A new approach to planning *in vitro* and *in vivo* experiments for cardiovascular stents
(2) Planning of experiments

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Abstract

Within our overall project to improve the design of stents in terms of reduced rates of re-stenosis, there are three main methods, namely computer simulation and *in vitro* and *in vivo* experiments. These methods are closely integrated using contemporary design procedures described below, especially to accommodate patient-to-patient variation. Clinical experience shows that a small variation has considerable effects on flow characteristics of stents and in engineering terms may be described as a 'geometric risk factor'. The Robust Engineering Design procedure readily incorporates this factor which may thus become a component feature in our experimental planning. We envisage that this approach could be applied to other invasive implants with a view to enhancing their quality.

Introduction

The basic working principle of cardiovascular stents has remained unchanged since they were introduced. Typically, a self-expanding or balloon-expanded metal device is inserted into an artery in order to relieve a stenosis. Thus the primary function of a stent has been considered to be its structural role. However, clinical evidence suggests that the worrying incidence of re-stenosis (20%-40% of cases world-wide) is a function of the flow characteristics of a stent. Therefore in searching for improved design configurations of stents it is important that both the structural and the flow requirements are addressed. In this investigation the design problem focuses on changes to the arrangement of important features rather than attempting to create a new working principle.

Stent design configurations

Early stent designs were woven from fine wire[1] but today more elaborate designs are used, commonly laser-cut from a thin cylinder or sheet as shown in Figure 1.

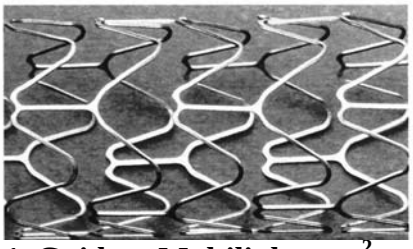

Fig. 1. Guidant Multilink stent[2]

Thus the numbers of possible contemporary design configurations is very large and coverage of the associated design space requires efficient design procedures such as Robust Engineering Design (RED) and Genetic Algorithms (GA).

Table 1 summarises some of the basic features of stents from a comparison of several products[3]. The number of design factors that might affect these features is estimated to be in the region of 4 to 10.

	Typical values
Pattern descriptions	Rings with links at 120deg, diamond, sine wave, zig-zag rings with spine
Strut thickness	0.05mm to 0.15mm
Degree of cross-struts (>80deg)	7% to 77%
Max. axial space between struts	0.7mm to 3mm
Max. circumferential spacing	0.7mm to 4.7mm

Table 1. Typical values of stent design features

Stent structural characteristics

Table 2 shows typical values for the structural characteristics of stents as summarised from data available in the literature[2].

	Typical values
(a) Radial force	Good to excellent
(b) Longitudinal flexibility	low to excellent
(c) Contact area	12% to 20%
(d) Shortening on expansion	0 to 9.5%
(e) Recoil	1% to 4.8%

Table 2. Typical values of stent structural characteristics

Minimisation of contact area, shortening on expansion and recoil are important in limiting the physiological damage potential of a stent design. Radial strength and longitudinal flexibility determine the suitability of a stent to a specific application.

Stent flow characteristics

The literature[4, 5] reveals several flow characteristics suggested to be linked with restenosis, namely:

(a) Wall shear stress.
(b) Flow separation.
(c) Blood particle residence time.
(d) Flow field under pulsatile flow.
(e) Secondary motion.

Performance data for the flow characteristics of various products are unavailable although they are likely to be strongly patient-dependent[6]. Understanding of the role of flow characteristics in restenosis is incomplete. In addition, by collecting the above structural and flow characteristics together, it is clear that stent design is a multiple objective problem and furthermore that the 'optimal' design is somewhat open to interpretation.

RED Experiment

Design Factors

Design factors are selected in relation to the output response(s) of interest, which in this case have been identified as potentially numbering ten or more. We will focus on the design factors that can be judged to affect the important flow characteristics above. However, in order to maintain additivity[7] of effects throughout the RED analysis, interactive effects between design factors must be avoided. Thus after some consideration a potential list of design factors includes:

(a) Leading strut angle, α (Figure 2).

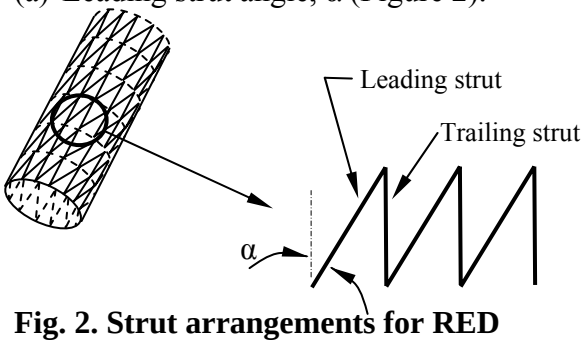

Fig. 2. Strut arrangements for RED

(b) Strut thickness.
(c) Strut section shape.

(d) Strut plan shape.
(e) Number of struts around circumference.
(f) Trailing strut configuration (Figure 3).

