# A new algorithm for bioprocess feasibility index under uncertainty

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## *Abstract*

To comply FDA strict regulatory requirements, it is necessary to design the bioprocess so that the process performance satisfies the specifications not only at set points but also in a wide range of set points, and limit for the process failure occurs needs to be defined as well. It is crucial to understand the bioprocess feasibility under uncertainty in order to design safe and robust manufacturing process for the new generation therapeutic products arising from advanced life science discovery.

Motivated by the needs for feasibility studies of bioprocess operational variables, a new feasibility index to indicate the robust operating ranges for the process has been defined in the sense of worst case scenario, i.e., the operating point is robustly feasible if it is feasible under all of the range of variations of the variables. A largest hyperrectangle centred at the operating point is sought to define the process feasibility and its upper and lower bounds for the variations of operating variables. Up to date, the process feasibility under uncertainty is often formulated as complicated max-min-max problem e.g. Swaney and Grossmann's work, which posts a great computational challenge because of the non-smoothness of the objective functions and non-convexity of the feasible space. A different problem formulation for the problem was presented in our earlier work (Kim et al, 2005). In stead of searching for the largest hyperrectangle, a largest hypersphere inscribed in the feasible space is sought so that the difficulty over non-convexity of feasible space can be overcome. Hence, a hyperrectangule can be defined within the hypersphere. The solution obtained is a lower bound approximation of the true solution. By discretisation, the problem can be formulated as finding the minimum distance between a point and a point set so that the complexity of the algorithm has been reduced significantly. Such algorithm can be utilised to find the feasibility index for a given operating point and the optimal operating point with largest feasibility index in the feasible space. In this paper, a general feasibility problem is investigated and a method for solving such a problem has been indicated.

Keywords: Feasibility index, feasible region, min-max optimisation, uncertainty.

## Introduction

More and more new biological drugs have been seen on the market in the last decade and the biopharmaceutical industry has enjoyed a fast growth and contributed tremendously to the cure of many deadly diseases. At the same time, the development times and costs for the new biological drugs have also increased substantially as the new drug molecules are getting more and more sophisticated and complicated and post great challenge on large scale manufacturing. To reduce drug development effort, bioprocess modelling and simulation have played an important role in understanding bioprocessing system better and as a tool to assist rapid bioprocess design. Windows of operation is one of the examples where feasible operating conditions for a bioprocess unit operation have been visualised for rapid decision-making on bioprocess operations.

It is well known that there exist uncertainties in the bioprocesses. One of uncertainties is caused by inaccuracy in operating parameters due to manual operation. Another one is the environment variations in which the microorganisim are developing. To ensure the safety and quality of the medicines, regulatory organisations such as FDA set up strict requirements on bioprocessing. It is necessary to design the bioprocess so that the process performance satisfies the specifications not only at set points but also in a wide range of set points, and limit for the process failure occurs needs to be defined as well. These ranges need to be validated using experimental runs before the drug's approval to the market. It is crucial to understand the bioprocess feasibility under uncertainty in order to design safe and robust manufacturing process for the new generation therapeutic products arising from advanced life science discovery.

When taking uncertainties into consideration, we need to be able to evaluate the feasibility of an operating point to determine these ranges during design stage. Motivated by the needs for feasibility studies of bioprocess operational variables, Our recent work (Kim et al, 2005) has defined a new feasibility index to indicate the robust operating ranges for the process in the sense of worst case scenario, i.e., the operating point is robustly feasible if it is feasible under all of the range of variations of the variables. A largest hyperrectangle centred at the operating point is sought to define the process feasibility and its upper and lower bounds for the variations of operating variables. A brief summary of the feasibility concept and feasibility index is given as follows.

Given an operating space, the feasibility for a given operating point is defined by finding the largest hyperrectangle centred at the operating point and inscribed within the window of operation. The feasibility index is expressed as the half of the hyperrectanglar lengths. The hyperrectangle represents the maximum amount of variations which the process can tolerate and thus gives the upper and lower bounds for the operating variable. Therefore, the process performance is guaranteed in any possible variation within the generated hyperrectangle. If the related variations are larger than the range formed by the upper and lower bounds, the process may no longer remain satisfied due to one or more constraints being violated.

