Design optimisation of coronary artery stent systems

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Abstract

In recent years, advances in computing power and computational methods have made it possible to perform detailed simulations of the coronary artery stenting procedure and of related virtual tests of performance (including fatigue resistance, corrosion and haemodynamic disturbance). Simultaneously, there has been a growth in systematic computational optimisation studies, largely exploiting the suitability of surrogate modelling methods to time-consuming simulations. To date, systematic optimisation has focussed on stent shape optimisation and has re-affirmed the complexity of the multi-disciplinary, multi-objective problem at hand. Also, surrogate modelling has predominantly involved the method of Kriging. Interestingly, though, optimisation tools, particularly those associated with Kriging, haven't been used as efficiently as they could have been. This has especially been the case with the way that Kriging predictor functions have been updated during the search for optimal designs. Nonetheless, the potential for future, carefully posed, optimisation strategies has been suitably demonstrated, as described in this review.

Key terms: computational, modelling, Kriging, multi-objective optimization

INTRODUCTION

Impressive engineering innovation and clinical expertise have made it possible to routinely deliver stents in narrowed coronary arteries such that these tubular structures can be expanded into atherosclerotic plaques to recover arterial flow area. In clinical terms, the aim is to maximise the minimum lumen area (MLA) by achieving the optimal minimal stent area (MSA). Furthermore, considering that stenting (or percutaneous coronary intervention, PCI) is procedurally successful in the majority of cases, this suggests that state of the art stents and delivery systems may have reached close to design optimality for delivery. Is it possible, or even necessary, therefore, to improve the PCI toolkit, including stents, delivery systems and/or imaging? A key driver in answering these questions is that clinical events, representing later complications (i.e failures) of the stent, such as stent thrombosis (ST) or restenosis, are more likely in circumstances in which stent expansion is suboptimal. Sub-optimal stent deployment is an independent risk factor for both restenosis and stent thrombosis. Restenosis, an exaggerated inflammatory healing response to the vessel injury inherent to PCI, results in recurrent angina or heart attack. It occurred clinically in around 10% of patients after bare metal stents and the incidence is now a few percent in the days of drug-eluting stents (DES). The minimal stent area is inversely related to the incidence of these complications (Caixeta et al.).Given the millions of stent deployment procedures being carried out worldwide, even rates of complications in low single digit percentages of the total represents a large cohort of patients. In this context, there is clearly room for improvement in the precision of stent delivery and optimisation.

If further advances are to be made, how likely is it that computational engineering will be utilised more significantly than it has been in the development of PCI technology

to date? Curiously, the earliest simulations of stent expansion performance only began to appear in the literature (Dumoulin and Cochelin, Etave et al. and Migliavacca et al.) at the time that the first generation of drug eluting stents were undergoing clinical trials (Morice et al. and Moses et al.). These early finite element analysis (FEA) studies focussed on stent structures and neglected the fundamental interactions that occur during deployment between the stent, balloon and vessel wall/tissue. Even the earliest FEA studies that included idealised stenotic artery models, didn't incorporate balloons to expand the stent, using pressure on the internal surface of the stent, instead (Auricchio et al.). It wasn't until 2008 that patient-specific artery reconstructions were first used in simulations of stent deployment (Gijsen et al.). The review of computational structural modelling of coronary stent deployment by Martin and Boyle provided a detailed consideration of this history and there was a review of computational fluid dynamics (CFD) prediction of neo-intimal hyperplasia (or restenosis) in stented arteries by Murphy and Boyle. Subsequently, Morlacchi and Migliavacca reviewed numerical modelling of stented coronary arteries more generally, including FEA, CFD and drug elution.

At the same time that the first stent deployment studies were appearing in the literature, Stoeckel et. al. published a survey of stent designs in which approximately 100 different stents were identified. Whilst commenting that such diversity was largely the result of commercial drivers, they also acknowledged that conflicting design requirements underpinned the competition to optimise scaffolding characteristics, largely in terms of radial strength and flexibility. Why is it that, since that time, there has been an increasing frequency of stent related optimisation studies appearing in the academic literature?

This article focuses on answers to the above questions primarily from the perspectives of what has already been reported on systematic coronary artery stent design optimisation and, more especially, that which might now be possible. There are a number of articles comprising parametric studies (e.g. He et al., Wang et al. and Conway et al.) but they haven't been considered in detail here due to the focus on systematic optimisation approaches. It should be acknowledged, however, that these types of study often help to inform more detailed searches for optimal designs (De Beule et al.).