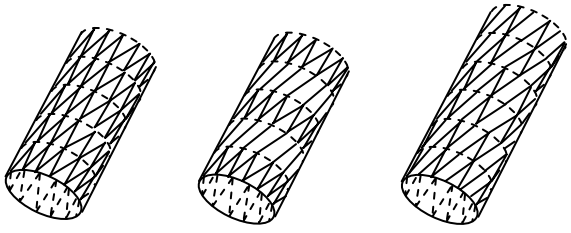

Fig. 3. Trailing strut configurations

Thus the stent strut elements are predominantly aligned with the flow axis as a first approximation for promoting good flow characteristics and also in addressing additivity of design factor effects. This stent architecture needs to be evaluated in terms of broadly satisfying the structural objectives before RED experiments begin.

Noise Factors

A key principle of RED is to reduce the effects of noise factors. For stents we expect these noise factors to come from two general groups:

(i) Differences in geometry of the stent due to variations in manufacture and clinical deployment.
(ii) Patient-to-patient variations (*'Geometric Risk Factor'*) such as blood rheology, artery geometry, artery wall compliance and calcification. Also distribution of endothelial growth around the stent.

Representing manufacturing variations is relatively straightforward. Computational Fluid Dynamics (CFD) studies into the effects of under-expansion, ideal stenting and over-expansion[8] have shown that the resultant pulsatile flow fields are substantially different. Work on patient-to-patient variations for arterial bifurcations[9, 10, 11, 12, 13] suggests that the Geometric Risk Factor (GRF) may be responsible for variability in the formation of thickened arteries and stenoses.

Stent design configurations that are tolerant to non-ideal geometries will be found by incorporating carefully selected representative values from both groups of noise factors in all the RED experiments.

Orthogonal Array

Three levels of each of the six design factors are identified in Table 3 in a standard L_{18} Orthogonal Array[14].

							RESULTS	
Run	2 N° of leading struts circum.	3 leading strut angle, α	4 trailing strut configuration	5 strut thickness	6 leading strut section	7 strut plan shape	ideal artery ideally expanded stent uniform endothelial growth	distorted artery under/over-expanded stent non-uniform endothelial growth
1	5 struts	25 deg	regular	0.03mm	rectangular	straight		
2	5 struts	35 deg	alternate rings	0.05mm	semicircular	curved		
3	5 struts	45 deg	double offset	0.07mm	streamlined	sinusoid		
4	6 struts	25 deg	regular	0.05mm	semicircular	sinusoid		
5	6 struts	35 deg	alternate rings	0.07mm	streamlined	straight		
6	6 struts	45 deg	double offset	0.03mm	rectangular	curved		
7	7 struts	25 deg	alternate rings	0.03mm	streamlined	curved		
8	7 struts	35 deg	double offset	0.05mm	rectangular	sinusoid		
9	7 struts	45 deg	regular	0.07mm	semicircular	straight		
10	5 struts	25 deg	double offset	0.07mm	semicircular	curved		
11	5 struts	35 deg	regular	0.03mm	streamlined	sinusoid		
12	5 struts	45 deg	alternate rings	0.05mm	rectangular	straight		
13	6 struts	25 deg	alternate rings	0.07mm	rectangular	sinusoid		
14	6 struts	35 deg	double offset	0.03mm	semicircular	straight		
15	6 struts	45 deg	regular	0.05mm	streamlined	curved		
16	7 struts	25 deg	double offset	0.05mm	streamlined	straight		
17	7 struts	35 deg	regular	0.07mm	rectangular	curved		
18	7 struts	45 deg	alternate rings	0.03mm	semicircular	sinusoid		

Table 3 RED experiment using an L_{18} OA (six columns assigned out of eight)

With six three-level design factors there are 3^6 = 729 possible 'full factorial' permutations. Only 18 of these will need to be tested. Each of the experiments will be repeated for two compounded noise conditions.

Genetic Algorithm experiment

Parameterisation of a stent

Design factors (RED terminology is used here for consistency) are addressed early in Genetic Algorithms (GA) and can be a more arbitrary selection than those for RED. This is partly because the additivity of factor effects is not important. Therefore, a stent can be specified here as being formed of regular, repeating patterns. Several possible repeating patterns are illustrated in Figure 4.

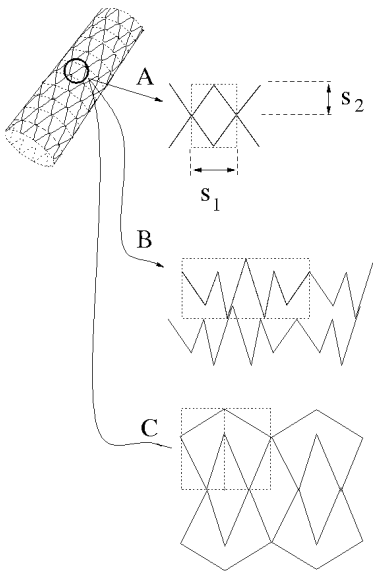

Fig. 4. Possible pattern arrangements for GA

Pattern A is the simplest version comprising a regular corrugation defined by its width, S_1, and height, S_2. Material thickness as a third design factor would complete a minimum design specification for the stent.

