A new approach to planning *in vitro* and *in vivo* experiments for cardiovascular stents
(1) Fundamentals of design procedures

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Abstract

While the use of cardiovascular stents is internationally widespread re-stenosis remains a common problem. There are a number of different designs, and this project seeks for design improvements leading to a reduction in re-stenosis rates. The haemodynamics of the stent as used in a patient is viewed as one of the major concerns, and the authors have already applied Computational Fluid Dynamics in investigating this. In this more comprehensive study, however, the novel approach of applying two formal engineering design procedures is used, namely Genetic Algorithms (GA) and Robust Engineering Design (RED). In this paper, the two procedures are explained and compared in the context of their application to the design of stents.

Introduction

Design and science

Engineering design can be viewed as an art and a science[1, 2]. By this it is meant that there are aspects of design process that rely upon learning by doing (art), and others concerned with developing method or procedure (science). The latter is the focus of this paper.

Comparing scientific method with engineering design procedure draws out two important points: Firstly, the impetus for science is the thirst for knowledge and the impetus for design is the needs of society[2]. Secondly, in science problems are explored for their underlying rules, i.e. a problem-focused approach, whereas in design the quest is to suggest possible solutions, i.e. a solution-based approach[3]. In relation to cardiovascular stents this could be interpreted as 'scientific' activity concerned with understanding haemodynamics and 'design' activity concerned with employing this understanding in seeking to reduce rates of restenosis (Table 1).

	impetus	objective for stents
science	seek knowledge	understand haemodynamics
design	satisfy demand	reduce restenosis

Table 1. Role of science and design in cardiovascular stent research

Types of design problem

Types of design problems may be described as original design, redesign or routine design[4].

Original design is concerned with radical new working principles or innovative features.

The focus of *redesign* is on modifying an existing working principle or changing the arrangement of important features.

Routine design is typified by the detail changes required to produce a new size within a common range of components. Thus the types of design problems are distinguished by the degree of creative effort deployed on working principle as opposed to detailed refinements. In the context of this study stents are considered to be a redesign problem. This is by virtue of aiming to reduce restenosis through changes to the arrangement of important features of the stent rather than relying on a radically new working principle (Table 2).

Original design	Working principle = expanding structure that dilates the stenosis and allows blood to flow.
Redesign	**Arrangement of structural elements in relation to interaction with artery wall and blood flow characteristics.**
Routine design	Geometry values for different sizes of stent.

Table 2. Stent design problem

Design search

The underlying rules uncovered in science are unique to certain aspects of the problem whereas in design there may be many solutions for satisfying a stated need. Thus the engineering design process is generally concerned with exploring design situations, exploring the problem structure, searching for ideas and evaluating solutions[5]. The rational aspects of such are more commonly regarded as design methods or procedures as they encourage a systematic approach.

It is convenient to picture the engineering design process as a search in an imaginary space in which the goal is to find the solution(s) that satisfies specified needs. The search approach adopted depends to a large extent on the type of design problem. Conventionally, a random search is employed in original design, whilst redesign is accomplished in a heuristic fashion through improving understanding of the problem and in turn finding a better solution. Routine design however requires virtually no search activity. However, such trial-and-error described above is too uncertain.

Illustrative engineering example

Conventional engineering design is illustrated by the following example:

In power plant there is a need to exchange heat between inlet air flow to the furnace and outlet flow of flue gases, by what are known as rotary air preheaters. Typical rates of heat transfer are of the order of Megawatts. The key performance measures of an air heater are high heat transfer rates, low pressure losses and low sensitivity to fouling. The rotary air preheater is a design concept, in which the working principle is based upon a rotating corrugated steel matrix (see Figure 1).

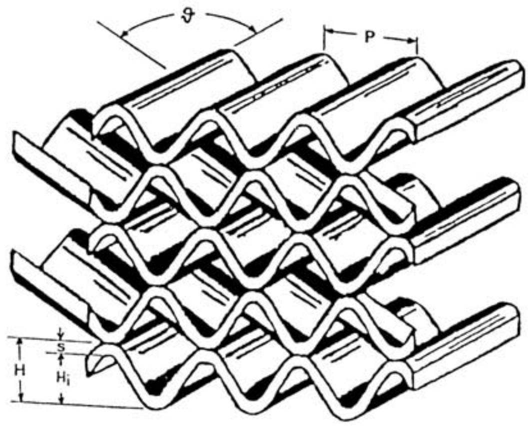

Fig. 1. Symmetrical cross-corrugated heat transfer elements of a rotary air preheater (from Stasiek et al[6]).