Starting with a consideration of clinically optimal stenting, attention is drawn to the causes of PCI failure and poor outcomes. An overview is then presented of measures of performance (or objective functions) that can be evaluated computationally, in preparation for a review of the design optimisation of coronary artery stent systems. The article is concluded with some recommendations for future work.

CLINICALLY OPTIMAL OUTCOMES

In the 2011 ACCF/AHA/SCAI[1] PCI guidelines, an angiographic benchmark for stent results was defined by a minimum percent diameter stenosis of <10%, or optimally as close to 0% as possible (Levine et al.). This is re-iterated in the 2013 update on clinical competencies for PCI but with recognition that angiography provides "an imperfect assessment of coronary structure and stenosis severity" (Harold et al.). Thus, it is recommended that "other diagnostic modalities such as intravascular ultrasound (IVUS) and fractional flow reserve should be available" during PCI.

[1] ACCF/AHA/SCAI: American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions

Indeed, Yoon and Hur (2012) highlight four criteria for optimal stent deployment when using IVUS:

a) Complete stent expansion;
b) Complete stent apposition to the vessel wall;
c) Avoidance of edge dissection and
d) Complete lesion coverage.

Criteria 1-3 are depicted in Fig. 1 as they might appear in IVUS slices and aligned with a longitudinal cartoon to show where along a stented segment they are likely to occur. In practice, sub-optimal performance in terms of stent under-expansion and malapposition can be addressed by post-dilatation in which a non-compliant balloon is inflated inside the partially deployed stent so as to overcome the failings of the original stenting procedure. Whilst it is important for the interventional cardiologist to have methods such as post-dilatation to correct shortcomings of an initially sub-optimal stent expansion, this can introduce other dangers including tissue dissection, longitudinal stent deformation and changes to stent fatigue resistance. An example of malappostion and post-dilatation is shown in Fig. 2 as obtained using the more recently developed intravascular imaging technique of optical coherence tomography (OCT).

Although PCI is now a relatively mature practice, there are two areas in which computational modelling might result in improved stent deployment: (1) preclinical testing of modern iterations of stents and (2) design of novel stent/delivery system characteristics.

COMPUTATIONALLY MEASURABLE OPTIMALITY

Overview

Procedural optimality as defined above is largely unequivocal and can be measured using intravascular imaging methods. However, there are other metrics of stent performance that are not readily obtained during PCI but which can have a very significant influence on PCI outcome. These metrics include:

a) Radial (and longitudinal) strength;
b) Fatigue resistance;
c) Flexibility;
d) Stent malapposition;
e) Tissue damage;
f) Drug distribution (for DESs) and
g) Flow metrics, particularly related to flow disturbance and the wall shear stress environment.

Whilst it is possible to selectively combine any of these metrics in research studies, regulatory guidance by the Food and Drugs Administration (FDA) on non-clinical engineering tests provides a long list of recommendations primarily based on mechanical and structural attributes (FDA, 2010). Whilst measures of performance could be defined and simulated for all of the FDA recommended tests, the focus here is primarily on those that have featured in reported optimisation studies. Indeed, some of these (e.g. tissue damage, drug distribution and flow disturbance) don't appear in the FDA recommendations or in the draft update of 2013.

FEA and CFD are the two principal simulation disciplines that are employed to generate these measures of stent performance. Other physical models have been used (e.g. corrosion modelling by Grogan et al. and drug kinetics by Bozsak et al.) but the majority of optimisation studies have employed FEA to obtain structural metrics including recoil, radial strength, foreshortening, flexibility, malapposition, fatigue resistance and tissue stress. Others have focussed solely on CFD simulations to extract and compare wall shear stress metrics. A small number of articles have reported multi-disciplinary optimisations wherein a stent deployment simulation using FEA is followed by a CFD blood flow simulation through the deformed vessel and over the expanded stent and/or by a drug elution simulation using a CFD based scalar transport model.

FEA and structural optimality

One way to characterise the various optimisation studies is to consider the level of detail included in the simulation models. For example, the majority of FEA studies have used single unit stent models, completely neglecting interaction with arterial tissue. Others have used high levels of detail including full three-dimensionality and models for a complete balloon delivery system and a diseased artery with contact interactions between balloon, stent and tissue (Pant et al. and Grogan et al.).

