and factor level combinations necessary to fully and efficiently represent all possible scenarios for the defined model.

REFERENCES