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General Definition of Numerical Determination of the Critical Parameters

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Abstract:

Numerical determination of the critical parameters is a new methodology which enables systematic and transparent transfer of knowledge from the development phase to scale-up and production phase in an easily readable and simple form. In addition, it is the tool for comparison of the suitability of different production units/sites for a specified newly developed synthesis procedure.

Introduction

Currently, it is often the case that the technologies for chemical synthesis of the new chemical entities are developed in one side of the world but are tested and produced in the pilot and production plant on the other side.[1,2] Because of such worldwide transferring of knowledge, it often occurs that a part of the knowledge from the development stage is lost or not well transferred to the scale-up or production staff, especially the knowledge about the criticalness of the technological parameters. This knowledge is transferred orally, thus having an impact on higher costs, or is sometimes not even transferred at all for various reasons. In view of this, a need has evolved for a systematic tool for standardization of the output of the development stage (procedures, synthesis technologies). Such a tool would help transfer the gained knowledge in an easy, uniform, and understandable form. In this article we present such a tool, called numerical determination of the critical parameters. As can be seen, it is a very strong link and lever that connects the development people, the production staff, and management.

Numerical determination of the critical parameters is a logical consequence of the automation on the laboratory scale and the use of DoE[3] and multivariable analysis in the development stage. It is also a link between the chemical synthesis technology (procedures) and production-plant equipment. Finally, it is also a tool that could be used by the management for better evaluation of the development work performed in the synthesis development technology.

The Bases

The bases for the numerical determination of the (non)-critical parameters are the following:

(1) the symbol for designation of (non)criticalness of the working parameter,

(2) the working interval which is determined on the industrial scale,

(3) the factor of criticalness determined in the development stage, which depends on the size of the working interval.

Here is the standard expression for the description of the (non)criticalness of some working parameters:

$$P(\mathrm{sp}) := o(I_{\mathrm{working}}, y)$$

where

P stands for working parameter (variable) and for the labeling that should be used as the standard denomination, such as *T* for temperature or *p* for pressure; sp is a set point for the particular working parameter (etc. 25 °C for the *T*);

o is the symbol of the (non)criticalness, and only one of two characters is used for that reason (*C* for critical working parameter and *N* for noncritical working parameter).

$\boldsymbol{I_{\mathrm{working}}}$ is the working interval for a particular working parameter on the production line (or on the laboratory equipment and/or automated robotic systems) and depends only on the quality of the used equipment (e.g., 2 °C for *T*). It can be measured during the QC procedure for the working equipment or independently whenever needed (for the specified solvent, which is used and for the specified working interval of the selected parameter).

y is the factor of criticalness, and it is calculated from the equation $y = I_{\mathrm{confirmed\ interval}}/I_{\mathrm{working\ interval}}$. Parameter *P* is critical if $y \leq 3$ and noncritical if $y > 3$. Confirmed interval will be explained later.

:= is the sign for assignment.

Relative portions should be used for the working interval (I_{working}) only in molarity, volume of the solvent or the reactants, and the reaction time, whereas for other parameters the unit of the parameter should be written.

Here is an example for the general expression given above:

$$T(25\ ^\circ\mathrm{C}) := C(2\ ^\circ\mathrm{C}, 2)$$

The explanation of this statement is: **parameter temperature (*T*), which is set to the set point 25 °C is critical on this production line with the predefined working interval 2 °C because the factor of criticalness is smaller or equal to 3** (it will be later explained why the limit is 3). **The confirmed interval for this example was previously experimentally determined, and it was 4 °C.**

The main question that arises from the above statement is how the working intervals and the factors of criticalness are determined. Below is presented the principle according

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(1) http://www.arcweb.com/Community/arcnews/arcnews.asp?ID=375.

(2) http://www.atkearney.com/shared_res/pdf/CMR_BPO_Article_lckd.pdf.

(3) Roy, R. K. *Design of experiments using the Taguchi approach*: *16 steps to product and process improvement*; John Wiley & Sons: New York, 2001.