In addition to the review by Martin and Boyle, Migliavacca et al. provided a succinct overview of early FEA studies of stent behaviour and performance. Notable among them was the two-dimensional study by Rogers et al. who focussed on the need to minimise vascular injury during stenting. This work is particularly pertinent since it addressed vascular injury induced by balloon contact forces combined with stent strut lacerations with the aspiration to optimise long-term outcomes for patients.

Whilst Rogers et al. focussed on clinical effects, Migliavacca et al. noted that FEA could be used in the optimisation of coronary stents by investigating the effects of different geometrical parameters on mechanical performance. Indeed, nearly all stent optimisation studies have employed geometry variation to define the optimisation design parameters including strut width, strut thickness, strut length, crown curvature, connector shape and a range of other shape variables set up to generate more complicated cell shapes. A detailed consideration of structural metrics as used in optimisation is provided in *Supplementary Material A* but the following key elements are noted here for certain metrics that: (i) should be checked globally along the stent and in the tissue but for which, numerically, single values are needed for optimisation; (ii) can be obtained numerically and/or experimentally (e.g. radial strength); (iii) have not been used in optimisation studies since they have been only recently defined (e.g. longitudinal stent deformation); (iv) have been under used (e.g. fatigue resistance) and (v) are difficult to quantify (e.g. tissue damage).

CFD and transport: flow and drug optimality

CFD based coronary artery stent optimisation has featured in six key studies (Atherton & Bates, Blouza et al., Srinivas et al., Pant et al. (2011), Gundert et al. and Amirjani et al.). Similarly to FEA studies, these can be characterised by simulation detail. Atherton & Bates used a simplified model involving steady state 3D CFD for single stent units whilst Blouza et al. and Srinivas et al. applied steady state 2D CFD over displaced strut cross-sections. Gundert et al. and Amirjani et al. employed pulsatile and steady state 3D CFD, respectively, but both used idealised vessels and stents constructed in expanded configurations from a repeating cell unit. With further complexity, Pant et al. (2011) performed pulsatile 3D CFD through representative diseased vessels deformed using FEA stent deployment simulations. Further,

Atherton & Bates, Srinivas et al. and Gundert et al. only considered flow optimality whereas the others adopted a multi-disciplinary approach.

To capture the effect of flow on arterial walls, metrics are needed that can be minimised with respect to the flow disturbance caused by the presence of stent struts embedded in an irregular arterial wall boundary. This is based on the assumption that an optimal flow environment exists for a smooth vessel in the absence of a stenosis. Gundert et al. extracted time averaged wall shear stresses that were averaged over the arterial surface exposed to flow in the central rings of the stents. Blouza et al. and Srinivas et al. considered multi-objective optimisation, respectively, for two metrics (steady state wall shear stress and swirl) and three metrics (vorticity, recirculation distance and reattachment lengths between struts). Atherton & Bates calculated power dissipation as a surrogate for wall shear stress.

Pant et al. (2011) devised a haemodynamic low and reversed flow index (*HLRFI*), as a function of regions where wall shear stress was below a prescribed level or reversed relative to the main flow direction. *HLRFI* was minimised to reflect the fact that strut distribution can influence the extent of disturbed flow on the arterial wall.

Similarly to tissue damage, the efficacy of drug delivery can be defined by a volume averaged concentration, which needs to be maximised. Drug concentration can be calculated within the tissue by solving a CFD-based transport equation for drug concentration or through heat transfer equations in FEA solvers. However, optimisation of drug delivery has been considered in far more significant detail by Bozsak et al. Solely focussing on the drug kinetics of sirolimus and paclitaxel, a single measure of performance was derived to combine drug efficacy in the media with an average toxicity metric across the lumen, sub-endothelial space and the

media and penalised by a buffer term to avoid drug concentrations close to the toxicity limit. Notably, optimal paclitaxel-eluting stents were identified with far lower concentrations than existing DESs and designed to release the drug either very rapidly or very slowly (up to 12 months).

Multi-disciplinary optimality

The procedural and long-term efficacy of PCI is known to be dependent on a wide range of factors related to structural performance, haemodynamics and the bio-chemistry of disease, inflammation, drug delivery and healing. Patient-specificity with respect to anatomy and disease is also important. Although no optimisation study to date has included more than six separate objectives, obtained from multiple disciplines, it is encouraging that a small number of studies have successfully demonstrated that it is possible to conduct high fidelity multi-disciplinary optimisation.