Despite the size of a preheater, it is composed of very many corrugated sheets of a relatively small unitary geometry. The symmetrical cross-corrugated arrangement shown is one of a number developed on an empirical basis. An extensive investigation[6] into the dependence of heat transfer and pressure drop on Reynolds Number (Re) and corrugation geometry limited to P, H, s and θ (Figure 1), aimed to reveal new information on these relationships. Therefore this was redesign (Table 2).

Original design	Working principle = metal matrix rotating through hot and cold flow to exchange heat absorbed.
Redesign	**Arrangement of structural elements in relation to heat transfer and pressure drop.**
Routine design	Geometry values for different sizes of preheater.

Table 3. preheater design problem

Results indicated that the dependence of pressure drop on θ was stronger than that of heat transfer on θ. However, there was difficulty in separating the former relationship from those involving P/h and Re.

Three aspects of this investigation are relevant to the current study. The first is that even a few parameters can generate large design space. Secondly and more importantly, that an unstructured search can result in inconclusive design information. Thirdly, that the symmetric design had been found to be more tolerant to fouling.

Systematic design procedures

A systematic engineering design procedure should not rely on chance and should facilitate the search for optimal solutions[1]. The use of analytical work at an early stage in order to understand the design problem is a common feature of systematic approaches[5, 7, 8]. Another common feature is to decompose the problem into smaller sub-problems for solving and subsequent clustering into an integrated solution - known as *function decomposition* [1, 9, 10, 11].

This paper explains two methods for systematically searching design space and deciding parameter values for improved performance. Furthermore, the study goes beyond the deterministic approach of conventional design, which disregards the fact that material properties, component dimensions and application conditions are all statistical in their nature.

Robust Engineering Design

Parameter classification

In Robust Engineering Design (RED) methodology there are three types of parameter considered to constitute a system[12]. These are represented in Figure 2 as a parameter diagram.

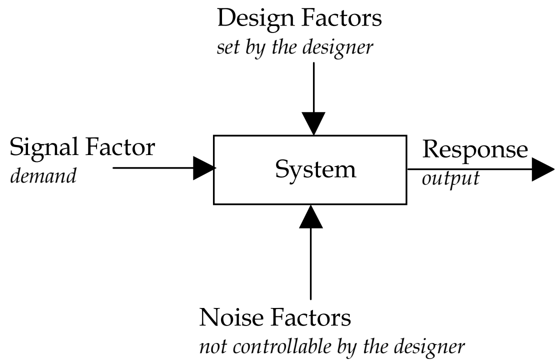

Fig. 2. Parameter diagram for a system

Signal	Artery size
Response	Flow and structural characteristics
Design	Stent geometry
Noise	Patient-to-patient variations, clinical deployment and manufacturing variability

Table 4. Types of factor for stent design.

The Signal Factor represents the performance expected of the system. This is assumed to be a constant value here and thus ignored. *Design factors* are parameters that are set or controlled by the designer. *Noise factors* are those that cannot be controlled by the designer but which have an influence on the behaviour of the system, such as conditions of operation and manufacturing variation. RED is concerned with finding nominal values of the design factors that reduce the effects of the noise factors on the system output response. This improved *robustness* of the system is achieved through an ordered search for nominal values (levels) of design factors.

Orthogonal search

The systematic search is arranged according to an *Orthogonal Array* (OA), which specifies the design factor levels to be used in any given experiment. Table 5 shows the OA arrangement for a simple experiment involving 3 design factors of 2 levels each.

	design factor A	design factor B	design factor C	results
Exp 1	1	1	1	SNR_1
Exp 2	1	2	2	SNR_2
Exp 3	2	1	2	SNR_3
Exp 4	2	2	1	SNR_4

Table 5. Simple Orthogonal Array (L_4)

The OA is a predetermined matrix in which each column of numbers signifies the values of a design factor assigned to it. Therefore each row represents the factor settings for an individual experiment. Note that between experiments (rows) more than one design factor level will be changed, which distinguishes this approach from the conventional one-factor-at-a-time method. Another feature to note is that the allocation of levels in each column is balanced, i.e. between any two columns each factor level is paired an equal number of times with the levels of the other column and vice versa.