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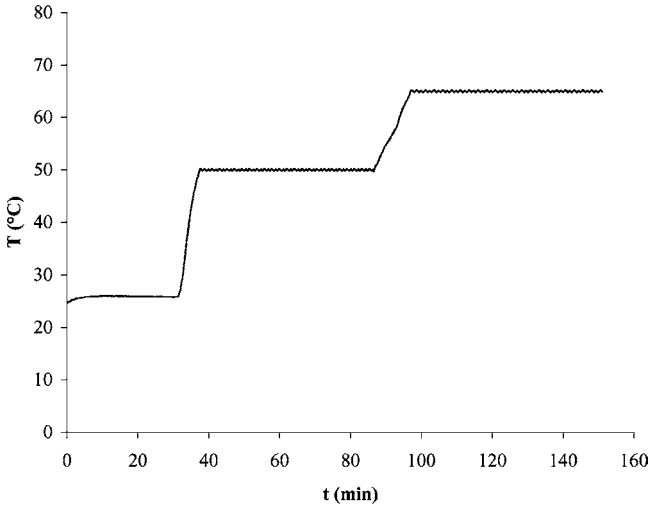

Figure 1. **Heating graph for the production system with the better fitness than the system in Figure 2 or 3. $I_{working}$ is 0.3 °C for the temperature range between 50 and 70 °C.**

to which these two numbers are determined during the development phase.

Let us assume that we start with a known synthesis route and that we need to perform the reagent and solvent screening for the reaction, as well as optimization and validation. At the end of this work we use the gathered information about the field of all synthesis parameter varieties for determination of the factor of criticalness.

Determination of Working Intervals. Working intervals are determined on the laboratory, pilot, and industrial scale during and/or after the calibration period and are determined as the maximum deviation of the reaction parameter (for example, a reactor with the temperature sensor and solvent (or reaction mixture) used for a specified reaction) from the set point in some working region for that parameter (in our case temperature). (More correctly, instead of the maximum deviation, the average of the absolute values of all deviations for that parameter in the specified region should be calculated; however, for the sake of simplicity and because the difference between the maximum deviation and average value is often small, maximum deviation could be taken for the determination of the working interval.)

Usually, the reaction solvent is used as a medium for determination of the working intervals. When the properties which influence the size of the working intervals of the reaction mixture (solvent + reagents) and the solvent itself differ too much, the reaction mixture is used for determination of the working intervals, especially in the pilot and industrial scale-up experiments. It should be remembered that the parameter for which the working interval is determined on the specified equipment must be constant for the measured set point or region.

Figures 1−3 show the example graphs for determination of the working intervals. Figure 1 shows the heating graph for more "accurate" system ($I_{working}$ = 0,3 °C), and in Figure 2 the same graph for less "accurate" system ($I_{working}$ = 2 °C) is shown. Figure 3 shows the worst (less accurate) system for temperature control ($I_{working}$ = 4 °C).

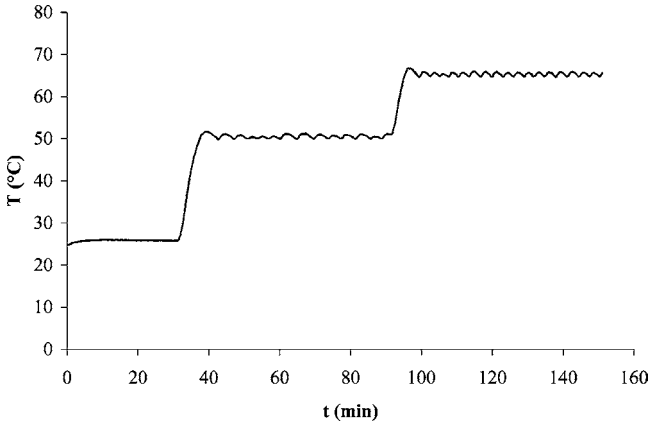

Figure 2. **Heating graph for the production system with the better fitness than the system in Figure 3 and worse than the system in Figure 1. $I_{working}$ is 2 °C for the temperature range between 50 and 70 °C.**