Pant et al. (2011) and Amirjani et al. conducted FEA and CFD simulations to generate a range of multi-disciplinary objectives. Amirjani et al. combined stent and tissue stress metrics with stent recoil and a flow induced wall shear stress metric in a single aggregated objective function.

Pant et al. (2012) used structural deployment and flexibility objectives with a drug elution metric in a constrained optimisation study in which optimal designs were found for each metric without diminishing any other metric. It was only in Pant et al. (2011) that structural (stent recoil and tissue stress), flow and drug elution metrics were used in a fully multi-disciplinary, multi-objective framework.

Although CFD wasn't included in the study by Grogan et al., multi-disciplinary optimisation was performed by coupling a corrosion algorithm to FEA of a stent system that was tested for radial collapse strength.

OPTMIZATION FRAMEWORK – THE STENT DESIGN CHALLENGE

Overview

Having discussed stent optimality from both clinical and mechanical engineering perspectives, different ways of framing stent optimisation studies is now considered. Whatever method is used, there are four key, common elements:

a) Design variables which are the inputs (often geometry parameters) to be varied;
b) The objective function comprising one or more quantified measures of performance that can be used to compare different designs;
c) Constraints defining regions of the design space that cannot be included – lower and upper bounds are needed for the design variables and it may be necessary to specify values of derived quantities that must satisfy prescribed equality or inequality constraints;
d) An optimisation algorithm in which, simply stated, the optimiser needs to find a combination of design variables that are optimal with respect to the objective function subject to satisfying the specified constraints.

Generally, these separate elements should be considered simultaneously such that the design variables and the objective function(s) are defined appropriately for a given problem and for a particular optimisation algorithm. For example, if considering flexibility, design variables for the connectors should be included. With respect to the

optimisation, whilst it might be possible to have many (>10) design variables when optimising a single strut using a direct search method such as a genetic algorithm, it is advisable to reduce the number of inputs when using computationally expensive full stent deployment simulations within a response surface modelling approach.

Design variables

In the optimisation studies considered here, the largest number of design variables was seven in Grogan et al. and Wu et al. (2010), and most reported research has used three or four variables. Strut width is the most commonly included design variable and strut thickness (measured radially), strut length and parameters to control crown shape are also relatively common. More detailed control of stent unit shapes has been considered by Clune et al. using a set of NURBS weights, by Grogan et al. with various strut lengths and heights and by Wu et al. (2010) with a variety of strut widths and arc radii. When flexibility has been of interest, design variables have been used for the connectors as in Pant et al. (2011 & 2012). In cases when haemodynamic optimality has been sought, Atherton & Bates and Gundert et al., the angle of struts to the flow has been included. In contrast to the majority of studies that employ shape optimisation, Bozsak et al. considered only drug kinetics design variables: the initial drug concentration and the drug release time.

Objective functions (a multi-objective, multi-disciplinary problem)

Whilst most optimisation studies have incorporated multiple objectives, some earlier articles considered a single objective function. Atherton & Bates used power dissipation as a surrogate for wall shear stress and Harewood et al. focussed on radial stiffness of a single ring. More recently, Li et al. (2013) sought to just focus on

stent dog-boning. When considering multiple objectives, the majority of studies have either combined them in a single weighted objective function (Timmins et al., Li et al. (2009), De Beule et al., Amirjani et al. and Bozsak et al.) or have endeavoured to construct and search the Pareto fronts generated by treating each objective separately. One of the earliest attempts to do this by Blouza et al. used the multi-objective evolutionary optimisation algorithm by Deb et al. (2003) to analyse the trade-off between wall shear stress and swirl within a two-dimensional flow disturbance model of stent struts. Similarly, Srinivas et al. sought to minimise vorticity and recirculation distances whilst maximising the reattachment length between struts.

More advanced incarnations of this approach, using the non-dominated sorting genetic algorithm, NSGA II by Deb et al. (2002), have been adopted by Pant et al. (2011) for six objectives (obtained from multi-disciplinary structural, haemodynamic and drug elution simulations) and by Clune et al. for the trade-off between fracture resistance and flexibility. Finally, multiple objectives have also been incorporated in slightly different ways by Wu et al. (2010) and by Pant et al. (2012). In the former, the dual objectives of maximum principal strain and mass of material were treated in a two stage process of maximising mass once the maximum principal strain had been minimised. In contrast, Pant et al. (2012) used constrained single objective optimisation to separately minimise one of four objectives in turn, constrained by the requirement for the other objectives not to deteriorate.