Figure 3 illustrates the 3D design space search specified by the OA in Table 5.

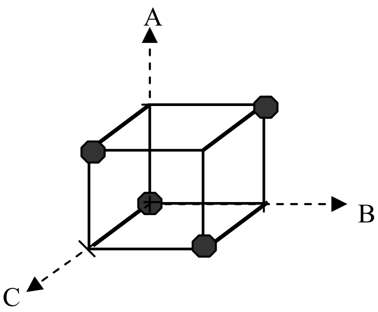

Fig. 3. L_4 OA search of 3D design space

Only four experiments are required to gather sufficient information for evaluating the significance of the three design factors, compared with the necessity for eight experiments in the conventional 'full-factorial' one-factor-at-a-time approach. The OA also tests each factor evenly against changes in the levels of the other factors, which is an important test of interaction effects between design factors.

Each experiment is exposed equally to representative values of the noise factors in order to perturb the system function according to expected conditions. Typically this is conducted by means of collecting results under two noise groupings for each experiment, namely 'low noise' values and 'high noise' values.

Performance evaluation

The results of each experiment may be summarised by a noise performance measure such as a Signal-to-Noise Ratio[12] (SNR) that uses a squared ratio of mean to variability. Thus what is desired in the output (mean value) is compared with what is not desired (effect of noise) in the output.

From the OA (Table 5), the overall relative effect of each design factor level is evaluated by comparing the mean of the performance values for experiments incorporating that factor level.

For example, from Table 5 the relative effect of design factor A is calculated, according to the first column, by the difference between the mean SNR of the first two experiments and that of the last two.

Rel. effect of A = abs($\bar{A}_1$-$\bar{A}_2$) (1)

Where:

$\bar{A}_1$=½(SNR_1+SNR_2) and

$\bar{A}_2$=½(SNR_3+SNR_4)

Additivity and prediction

The design factors are assumed to be independent and related to an estimate of the output by a simple linear model (Equation 2).

$$E(y) = \mu + a_I + b_j + c_k \quad (2)$$

Where a_i, b_j & c_k are the modifications to the grand mean, μ, made by factors *A, B & C* at the levels *i, j and k* respectively of a given configuration. For example, $a_I = \bar{A}_1 - \mu$ and thus Equation (2) becomes:

$$E(y) = \overline{A}_i + \overline{B}_j + \overline{C}_k - \mu \quad (3)$$

The predictive accuracy of Equation 3 relies upon the implicit *additivity* being true for the system under investigation. Additivity is undermined if there are any interaction effects between design factors, which renders the prediction unreliable. Thus design factor selection and experiment planning are important stages in RED for promoting improvements in the system design configuration.

Statistical methods such as Analysis of Variance[13] and half-normal plots[14] are used to identify the significant factors for use in the prediction equation. Design factors considered to be insignificant are pooled together as an error term. The validity of the linear model is finally evaluated through a confirmation experiment on the chosen configuration. Close agreement between the results of this and the prediction opens the way for further experiments in which new design factors and levels are entered to replace insignificant items and thus continue the search of design space.

Genetic Algorithms

Reproduction

Genetic Algorithms (GA) are founded on the theory of 'survival of the fittest' combined with the information exchange processes of natural genetics[15]. This information exchange, which is structured yet random, forms the basis of the search method. The random aspect renders the search much less 'balanced' than for the OA search in RED with a commensurate reduction in the need to carefully select design factors in order to avoid interactions. Indeed GA relies upon the assumption that in nature the complex non-linear relationships between design factors have to be efficiently processed. Therefore the system under investigation is considered to be a black box in which there are only two aspects of interest, namely the coding of the design configuration and its performance or 'fitness'. The GA procedure is illustrated in Figure 4.