Up to date, the process feasibility under uncertainty is often formulated as complicated max-min-max problem (Grossmann and Halemane, 1983; Swaney and Grossmann, 1985a; Swaney and Grossmann,1985b; Grossmann and Floudas, 1987; Grossmann and Floudas, 1988; Pistacopoulos and Floudas, 1988; Pistacopoulos and Floudas, 1989), which posts a great computational challenge because of the non-smoothness of the objective functions and non-convexity of the feasible space.

In our method, the geometric problem of finding the largest hyperrectangle centred at the operating point and inscribed within the window of operation has been formulated as a maximisation problem. In stead of searching for the largest hyperrectangle, a largest hypersphere inscribed in the feasible space is sought so that the difficulty over non-convexity of feasible space can be overcome. Hence, a hyperrectangule can be defined within the hypersphere. The solution obtained is a lower bound approximation of the true solution. By discretisation of the feasible region, the problem can be formulated as finding the minimum distance between a point and a point set so that the complexity of the algorithm has been reduced significantly. Such algorithm can be utilised to find the feasibility index for a given operating point and the optimal operating point with largest feasibility index in the feasible space.

In this paper, attention is particularly paid to the issue of scale transform which has been mentioned in the previous work (Swaney and Grossmann, 1985a; Swaney and Grossmann,1985b; Kim et al, 2005) but not investigated in depth. The current methods of scale transform will be reviewed and a modified algorithm for general feasibility index is developed.

## Scale transform

The windows of operation represent the feasible region of the process operation to achieve certain defined goals (Woodley and Titchener-Hooker, 1996; King et al, 2004; Zhou and Titchener-Hooker, 1999; Zhou and Titchener-Hooker, 2003). For example, one of our recent work uses windows of operation for the design and analysis of chromatographic steps (Joseph et al, 2006). The effects of column diameter, bed length and linear flow rate on cost of goods (COG/g) and productivity (g/h) are investigated for a Protein A separation so as to identify the optimal operating strategy. Figure 1 shows the window of operation for column diameter and linear loading flowrate to achieve at least 100g/h productivity and production cost no more than 50$/g. Notice the shape of the window of operation is quite ill regular. Detailed information on the assumption and computational method can be found in (Joseph et al, 2006).

The axes represent different operating variables with different units such as the linear loading flowrate (cm/h) and column diameter (cm). There exist many different rectangles in a window of operation if using different ratio of length and width. For example, two rectangles for a point X are shown in Figure 2 based on the previous example. Rectangle A gives column diameter ±4 cm feasibility and linear loading flowrate ±100 cm/L feasibility while rectangle B gives column diameter much more feasibility, ±15 cm and linear loading flowrate much less feasibility, ±50 cm/L. From design point of view, when a column diameter is chosen, it will not change, i.e., zero variation. However, the operational variable, linear loading flowrate can vary and it is more important to understand the feasibility of the linear loading flowrate.

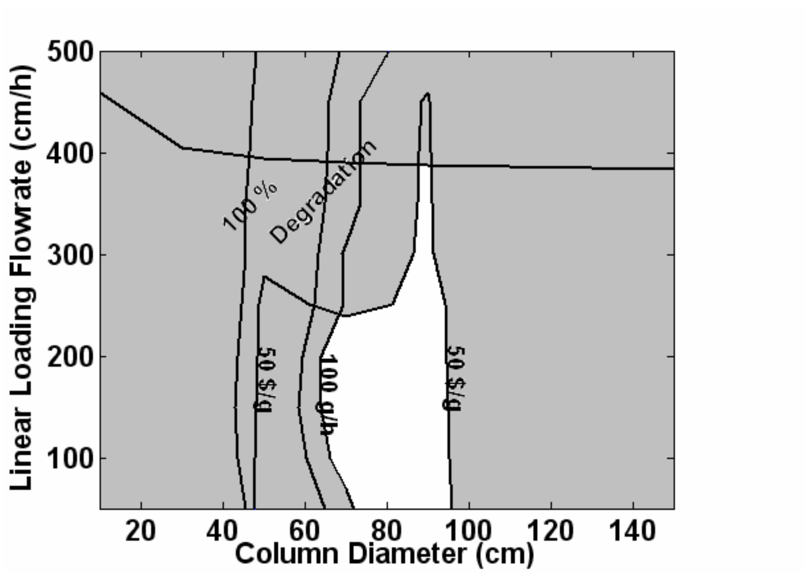


Figure 1. The window of operation produced when constraining both cost at 50$/g and productivity at 100g/h for a column length of 10cm.