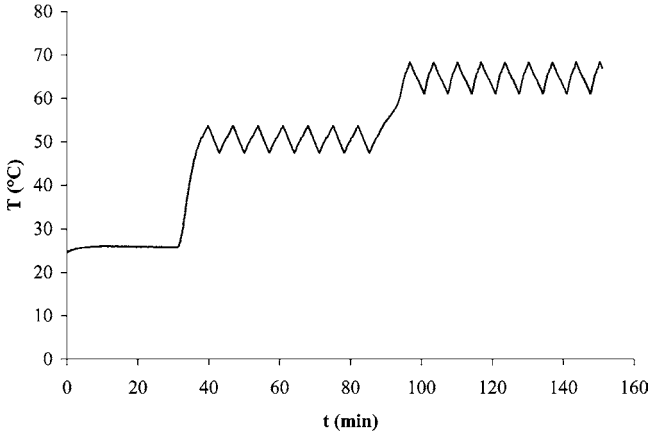

Figure 3. **Heating graph for the production system with the worst fitness. $I_{working}$ is 4 °C for the temperature range between 50 and 70 °C.**

Thus, if we have to determine the working interval for the solvent DMSO at temperature 50 °C, we just agitate the solvent in the reactor with a standard temperature probe used for performing the optimization and measure the maximum deviation from the set point. It is obvious, however, that all sensors must be calibrated. Working intervals could be different for the same parameter along the parameter's working region, meaning that the working interval for one system could be 2 °C between 20 and 100 °C and 3 °C between 100 and 200 °C. This change must be confirmed. It is suggested, on one hand, that determination should not be too rigorous and too tight in order to cover all oscillations during the working time. On the other hand, these working intervals should not be too broad because of limitation of the number of critical parameters. Working intervals are the shortest record of the suitability (fitness) of the production site.

It could be expected that the working intervals determined with different solvents would not be too different, and the uniform value could be used for the majority of them. This leads to rationalization in the working interval's determination procedure.

Some Bases and Rules for Determination of the Factors of Criticalness. Production staff and production

systems contribute essentially to the quality of the product, so it is very important that the staff get as much development information as possible in a clear and easily understandable form.

(i) The only criterion for numerical determination of the (non)critical factors is the quality of the product (intermediate).

(ii) The procedure for determination of the factor of criticalness is based on the presumption that there is only one source in the production path of a particular chemical substance which is very often the reason for the mistake (unexpected deviations) in executing the time frame of the specific working parameter. This means that because of the successive nature of production we are able to evaluate the impact of such a deviation with a systematic examination of controlled deviation of a particular synthesis parameter in addition to simultaneous fixation of all other parameters.

(iii) A confirmed interval ($I_{\text{confirmed}}$) is the interval between $X_{\text{determined}}$ (higher or lower value of an optional working parameter which is determined experimentally or by calculation (using DoE model)) and the set point (sp) inside which the product (intermediate) complies to the specification.

(iv) The working parameter can be critical in one or in both directions.

(v) Criticalness of the process (parameters) is determined in the process which is already optimized and validated[4] according to the relation quality/yield using standard screening and the DoE optimization principle.

(vi) Values of the working parameters should be evaluated in the laboratory scale in the same range as they will be used in the production scale.

(vii) Criticalness of the process step in the technological procedures is determined with the numerical determination of the critical parameters. If there exists no critical parameter in the specified process step, then this process step is noncritical. If there is one critical parameter in the specified process step, then this process step is critical, and if there is more than one critical parameter, then this process step is very critical.

(viii) In the MBR (master batch record) the set point and also the numerical determination of the criticalness of the same specified parameter for the same set point should be written.

(ix) The limit of criticalness ($y = 3$) is chosen according to the analogy with the probability interval of $3^*\sigma$ from statistical (analytical) methods.[5] The reason for choosing value 3 as limit point between critical and noncritical area is that deviations which are above 3 are due to unexpected external reasons—gross error (human error or technical malfunction).

(x) If $y < 1$, it can be concluded that the existent production equipment is not appropriate for this product and technology. This statement is not correct in cases when it is assured with the operation conditions (e.g., reflux) that $I_{\text{confirmed}} < I_{\text{working}}$. In such cases this point is called limit point.

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(5) Kellner, R., Mermet, J.-M., Otto, M., Widmer, H. M., Eds. *Analytical Chemistry*, Wiley-VCH: New York, 1998.