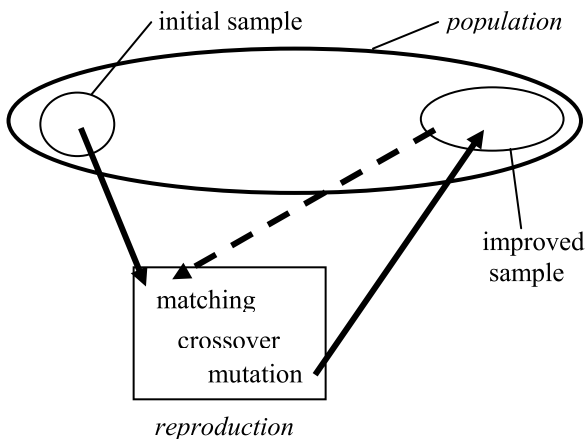

Fig. 4. General GA procedure

The starting point is an initial random sample population. In comparison with RED 'coding', (Table 5 and Figure 3) an initial sample in a simple design experiment comprising three two-level design factors could be as shown in Table 6.

	design factor A	design factor B	design factor C	fitness
Exp 1	1	2	2	31
Exp 2	2	2	1	104
Exp 3	1	2	1	48
Exp 4	1	1	1	52

Table 6. Initial random GA coding

Reproduction progresses typically in terms of giving the design configuration ('string') with a higher fitness a greater role in spawning a subsequent generation until fitness values converge at a maximum value. One method is to allocate a higher probability of contribution to a dominant string based on its percentage of the total fitness for the generation ('sample' in Figure 4), as shown in Table 7.

	A	B	C	fitness	% of total
Exp 1	1	2	2	31	13.2
Exp 2	2	2	1	104	44.3
Exp 3	1	2	1	48	20.4
Exp 4	1	1	2	52	22.1
				235	100

Table 7. Probability of selection

Strings selected for reproduction are entered into a mating pool. In Table 7, experiments 2 and 4 would have a relatively high probability of forming a mating pair based on their superior fitness.

Crossover

A position along the string is chosen as a crossover point, say between B and C in Table 7. Code either side of this crossover point is then swapped between the mating pair, as indicated below:

<u>First generation (parents)</u>
Exp 2 = 2 2 | 1
Exp 4 = 1 1 | 2

<u>Second generation (offspring)</u>
Exp 2' = 2 2 | 2
Exp 4' = 1 1 | 1

Mutation

This plays a secondary but important role in producing a 'random walk' through design space by virtue of an occasional alteration of the value of a design factor. For example if the first offspring in the second generation above underwent a random mutation of design factor B then perhaps Exp 2' = 2 1 2. The incidence of mutations is generally limited to the order of one per thousand crossover transfers.

In general, further generations would be evaluated until the improvement in fitness converged to the desired level. As the generations unfold it enables the identification of successful combinations of design factors to be identified. These schema or building blocks can then be fixed, which focuses subsequent searches of design space.

Discussion and conclusions

The amount of deliberation required in selecting design factors is different between RED and GA. It hinges mainly on the issue of interactions. In RED the concern is that interactions will be antisynergistic (working against each other). Conversely, the GA method is considered to work best with medium to high interactions amongst the design factors[13, 14]. To some extent interactions can be accommodated in RED using the sliding factor level technique[13]. Therefore, for complex systems two different sets of design factors are inevitable due to the differences in the preferred degree of interactions. In terms of design factor selection, this is perhaps best summed up as a bias towards insight and serendipity, respectively.

The arbitrary selection of design factors in GA allows a wider search of design space. Mutation is an important aid to this as it avoids the premature loss of important interactions between design factors before they have had an opportunity to 'shine'. However, whilst the search might be wider with GA it is also of a more uncertain duration compared with the fixed approach of balanced OA in RED. Thus for expensive experiments the commitment to a known number of experiments, hence cost and time, might be favoured.

Multiple objectives[17] have not been included in this study in order to keep the focus on the basic method and the presentation concise. It should be noted however, that multiple objectives are inevitable in the study of stent design and are identified in the accompanying paper.

The concept of robustness also appears to be different between RED and GA. In RED robustness is described explicitly in terms of reducing sensitivity to noise *through incorporating representative values of noise in all experiments*. Whereas in GA robustness is expressed as a central theme[15] that appears to be a quality of the search mechanism in terms of how it converges on configurations of a higher fitness. That is, 'robustness' in RED is describing the performance of the solution in use and in GA it is describing the reliability of the method. However, we feel that the principle of noise inclusion should be incorporated into both approaches.

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