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Simulation of Data for Drug Manufacturing Using Optimization Principles

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Abstract

This paper deals with formulation and solution of an optimization problem related to a drug industry wherein a drug manufacturing experiment is conducted with multiple reagent levels, a single incubation temperature, and a single incubation time. Since various experiments are conducted with multiple values of reagent levels, it is decided to have a common measurement factor for all the experiments for comparison purposes. This factor is taken as a scalar binding factor. This binding factor is expressed as a linear function of reagent levels, incubation temperature, and incubation time. All these three variables are treated as probabilistic and, hence, are supposed to have a certain distribution. It is also assumed that each drug manufacturing experiment is characterized by a single binding value or binding factor. The higher the binding, the experiment is considered better. Further, it is assumed in this study that the mean binding factor is a monotonically non-decreasing function of incubation time. Since the experiments are expensive to run and the cost is proportional to incubation time, and, also, since there is a cost of a reagent, this is a complex problem. It becomes even more complex because the stochastic aspects of the process are to be considered in the optimization problem formulation. This problem dealing with manufacturing of a drug [1, 2] is formulated as an optimization problem.

Key Words: Optimization, Pharmaceutical, Reagent, Incubation, Temperature, Binding Factor.

1 Introduction

The problem is formulated as an optimization problem where the objective function is the maximization of the Intensity of Binding Factor (IBF) subject to certain constraints on total cost. This is because the total cost is in turn a function of cost of incubation temperature and the cost of Reagents. The stochastic aspects of the problem will be considered by incorporating the probability distributions of the input parameters: reagents, incubation temperature, and incubation time. This optimization problem is then solved for a certain set of practical input data. The results are then analyzed. These results should be useful to pharmaceutical industry and corresponding engineering disciplines.

This work is based mainly on the concept of **high throughput screening** used to discover new drug compounds. The goal is to develop a new drug based on a known protein receptor associated with a particular disease. The aim is to select a drug compound that will bind effectively with the target protein. The testing is done using robots.

The basic procedure is as follows: A specific protein target is given. Series of experiments are run involving one compound, several reagent levels, an incubation temperature, and an incubation time, all of which are varying continuously. Optimization principles are used since the problem involves multiple objectives. The topic has lot of practical applications as soon as a compound is identified for a protein, the sooner the manufacturer can make profits.

2 Problem Formulation

2.1 Statement of problem including assumptions

The desired experiment involves 3 variables:

1. 3 Reagent levels (0-1)
2. An incubation temperature (30° C - 40° C)
3. An incubation time (10-100 seconds)

Assume Intensity of Binding Factor (IBF) is a linear function of Reagents (RA), Incubation Time (IT), Temperature (TEMP) and the corresponding binding factors.

This implies that:

$$IBF = \alpha_{RA} * S_{RA} * RA + \alpha_{IT} * S_{IT} * IT + \alpha_{TEMP} * S_{TEMP} * TEMP \quad (1)$$

Where,

$$0 \leq RA \leq 1 \quad (1a)$$

$$10 \leq IT \leq 100$$

$$30°C \leq TEMP \leq 40° C$$

α_{RA}, $\alpha_{IT,}$ and α_{TEMP} represent the randomness in binding factors in RA, IT, and TEMP for a probabilistic analysis. The S factors represent the scaling factors. S_{RA} varies from 0 to 1, S_{IT} varies between .01 to .1, S_{TEMP} varies between .025 to .033. This is to ensure that IBF >1. In a deterministic analysis, these α factors will be assumed as one. Then the functional relation of IBF can be assumed as:

$$IBF = S_{RA} * RA + S_{IT} * IT + S_{TEMP} * TEMP \quad (2)$$

Constraints remain the same as in Equation 1a. The following inherent assumptions are made in writing the above relation:

a. Mean binding factor is monotonically non-decreasing function of incubation time (IT).

b. S... factors are calculated using the maximum value of range of each of the variables – RA, IT, and TEMP.

c. Linearity assumption for binding factor is reasonable in the absence of any other information.

d. Equation 1 and Equation 2 take care of both deterministic and probabilistic formulation.

Maximization of intensity of the binding factor could easily be chosen as an objective function [3].

It can be assumed without any loss of generality that income for the pharmaceutical industry is directly proportional to the intensity of the binding factor (This would imply maximization of binding factor) and inversely proportional to variance (to keep uniformity in the final product, it is important that variance in binding factor is small). The variance can be measured through COV (coefficient of variation) used in statistical analysis. The expressions for mean value, standard deviation, and coefficient of variation can be obtained from literature [4].

2.2 Formulation of optimization problem

2.2.1 Deterministic formulation

$$\text{Max. } IBF = S_{RA} * RA + S_{IT} * IT + S_{TEMP} * TEMP \quad (3)$$

S.t. the constraints stated below in Equation 1a. They vary depending on Reagent level.

Reagent level 1:

S.t. . $0 \leq RA \leq 0.333$ (3a)

$10 \leq IT \leq 100$

$30°C \leq TEMP \leq 40° C$

Reagent level 2:

S.t. . $0.333 \leq RA \leq 0.666$ (3a)

$10 \leq IT \leq 100$

$30° C \leq TEMP \leq 40° C$

Reagent level 3:

S.t. . $0.666 \leq RA \leq 1.0$ (3a)

$10 \leq IT \leq 100$

$30° C \leq TEMP \leq 40° C$

2.2.2 Probabilistic formulation

$$\text{Max. IBF} = \alpha_{RA} * S_{RA} * RA + \alpha_{IT} * S_{IT} * IT + \alpha_{TEMP} * S_{TEMP} * TEMP \quad (4)$$

s.t. Equation 3a constraints as stated earlier.

Where,

$\alpha_{RA,}$ $\alpha_{IT,}$ and α_{TEMP} are randomness factors to take care of the inherent uncertainty in RA, IT, and TEMP measurements.

The above formulation of maximizes binding factor subject to given constraints on RA (3 ranges), IT, and TEMP. It captures the essence of the pharmaceutical engineering problem coupled with optimization aspects.

One optimization problem as stated above should be reasonably satisfactory answers for each of the reagent levels.
There is no need to solve multiple optimization problems.

The stochastic optimization problem can be captured by treating $\alpha_{RA,}$ $\alpha_{IT,}$ and α_{TEMP} as random variables.

3 Problem Solution

Standard optimization techniques [5] can be used to solve Equation 3 and Equation 3a for a deterministic optimization problem conclusion. Similarly Equation 4 and Equation 3 are to be solved for a probabilistic optimization problem. The problem converged and the optimization results will be presented at the conference. They are not included here due to space limitations.

Optimization principles have been applied to a drug manufacturing problem involving one compound, multiple reagent levels, an incubation temperature, and an incubation time. All are continuously varying quantity.

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