Enzymes and evolutionary operations

Trine Kvist and Peter Thyregod used 10 glasses of beer, Excel, and a statistical method developed in the 1950s to improve yield in a biotechnology plant

In biotechnology, production is often characterised by relatively few, large batches and uncontrollable background variables. Final optimisation usually has to be done in full-scale production. Traditionally, when attempting to improve yield, the industry has conducted relatively simple trials where the process engineers vary one factor at a time. This approach is inefficient and does not take account of interactions between variables. Engineers need a tool for optimisation that is more scientific but still easy to use.

Statistical methods for experimentation can provide invaluable information in the design stages of a new process. However, optimum conditions in laboratory or pilot plant often give yields that are lower than expected, when transferred to full scale production (see Figure 1). This is due to scale-up effects and to large inherent variations when dealing with biological material and processes such as fermentation. Any alternative experimental procedure should be robust to non-controllable variations; it should contain automatic safeguards to ensure that unsatisfactory material is not manufactured; and process engineers should be possible to make decisions while the trial is running.

The method of evolutionary operation (EVOP) suggested by George Box fulfils these requirements[1]. It is a method for continuous process improvement developed in the 1950s. The key point is to introduce small changes in the operating variables systematically. In theory, any number of variables can be included, but in practice it will be feasible to alter only two or three variables. A trial may consist of several small factorial designs run sequentially.

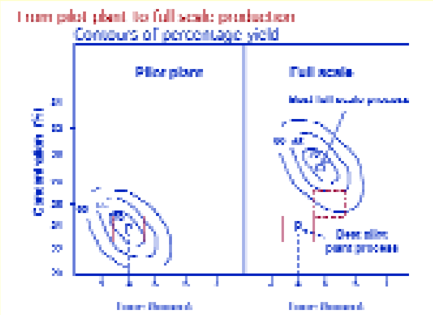

Figure 1: Possible appearance of yield surfaces, showing contours of percentage yield, for a process conducted on the small scale and on the plant scale.

We implemented EVOP at the biotechnology company Novozymes A/S, by making an Excel tool available to the production engineers. With this tool, the user can choose between four different designs: two and three factor designs with and without centre point. The Excel tool computes the effects and presents the confidence intervals for each effect. We extended the method by using historical data to estimate process variation, from about 25 batches.

The Excel tool is taught as part of a two-day all-round statistical course for production engineers. Here we emphasise the importance of focusing on the confidence intervals rather than the p-values. The problem with focusing on p-values in such trials is that the trials are not designed to find a difference with a certain probability. Thus, an effect that is insignificant may still be interesting. If the confidence interval encompasses interesting yields, the effect may still be important even though it is not statistically significant. In such a case, the trial would need to be extended by another round.

Figure 2: Measurement of froth height.

To train the engineers in using the EVOP tool, we run a beer game as part of the course. The objective is to find what factors affects the frothing – the 'head' – when pouring beer. The experimental result is the froth-height, measured with a ruler (see Figure 2). The participants come up with the variables to be included. Common suggestions are: beer type; glass angle; beer temperature; pouring speed; and glass type.

At Novozymes, EVOP was used to optimise a specific process for the fermentation of an industrial enzyme. Industrial enzymes are produced using a process called 'submerged fermentation'. This involves growing carefully selected micro-organisms (bacteria and fungi) in closed vessels, containing a rich broth of nutrients (the fermentation medium) and a high concentration of oxygen (aerobic conditions). As the micro-organisms break down the nutrients, they release the desired enzymes into solution. The three variables chosen for the trial were pH, temperature, and nutrient dosage. A 2^3 experiment was run, and an interaction between temperature and dosage was found to have a potential effect on the yield. Changing the setting of these variables led to a 45 per cent increase of the yield (see Figure 3). Eight batches were used in the trial, and they were all approved finished goods.

We recommend EVOP when experimenting during the course of production. We found it to be extremely useful in industrial bulk production.

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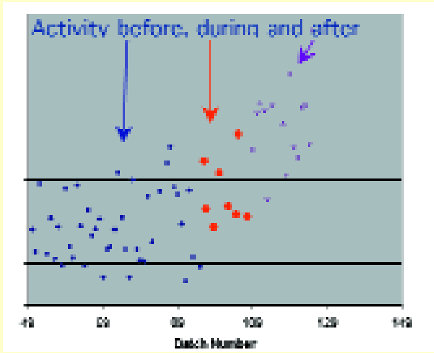

Figure 3: Activity of batches produced before, during and after the trial. The trial was a 2^3 experiment performed in eight tanks. All batches should be and were saleable.

References

[1]: G. Box and N. Draper: Evolutionary Operation, John Wiley & Sons 1969.