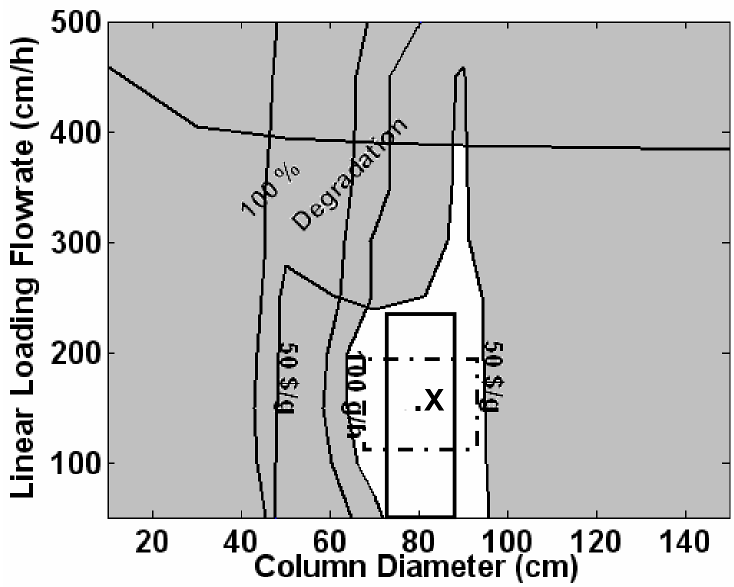


Figure 2. The window of operation produced when constraining both cost at 50$/g and productivity at 100g/h for a column length of 10cm. X is an operating point at 80 cm column diameter and 150 cm/L linear loading flowrate.

When come to define the largest rectangle, it is necessary to define the type of rectangle before a method can be devised. The question is how to define the appropriate ratio so that the most robust measure of the process is captured.

Swaney and Grossmann (1985a) proposed a transform of the feasible set at the nominal point using the expected deviations of the uncertain parameters as a scaling factor so that a hyperrectangle appears as a hypercube located at the origin. When many feasible points need to be assessed, the transform must be repeated each time which is tedious. A normalisation of the operating space for the problem based on an operating range was also proposed (Kim et al, 2005). For each operational variable, the normalisation transforms the considered range from minimum value to maximum value into a range of 0 to 1. A brief summary of the method is given as follows.

Let $X$ be the vector of operational variables and $X^N$ be the vector of normalised operational variables. The normalisation is defined by

$$x_j^N = \frac{x_j - x_{j\max}}{x_{j\max} - x_{j\min}}, \qquad j = 1,\ 2,\ 3, \ldots\ldots, n, \qquad (1)$$

where $n$ is the number of uncertain operational variables, $x_j$ is the j$^{th}$ operational variables, $x_j^N$ is the j$^{th}$ normalised operational variables, $x_{j\ min}$ is the minimum feasible value and $x_{j\ max}$ is the maximum feasible value for $x_j$.

Then the largest hypercube within the window of operation and centred at the given operation point is used to define the feasibility index $F$, as half length of the side of the rectangle. After $F$ has been obtained, the upper and lower bounds for the normalized variables is,

$$x_j^N - F \le x_j^N \le x_j^N + F, \qquad j = 1, 2, 3, \ldots\ldots, n, \qquad (2)$$

From the inverse transformation using (2), the upper and lower bounds for $x_j$ is

$$x_j - \Delta_j \le x_i \le x_j + \Delta_j, \qquad j = 1, 2, 3, \ldots\ldots, n, \qquad (3)$$

where

$$\Delta_j = F\,(x_{j\max} - x_{j\min}), \qquad j = 1, 2, 3, \ldots\ldots, n. \qquad (4)$$

From this method, the largest hyperrectangle is defined so that the feasible range is propotional to the maximum range of interest. So it gives relative measure of the feasibility. As shown in Figure 2, the useful rectangle may require a very small range for column diameter and a big range for linear loading flowrate such as rectangle A type. It will be very interesting to know how to find any required rectangule with a given ratio. In the following section, a method will be proposed after the discussion of handling scale transform.