A key issue related to the treatment of multiple objectives concerns the trade-off between measures of performance that are in competition. When using a weighted single objective function the balance between objectives can be controlled by the values of the weights. This approach is exemplified by Timmins et al. who assessed

different weight combinations to generate stent designs optimised for critical tissue stress, luminal gain or cyclic radial deflection. Further, discussion of “lesion-specific stenting” alluded to the possibility of maximising minimum lumen area at the expense of high wall stress for stiff, calcific plaque by having lower distances between stent rings in contrast to the minimisation of wall stress for softer lipid type lesions by having wider strut spacing.

Various paradigms for stent selection were considered by Pant et al. (2011). Fig. 18 from that work is reproduced in Fig. 3, depicting the trade-off between recoil and volume averaged stress and how a design based on the Cypher® platform was predicted to be biased towards low recoil at the expense of potential tissue damage. A conservative approach to selection would seek designs closest to the so-called utopia point (located at the lowest values of the respective objectives). However, noting that six objectives were considered (and other important measures of performance were neglected) a more experiential paradigm would suitably bias selection to the specificity of a particular patient and lesion. Indeed, the rigid, closed cell design of the Cypher® platform is emblematic of the fact that minimal recoil and maximal radial strength were likely to have been the prominent considerations when it became the PCI work-horse in the first generation of drug-eluting stents.

Constraints

All systematic optimisation studies require constraints on the design variables. These constraints are commonly referred to as bounds and act to define the design space of the problem. For example, when varying strut width, the lower and upper bounds define/constrain the range of variation of strut width during optimisation. Other constraints are typically imposed on a problem such that certain requirements aren’t

violated. Most constraints used in coronary stent optimisation studies have been based on structural requirements. Harewood et al. applied constraints on the mean magnitude of the principal tensile stresses during pressure loading and bending and the difference between them. In this way, radial stiffness was maximised without compromising fatigue resistance.

The application of constraints can be implied as well as in the two stage process by Wu et al. (2010). De Beule et al. sought to reduce foreshortening by 20% whilst maintaining radial stiffness relative to the reference geometry of a self-expandable braided stent.

Only four studies have been identified that applied constraints directly during optimisation. In addition to Pant et al. (2012), (i) Wu et al. (2008) combined a constraint on the drug holding capacity of a Conor stent (Conor Medsystems Inc.) with manufacturing constraints related to the extrusion of strut geometry and minimum member size control, to optimise strut stiffness; (ii) Azaouzi et al. optimised fatigue resistance of a nitinol stent with constraints on the minimum radial force that it could support and on the maximum strain amplitude when exposed to a physiological pulse and (iii) Bozsak et al. penalised the objective function by introducing a term to keep eluted drug concentrations away from a predefined toxicity level.

Optimization methods

Due to the long computational times needed to simulate stent performance, the majority of coronary artery optimisation studies have adopted a surrogate modelling approach in which response surface models (RSMs) have been constructed to represent the relationship between objective functions and design variables. Simply

stated in the current context, a RSM is a surface fit of one or more measures of performance against multiple design variables. Earlier RSM optimisations (Harewood et al., Li et al.(2009) and Wu et al. (2010)) used polynomial based least squares functions but more recent studies have adopted Gaussian Process Models, commonly referred to as Kriging (Jones) after the South African geo-statistician, D. G. Krige (Krige). Before describing Kriging in more detail below, optimisation using RSMs is described in general, with reference to Fig. 4.

At the start of a study, it is necessary to setup a baseline model (1), the definition of the problem (2) and the simulations that are to be performed (dashed box). Then, an initial RSM is constructed (3) from a sample of design points defined by a design of experiments (DoE). The DoE may be generated randomly but a number of methods have been developed with better space filling properties, e.g. optimised Latin hypercubes (Morris and Mitchell, Forrester et al.) and LP_τ (Statnikov and Matusov). For each point, simulations are performed to evaluate measures of performance (4). The construction of the RSM (5) involves the derivation of a function from the values of the objective function obtained for a set of design variables (defined by the DoE for the initial sample). In a multi-objective problem, separate RSMs are constructed for each objective and, similarly, in a constrained optimisation, separate RSMs can be constructed for each constraint. Importantly, RSMs only provide a *prediction* of the complete response of the system and, since the goal of the optimisation method is to find optimal designs, it is likely to be necessary to improve the accuracy of the RSM before determining an optimum. RSMs are improved (or updated) by generating new design point data (or updates) at appropriate locations in the design space (6). Updates are generated by searching the current RSM and running further simulations at appropriately selected design points to obtain the value(s) of