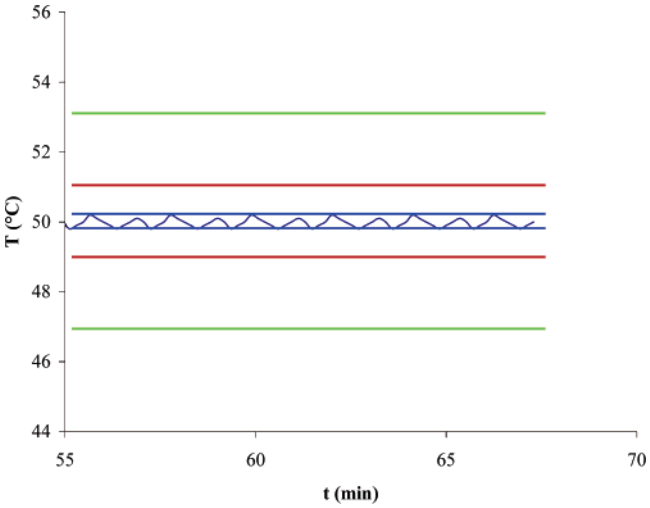

Figure 4. **Fitness graph for the production system 1 (I_{working} = 0.3 °C, blue line) with criticalness separation border (for y = 3, 0.9 °C, red line) and confirmed interval limit (3 °C, green line). For this system the temperature setting is uncritical because the (un)criticalness separation border (0.9 °C, red line) is far below the confirmed interval limit (3 °C, green line). Thus, we may conclude that the temperature is an uncritical parameter for production system 1, and the expression for criticalness would look like this: T(50 °C) := N(0.3 °C, 10).**

(xi) For noncritical parameters ($y > 3$) the critical factor should be first determined for the parameters which have $3 < y < 9$, and only in special cases should it be determined to be the values higher than 9.

It is suggested that the factor of criticalness should be determined for all critical parameters ($y \leq 3$) and all noncritical parameters with a factor of criticalness between 3 and 9.

The factor of criticalness for some parameter which is estimated to be higher than 9 should be determined by the development people. If numerical determination of such critical parameter is not performed, the expression should be:

$$P(\text{sp}) := o(I_{\text{working}}, y > 9)$$

Example:

$$t(1\text{ h}) := N(0.05, y > 9)$$

When critical factors are determined for some synthesis procedure on a specified production line, the new ones could easily be calculated for the other production line, taking in account the working intervals for this new line. Thus, there is no need for new experimental determination of critical factors; however, with such a calculation, we can obtain new critical parameters for a new production line.

Figures 4, 5, and 6 show how criticalness for temperature as the parameter is changing when the confirmed interval is 3 °C (green line) in both directions on the production systems 1, 2, and 3.

Expression for the Special Cases. In the case when the influence of some working parameter is very time defined and limited to a small portion of the total working time interval for that parameter, the new variable is introduced

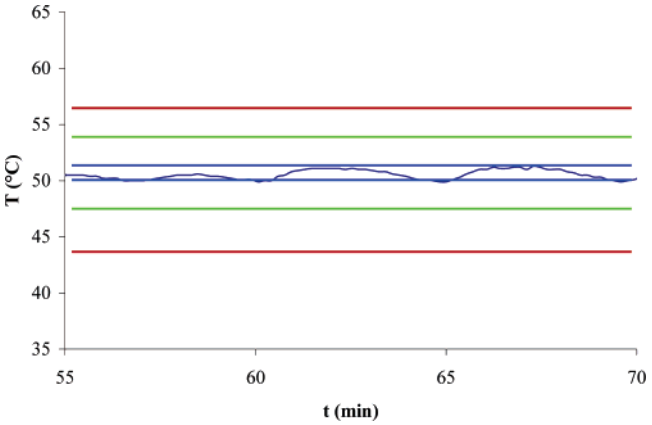

Figure 5. **Fitness graph for the production system 2 ($I_{working}$ = 2 °C, blue line) with criticalness separation border (for y = 3, 6 °C, red line) and confirmed interval limit (3 °C, green line). For this system the temperature setting is critical because the (un)criticalness separation border (6 °C, red line) is above the confirmed interval limit (3 °C, green line). Thus, we may conclude that the temperature is a critical parameter for production system 2, and the expression for criticalness would look like this: T(50 °C) := C(2 °C, 1.5).**