Tube Welding

Xavier Tort-Martorell and Lluís Marco describe the steps and lessons that led to process improvement

CH Werfen is a Spanish multinational company that manufactures and distributes medical devices. It was having problems with the catheter production process – rejection levels were very high and so production costs were soaring. The quality manager contacted the department of statistics at the Technical University of Catalonia (UPC) and launched a project to study the process and understand what was causing the trouble.

Making catheters involves five steps: pointing, rather like sharpening a pencil; two welding steps; soft-tip welding; and finally conformation. All steps are performed in the same machine and one of them (step 3, the second welding step) involves the welding of two tubes made from different materials. This is the most complicated step and had the highest levels of rejects (an average of 12 per cent, with some machines close to 20 per cent). After welding, all catheters are inspected against five criteria. Even if it fails only one of these criteria, the catheter is rejected.

The company's idea was to perform a statistically designed experiment to understand how the different controllable factors (for example, driving pressure, temperature, time) affected the five important quality characteristics of this welding operation.

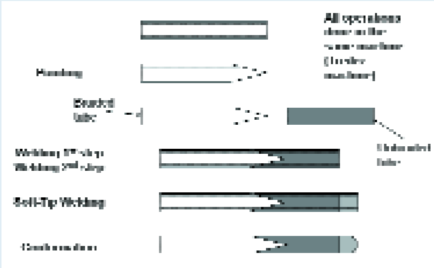

Figure 1. Steps for producing the catheter.

We proposed a different approach, which was firstly to learn about the process from data available – if necessary, from data collected in an organised way; and only then design and conduct a formal experiment.

The information gathered in the first stage would be helpful in designing the experiment and it could lead to significant improvements. The scarce data available showed large variability among welding machines, moulds and operators. Data sheets were therefore prepared to collect data, stratifying by operator, machine, mould, and raw material.

The data-collection phase lasted a month. Data was analysed using graphical presentation tools that everybody in the company could understand. Some were very basic and well known, such as Pareto charts, histograms, and scatter diagrams; others like the Multivari Chart (see Figure 2) were not as popular but still very powerful. Figure 2 shows the percentage of defects at second welding step. It shows:

- One mould (D) was in poor condition;
- One machine (6) was worse than the others; and
- Operators were performing differently – in fact, the data led to the discovery that they were using different machine settings.

Similar graphs showed a large variability due to raw material and it was found that humidity in the raw material was a very important factor.

Several actions were implemented from the information gathered:

- Training of operators (with detailed instructions on how to push the tube into the machine);
- Selection of best moulds and machines; and
- Slight changes in the process itself.

Fewer units were rejected through all steps of the process. The greatest reduction was at the second welding step – initially the step with most rejects – where the average rejection fell from 12 per cent to 7 per cent.

Following this success, we agreed to seek further improvements by conducting a simple experiment, focused on the welding steps and the raw material. We assembled a team of engineers and operators. As usual, they knew a lot about the process, but not in a quantified way.

Using their knowledge about the process, the information gathered from the data, and our knowledge of designing experiments, we designed and conducted a factorial experiment with each condition being replicated five times. We wanted to reduce the initial list of more than 30 process variables considered

FOCUS ON UPC

The Technical University of Catalonia (UPC) specialises in architecture, engineering, nautical science, economics, health sciences and applied mathematics. UPC was founded in March 1971 from several independent schools with long traditions in these fields, some of whose origins can be traced back to the mid-19th century.

UPC currently has 10 schools, 40 departments, 28,000 students and almost 3,000 lecturers. With a budget of more than €41 million, the technology transfer centre is one of the engines of research and development for the Catalan region's industrial sector, achieving economic self-sufficiency for the majority of its research work. UPC is currently working on more than 250 research areas with an increasing number of specific research and regional technology centres that also focus on social demands.

The statistics department is active in several areas, including:

- Integer programming and combinatorial optimisation;
- Optimisation and simulation of network flows;
- Computational statistics;
- Multivariate data analysis;
- Automatic identification of time series;
- Intelligent interfaces between users and statistical applications;
- Statistical methods for control and quality improvement; and
- Statistical methods for industrial process management including Six Sigma.

The last two can be grouped together under industrial and business statistics. The department is an active member of ENBIS and has collaborated, and continues to do so, with many public and private organisations including: La Caixa savings bank; Hewlett Packard; Transports de Barcelona; Catalan Institute of Statistics; Nissan European Technology Centre (NETC); Barcelona Provincial Council; Samsung electronics; BBVA (Spain's second largest bank); Procter and Gamble; Siemens VDO; and Alstom Transport.

as potentially important to only eight. We also wanted the welding process to be insensitive to the characteristics of the raw material (related to tube diameters, material humidity and tube concentricity) that were impossible to control in normal production.