objective(s) at these new points (7). This process can be repeated until a convergence criterion has been satisfied (8) or a computational budget exhausted. The accuracy/quality of the RSM can be evaluated/validated using cross-validation methods that sequentially compare predictions of at least one data point from RSMs constructed from the data-set with this (these) point(s) excluded. The use of leave one out and standard cross validation residual plots was demonstrated in Pant et al. (2012). An alternative, brute force approach can be applied, if affordable, by running additional simulations to generate new validation data. This was done by Harewood et al. in which a RSM constructed from a sixty point DoE was validated (and enhanced) by a separate twenty point DoE.

Kriging

There are a number of advantageous features of Kriging that make it particularly suitable for surrogate modelling and optimisation of engineering problems. Given a set of inputs and experimentally obtained outputs, the Kriging predictor:

a) Comprises a linear combination of tuneable basis functions;
b) Interpolates the data;
c) Has a statistical interpretation from which the mean squared error (MSE) of the predictor can be formulated and
d) Yields additional functions, including the expected improvement (EI), which can be used to enhance the search for optimal designs.

Both the MSE and the EI are particularly useful for defining update points when it is necessary to improve the accuracy of the predictor.

Derivation of the Kriging equations can be found elsewhere (Jones) but the predictor is described in Supplementary material B.

Srinivas et al. performed possibly the first Kriging based optimisation of coronary stents using a simplified 2D, steady-state flow model. With a three-dimensional Latin hypercube DoE for strut width, thickness and spacing, Krigs were constructed for three metrics from which non-dominated optimal designs were found. Evidence for the subsequent use of Kriging for the optimisation of coronary stents is sparse until Pant et al. (2011) constructed separate Krigs for six objective which were used in an NSGA II search of the design space. A sequence of three parallel updates was performed in which five designs were selected from the non-dominated Pareto front for each set of updates. New Krigs were constructed following the generation of data for each update. Starting from a fifteen point LP_τ DoE, the three updates produced a total sample size of thirty points.

Gundert et al. determined haemodynamically optimal stent geometries using the MATLAB DACE[2] implementation of Kriging (Lophaven et al.) within a pattern search algorithm based on the Surrogate Management Framework described by Booker et al. A single design parameter (the intra-strut angle) was optimised for a single objective (the area of low time averaged wall shear stress) for a range of intra-strut areas and numbers of circumferential units. Starting with a Latin hypercube DoE, most runs converged within 10-15 function evaluations and the optimal intra-strut angle was found to be independent of both vessel size and the intra-strut area of the stent cell.

[2] DACE: Design and analysis of computer experiments

Update points in Gundert et al. were identified from the predicted optima following a search of the RSM. The equivalent to this in the multi-objective problem is to select non-dominated points on the Pareto front as demonstrated by Pant et al (2011). However, as noted above, Kriging usefully provides alternative means for generating update points. Since the EI function blends exploration and exploitation, used repeatedly, it simultaneously improves the accuracy of the RSM throughout the design space and enhances the search for optimum designs. Grogan et al. and Li et al. (2013) used EI updates in their single objective optimisations for maximum radial strength and minimum dog-boning, respectively.

Grogan et al. performed an impressive number of simulations, running five separate optimisations, each starting from a different 28 point Latin hypercube DoE followed by 122 EI updates. It isn't clear why the separate optimisations were performed or whether the problem warranted so many updates. Multiple runs are often performed when assessing the mean and variance of an optimisation strategy but that wasn't the case in Grogan et al. Experience suggests that approximately 70 simulations would have been sufficient (i.e. ten times the number of design parameters) even though there was greater than 6% variation in the optimum designs found from the five optimisations. It's possible that mesh related issues compromised convergence and it may have been advisable to force the Krig to regress the potentially noisy data. The DoE size of 28 points was well judged for seven design variables but it should be possible to run smaller numbers of updates.

More modest numbers of EI updates were used by Li et al. (2013) for four slotted tube design parameters in four deployment simulation scenarios, the maximum number of updates being 22. Despite using a simplified stent model, shape optimisation using Kriging successfully led to designs with reduced dog-boning.