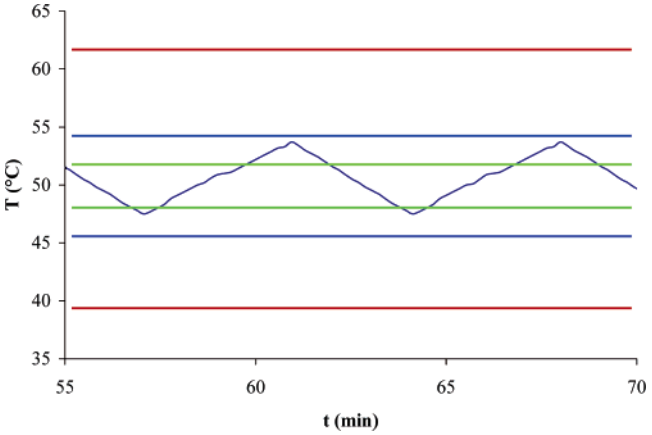

Figure 6. **Fitness graph for the production system 3 ($I_{working}$ = 4 °C, blue line) with criticalness separation border (for y = 3, 12 °C, red line) and confirmed interval limit (3 °C, green line). For this system the temperature setting is impossible to perform because the working interval border (4 °C, blue line) is above the confirmed interval limit (3 °C, green line). Thus, we may conclude that system 3 is not suitable for successful production.**

in the expression for the criticalness and is called relative time portion parameter, *z (the value should be written in italic)*. It describes for whatever time portion the critical designator is determined.

The expression for the criticalness would look like this:

$$P(\text{sp}) := o(I_{working}, y, z)$$

where P, sp, o, $I_{working}$, and y are the same as for the basic definition, and z is the relative time portion of some operation (e.g., *0.05−0.25*).

For example:

$$T(40\ °C) := C(0.2\ °C, 1.5, 0.05\text{-}0.25)$$

For cases when a parameter is changing over the whole working time interval, the parameter's first or higher derivative over time should be used as the parameter for determination of criticalness.

For example: temperature is changing during the heating period. In that case, temperature as a process parameter is replaced with heating velocity (dT/dt) as a process parameter, which is often constant and could be controlled.

In general, the parameter which is used for determination of criticalness should be constant in the time frame for which the factor of criticalness is determined.

Conclusion

What Is Gained with Numerical Determination of the Factor of Criticalness?

Where Are We now?

(1) We do not have a uniform numerical tool for determination and evaluation of critical parameters and critical synthesis steps.

(2) We do not have numerical tools for the exact determination of the suitability of an individual production line for a defined technology.

(3) The procedure for determination of the intervals of allowed variation is left to personal judgment and is often not completely accomplished.

(4) We do not have a simple tool for comparative evaluations of pretentiousness of chemical technologies.

What Are the Problems of Such Situations?

(1) The estimation of the magnitude of critical parameters in advance by all participants (chemists, engineers, technicians, workers) is very hard for the first scale-up batches in pilot and production plants.

(2) We must perform a set of scale-up industrial repetitions of the synthesis to know it better in detail and to learn which parts of the procedure are more important for positive end results.

(3) Preparations and risks are much higher when we transfer the technology to a distant production plant, especially in a foreign country.

4. The development chemist estimates with great difficulty the pretentiousness of the scale-up step when he/she is faced with a rather unknown pilot or industrial plant.

5. The costs of the technology transfer are consecutively higher.

What Do We Get with the Introduction of Numerical Determination of Critical Parameters?

(1) Faster and standardized scale-up procedures due to better transfer of the information gained during laboratory development.

(2) Technical staff in pilot and industrial plants can realize very soon where the critical points are and how much "spare room" they have in the production procedure. Signs *C* or *N* already reveal a lot about the importance of some production parameters.

(3) This system makes feasible better planning and organizing of scale-up, industrial validation, and production work.

(4) Comparison of different technological procedures is enabled, while also for the specified technological procedure the difference between different production plants could be estimated.

(5) The transfer of technological procedures between different countries is easier, and discussion and agreement between two QA about the transfer of the technology is easier and faster.

(6) There is a more systematic and qualitative development phase.

(7) There is systematic searching for "grey zones" in the synthesis procedures.

(8) There is necessity of systematic preparation in the development process for scale-up in the fields of determination of working intervals, suitability of working equipment, etc.

(9) There is easier estimation of the suitability of a particular production line for a particular technology.

(10) A tool for faster and adequate education of technicians and workers about the complexity of production phases is provided.

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