**Method for a general feasibility study**

The method summarised above showed that the largest rectangule is dependent on the feasibility index calculated from the above normalised windows of operation as well as the range of each variable selected.

From equation (1), the transform can be rewritten as

$$x_j^N = \frac{1}{x_{j\max} - x_{j\min}} x_j - \frac{x_{j\min}}{x_{j\max} - x_{j\min}} = a_j x_j - b_j, \quad j = 1,\ 2,\ 3, \ldots\ldots, n, \tag{5}$$

where

$$a_j = \frac{1}{x_{j\max} - x_{j\min}}, \tag{6}$$

and

$$b_j = \frac{x_{j\min}}{x_{j\max} - x_{j\min}} \ . \tag{7}$$

So in matrix form,

$$X^N = AX - b, \tag{8}$$

where

$$X^N = \begin{bmatrix} x_1^N \\ \vdots \\ x_n^N \end{bmatrix}, \qquad A = \begin{bmatrix} a_1 & & 0 \\ & \ddots & \\ 0 & & a_n \end{bmatrix}, \qquad b = \begin{bmatrix} b_1 \\ \vdots \\ b_n \end{bmatrix}.$$

The solution of feasibility index proposed in (Kim et al, 2005) satisfies the criteria:

$$F = \{ \max \varepsilon | W \cap H(X^N, \varepsilon) = H(X^N, \varepsilon) \} \ , \tag{9}$$

where W is a point set from the window of operation, $H\ (X^N,\ \varepsilon)$ is a hypercube inscribed in the set W and

$$H(X^N, \varepsilon) \stackrel{\Delta}{=} \{ X^N{}_i \in W | \| X^N{}_i - X^N \|_\infty \le \varepsilon \} \ . \tag{10}$$

It was obtained by introducing a hypersphere:

$$S(X^N, \delta) \stackrel{\Delta}{=} \{ X^N{}_i \in W | \| X^N{}_i - X^N \|_2 \le \delta \}. \tag{11}$$

Therefore, let $X_b$ be the boundary points of the hypersphere $S(X^N, \delta)$ and it satisfies

$$\| X^N - X_b^N \|_2 = \delta \ . \tag{12}$$

To transfer it back to its original scale by using equation (8), we have

$$\| AX - b - AX_b + b \|_2 = \| A(X - X_b) \|_2 = \delta \ , \tag{13}$$

or

$$(X - X_b)^T A^T A(X - X_b) = \delta^2 \quad , \qquad (14)$$

which is an ellipse. Hence, any type of hyperrectangule can be found simply by changing the range of each variable, or selecting matrix A. The normalisation method in (Kim et al is a special case where A equals identity matrix, which is determined by the maximum feasible region. By modifying the hypersphere into the ellipse, a new algorithm can be derived based on previous sphere algorithm. Due to the length limit, the detailed algorithm and its applications are omitted.

## Conclusions

The feasibility study for the windows of operation in bioprocesses under uncertainty is important. This paper extends the current definition of feasibility index to a general sense and allows the user to define any types of hyperrectangle to satisfy his/her needs. The method has been modified by using hyperellipse instead of hypersphere to accommodate the generality issue. Further work will investigate the numerical implication of introducing hyperellipse and understand further practical meaning of matrix A.


## Acknowledgements

The support of the Engineering and Physical Sciences Research Council Life Science Interface and Innovative Manufacturing Research Centre initiatives for the IMRC in Bioprocessing is gratefully acknowledged. The IMRC is part of The Advanced Centre for Biochemical Engineering, UCL with collaboration from a range of academic partners and biopharmaceutical and biotechnology companies.


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