We discussed the experimental ranges for each of these variables. This was critical since we wanted the range to be big enough for the variable to produce a detectable effect yet small enough so that the effect produced was

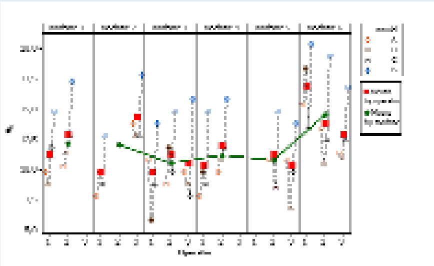

Figure 2. Multivari Chart for % Rejects

not 'weird' – dominated by measurement uncertainty. This process of variable and variation range selection helped engineers to organise and make explicit a lot of hidden knowledge.

Five responses were considered in the experiment, corresponding to the five criteria for accepting a catheter: cohesion between tubes (destructive test); tensile strength (destructive test); welding aspect; presence of traces and rough surface.

The experiment led to considerable learning, but the most important discovery was made during the preparation phase when the team realised that humidity, an important variable in the tube-injection process, was not being well controlled. Careful operation of a dehumidifier – for drying the pellets prior to injection of the tubes – accounted for much of the improvements. The rejection rate at the injection process went from 20 per cent before the study to 1.7 per cent at the end.

The most important discoveries in this project came from considering the data in an organised way and thinking about the process before actually conducting the experiment. The key to success was the very good interaction between the company's engineers and the statisticians.

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Prevention is better than detection

Chris Angus and Malcolm Irving show how statistical process control cut defects in the manufacture of compressed-air breathing equipment

Dräger Safety UK specialises in the design and manufacture of compressed-air breathing equipment for safety applications. The company screens for defects at different stages during manufacture: either at assembly/final test; or in-process quality control checks downstream. But operating a policy of detection rather than prevention resulted in recurring processing problems on the assembly lines, usually associated with component non-conformance or process instability.

The Industrial Statistics Research Unit (ISRU) at Newcastle University recently provided training in statistical skills and effective thinking for the company's High Performance Work Team (HPWT). Team members were asked to identify opportunities for improving a key process.

This article describes a project by Malcolm Irving from Dräger Safety, which will also be discussed at the ENBIS conference in September.

Project Overview

One of Dräger Safety products was suffering from a low First Time Yield (FTY) of only 84 per cent. The company identified the most prevalent failure mode as Low-Medium Dynamic Pressure (LMDP), a mode that occurs when two poorly fitting components do not allow a predetermined test pressure to be achieved. Operators had commented that assembling these two components had become harder because the individual parts varied too much. Testing ensured that operational use of the apparatus was not affected by this assembly problem.

The project's goal was to understand the causes of the process variation, correct them and to increase the FTY to 95 per cent or better.

Proposal

A methodology known as DMAIC (Define Measure Analyse Improve Control) was used:

Define: identify and define the problem, structure the project, and set up the team;

Measure: collect data to establish a baseline for how much the current process varies from specifications and to check that measurement systems are statistically reliable;

Analyse: identify potential causes and quantify their effect using statistical tools;

Improve: make process improvements as identified in the analyse stage and validate the results in an operational environment.

Control: ensure measurement systems and management tools are in place to monitor processes long term, and to maintain the gains.

A key element of successful continuous improvement projects is to ensure that an effective management structure is in place. At the start of this project, a steering group and a main project team were established. The steering group – consisting of the operations manager (project champion); manufacturing manager, senior quality engineer; and an HPWT member – helped ensure that the project was highly visible within the company and that management was committed to it. The project team consisted of: the project team leader (HPWT member); a quality engineer; four machine-shop setters; two cell leaders; and the machine-shop manager.

The groups developed a charter outlining the purpose of the project and a 'problem statement' to define objectives clearly. The project charter had the following five elements:

Opportunity statement: As part of the company's drive toward achieving business excellence, an opportunity exists to develop and implement statistical process control as an element of the continuous improvement programme/roadmap to excellence.

Project scope: Statistical process control shall encompass all manufacturing processes. However, for the purpose of this project a manufacturing cell shall be used as a pilot to develop the methodology into a functional format.

Problem statement: The assembly and test

Process Performance before Improvement		
Cost of Poor Quality	=	£1287.30
Overall Percentage Failure Rate	=	15.2 per cent
First Time Yield Value (per cent)	=	84.76 per cent
Process Performance after Improvement		
Cost of Poor Quality	=	£239.58
Overall Percentage Failure Rate	=	6.98 per cent
First Time Yield Value (per cent)	=	93.02 per cent

Table 1 Before and after analysis of process performance

facility is currently experiencing an abnormal failure rate for Low Medium Dynamic Pressure. Operators have commented that assembly of the piston and plunger is becoming increasingly more difficult. This is causing unnecessary rework and inflated production costs.