More complex designs could be considered as a generalised repeating pattern (B in Figure 6), where the corrugation is a curve defined by 9 vertices, i.e. design factors.

A series of closed curves, or 'tiles' presents a more general form of repeating pattern, shown in Figure 6 C. The tile patterns could be reversed in the axial direction from one tile to the next. Five vertices (design factors) would define the pattern and further potential design factors would be aspect ratio and frequency of tile.

In all three cases additional design factors could be added by displacing the patterns axially and joining them with short strut elements. These design factors could be the frequency of inter-ring links and the length of the links. In addition, the vertices of the straight-line segments shown could be the control points of a B-spline thus producing smooth curves.

Encoding the design factors

A repeating stent pattern of the tile form, as shown in Figure 5, is used here to illustrate the encoding stage of a GA.

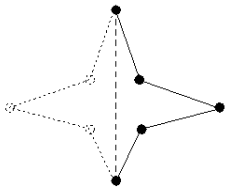

Fig. 5. Definition of a stent pattern

Design factors:

#1-5. Specification of the relative position of five vertices defines the basic shape of the pattern.
#6. Width of the tile.
#7. Height of the tile.
#8. Material thickness.

#9. Axial spacing between tiles.
#10. Number of links between one axial band of tiles and the next.

These design factors are then assembled into an artificial chromosome as illustrated in Figure 6.

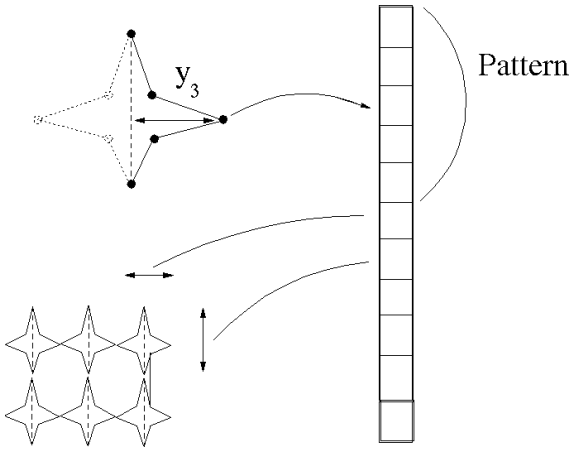

Fig. 6. Stent design encoding to artificial chromosome

Clinical context and planning of experiments

Our interpretation is that there are three distinct aspects of surgical experience, which determine how the experiments may be planned.

(i) The first is deployment of stents. The uncertainty of positioning the stent is in evidence by the fact of reliance on radio-luminescent markers. The *global* effect of calcification of the artery is variable and requires judgement in applying the necessary pressure to the angioplasty balloon. In addition *local* variations in calcification present further uncertainty in terms of possible circumferential and axial inconsistency in embedding.

(ii) Post-deployment experience associates restenosis with fluid dynamic effects - possibly highly disturbed flow. In addition long stents appear to be less successful than short stents.

(iii) The third aspect is uncertainty due to the lack of *in vivo* measurement methods. Data for endothelial growth/lumen diameter are simply not available.

As a consequence of the above the design procedures described are limited to computer simulations and *in vitro* experiments. While such simulations could indeed be made for post-operative conditions the lack of data (iii above) makes this impossible. The role of the *in vivo* experiment would be as a confirmation of simulation and *in vitro* experiments as part of the design procedures.

We are initially using moderate surgical input experience in assuming 50% embedding of the stent in the artery wall. On this basis the performance of two existing stent designs will be compared in computer simulations. This will be followed by further computer experiments determined by the design procedures. Having identified potentially advantageous designs we will then focus on a much smaller number of experiments *in vitro* similarly subject to the design procedures.

Discussion and conclusions

Engineering conduits tend to be geometrically regular and rigid, whereas anatomical vessels are irregular, individualistic and compliant in their behaviour. Understanding the fluid dynamics occurring within the human body is challenging in itself and will take years of scientific progress.

However, the increased demand for reliability in surgical procedures and related implants such as stents, grafts and heart valves requires improvements to be made in their design in the short-term.

This research seeks to address this issue by adopting the rationale of the applicability of formal engineering design procedures, RED and GA, within the medical engineering field. Specifically, the crucial aspect of patient-to-patient variation is the 'noise' issue within RED procedure to be addressed.

This paper has illustrated the difference in stent design arrangements that emerge from following RED and GA. GA can work with a more arbitrary selection of design factors, as they can accommodate a greater degree of interactions. The simplified GA encoding allows a greater variety of pattern shapes than those proposed for the RED experiment. The differences in approach have defined different sectors of design space for exploration. It will be interesting to compare the 'optimal' designs proposed from each approach. In addition the large number of important objectives that a stent must satisfy complicates the design challenge..

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