Goal statement: The goal is the systematic reduction/elimination of special cause variation, that enables a more predictive/stable process to be deployed and to increase the process first time yield.

Process visualisation: So that all the team members can visualise the manufacturing process in the same way, a SIPOC (Suppliers, Inputs, Process, Outputs, Customers) process map was developed. The SIPOC enables the process inputs and outputs to be visualised and starts the basis for process improvement solutions to be generated. It further helps to identify areas for data collection.

The aim of introducing statistical process control (SPC) here is to reduce non-conformance by attempting to produce only usable output. SPC allows the identification and subsequent elimination of causes of component non-conformance, thus improving process capability and reducing process instability. The long-term aim is for SPC to act as one facet of a prevention strategy by the use of control charts.

Outcome

This project provided an opportunity for the company to gain direct experience of using the DMAIC approach to tackle a real problem. This provided a suitable framework to apply SPC techniques to develop an error prevention strategy. Analysis and visualisation of the process enabled the team to identify and remove leading causes of process variation. Two major process improvements were achieved:

- A reliable measurement system was developed;
- A change in process from a boring bar to a reamer.

This resulted in a more consistent quality of the pre-burnish bore: the manufactured product has less variability. The team has used several statistical tests to verify that a reduction in variability had been achieved and that the improvements were statistically significant. As a result the product is well within specification limits, one of the key aims of SPC. The graphs below show the process capability before and after the interventions (process capability analysis is a key tool in SPC).

Figure 1 shows the process capability before improvement. Much of the product is out of specification, the process is not centred about the target value and the capability indices are very poor.

The process capability after the improvement project is shown in Figure 2. The overall variability has been greatly reduced and the entire product is centred and manufactured well within specification. In Figure 2 the 'Expected Overall Performance' shows that zero parts per million are expected to be out of specification. The improved performance is also apparent in the capability indices – 4.26 is much higher than the common benchmarks for industrial processes.

To monitor the process over a long term, the team has developed in-house process-specific control charts that are continuously updated with live data. This gives shop-floor operatives vital information on how the process is performing and an indication of when and when not to take corrective action.

With the process now in statistical control, it is much easier to communicate the performance of the process and the quality of the output to the producers (supply chain) and the consumers (assembly line). This has enabled everyone involved to understand how the improvements were made and understand the benefits. The effect can be seen from the table below.

Because of the improved manufacturing process, Low Medium Dynamic Pressure (Low MDP) is no longer the most commonly occurring failure mode in assembly and subsequent testing. The overall failure rate has fallen from 15.2 per cent (989 instances per month) to 6.98 per cent (451 instances per month). As a result of the process improvements the occurrence of Low MDP as a failure mode has dropped from 535 instances (~54 per cent of the total failures) to 91 (~20 per cent of the total failures).

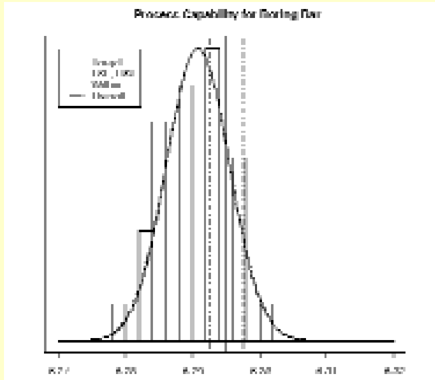

Fig.1 Process Capability using a boring bar

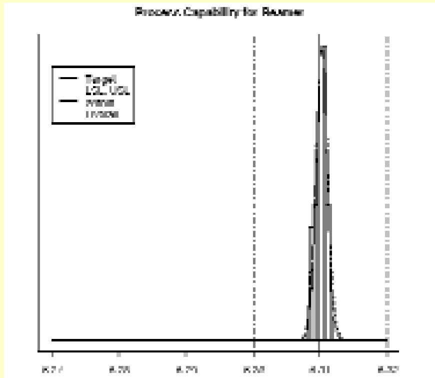

Fig.2 Process Capability using a reamer

First Time Yield (FTY) has increased from 84.76 per cent to 93.02 per cent. The team are working on further improvements to the system to increase the FTY.

In particular, SPC has:

- Identified the major failure mode;
- Indicated the process was not statistically capable;
- Validated process interventions; and
- Established long term monitoring mechanisms

The improvements have reduced costs significantly. Component piece part costs have reduced by £0.433p per component, a yearly saving of £28,000. Rework costs have reduced by £1,300. Cost saving due to the number of reduced process steps was £1,700. Due to the machining process being stable, unmanned running can be maximised giving a saving of £59,000 per year. The total cost savings were more than £90,000 a year.

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