Similarly to Gundert et al., Bozsak et al. used Kriging in a surrogate modelling framework but, during the search steps, update points were identified by maximising the probability of improving a current optimum by a prescribed margin.

In contrast to the aforementioned approaches to RSM updating, two other studies, both with a focus on shape optimisation of a single crown unit for the maximisation of fatigue resistance, have avoided using updates. Azouzi et al. adopted a trust-region strategy in which successive RSMs were constructed for increasingly smaller design space samples centred on optimal locations found from each search. Starting from a very large volume design of a Nitinol strut, five iterations were needed to reduce strut volume by 78% whilst satisfying constraints on the minimum outward force of the complete structure and the maximum value of the strain amplitude for all elements. As one of the few examples of RSM-based coronary artery stent optimisation studies to directly apply constraints, it is useful to note that separate Krigs were constructed for each constraint.

Updates can also be completely avoided by committing to an exhaustive number of points as undertaken by Clune et al. in a randomly generated Latin hypercube DoE for six geometry design variables. A Pareto front was successfully generated to represent the trade-off between fatigue resistance and flexibility. Using the MATLAB implementation of NSGA II, a range of designs was depicted along the front. Although very high accuracy was demonstrated for the respective RSMs using cross-validation, it would be interesting to determine the minimum number of designs that would actually be needed to achieve a similar level of predictive accuracy.

From this review of the literature, it would appear that, despite the increasing use of Kriging in coronary artery stent design, Krig tuning is hidden from and/or overlooked

by many users. Also, there is limited evidence for the efficient use of updating strategies.

FUTURE CHALLENGES AND OPPORTUNITIES

The emergence over the last ten years of systematic numerical optimisation of coronary artery stent design has been catalysed by advances in:

a) Surrogate modelling using response surface models, particularly Kriging;
b) Numerical modelling of structural performance using FEA and
c) Computing power and resources.

Taken together, these three elements have made it possible to perform multiple, detailed (and computationally expensive) simulations of stent behaviour as described by Pant et al., Grogan et al. and Bozsak et al. However, the majority of other reported studies have introduced significant simplifications into the numerical models, often involving the simulation of single crown units, that don't necessarily require high performance computing resources. Therefore, although it might be technically feasible to design bespoke, patient-specific coronary stents using detailed 3D simulations, the required computational run-times are likely to render such an approach unusable in the catheter-laboratory for the foreseeable future. Further, even if simplified models that can be solved quickly could be used in this way, regulatory approval is likely to act as a significant barrier. What remains to be seen is how detailed and simplified approaches to stent optimisation could be used to address the low percentage of PCI cases that have sub-optimal outcomes. Potentially, novel stent characterisations could be developed that are optimised for sub-sets of challenging patient cases. Another area to explore concerns optimisation of the delivery system wherein, for example, balloon unpressurised diameter and

inflation pressure could be optimised to balance strut malapposition against tissue damage. Other biological endpoints could also be targeted through pre-clinical trials, for example, aiming to minimise inflammation and/or restenosis. One of the biggest challenges in these areas concerns the need and value of validating computational predictions with *in vitro* experiments, pre-clinical and clinical findings and, ultimately, with clinical practice. Finally, since Kriging appears to be becoming a favoured optimisation technology, the knowledge gained as applied to coronary artery stents should be applicable to the design of bifurcation stents and bifurcation stenting protocols, heart valve frames, peripheral stents and other biomedical devices.

CONCLUSIONS

Common to the design optimisation of coronary artery stent systems considered here are the facts that:

a) The great majority of design variables have been geometric;
b) Only a subset of performance measures have been considered in each case;
c) Host vessel geometry has been, at best, idealised and often neglected completely;
d) Surrogate modelling using Kriging has become the dominant optimisation framework.

It is also clear that the growth in optimisation studies, often using Kriging, is a relatively recent phenomenon. Consequently, despite a range of weaknesses and limitations, the work to date has revealed a large array of opportunities for further systematic optimisation of coronary artery stenting, including enhanced accuracy of computational modelling, more efficient surrogate modelling, patient-specific device optimisation and the challenges of solving a complex, multi-disciplinary, multi-

objective problem. Using these methods it will be possible to design new iterations of stents and/or novel stent/delivery system characteristics. Ultimately, the aim of computational modelling applied in these ways is to facilitate clinical optimality for more patients in all interventional procedures.

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FIGURES

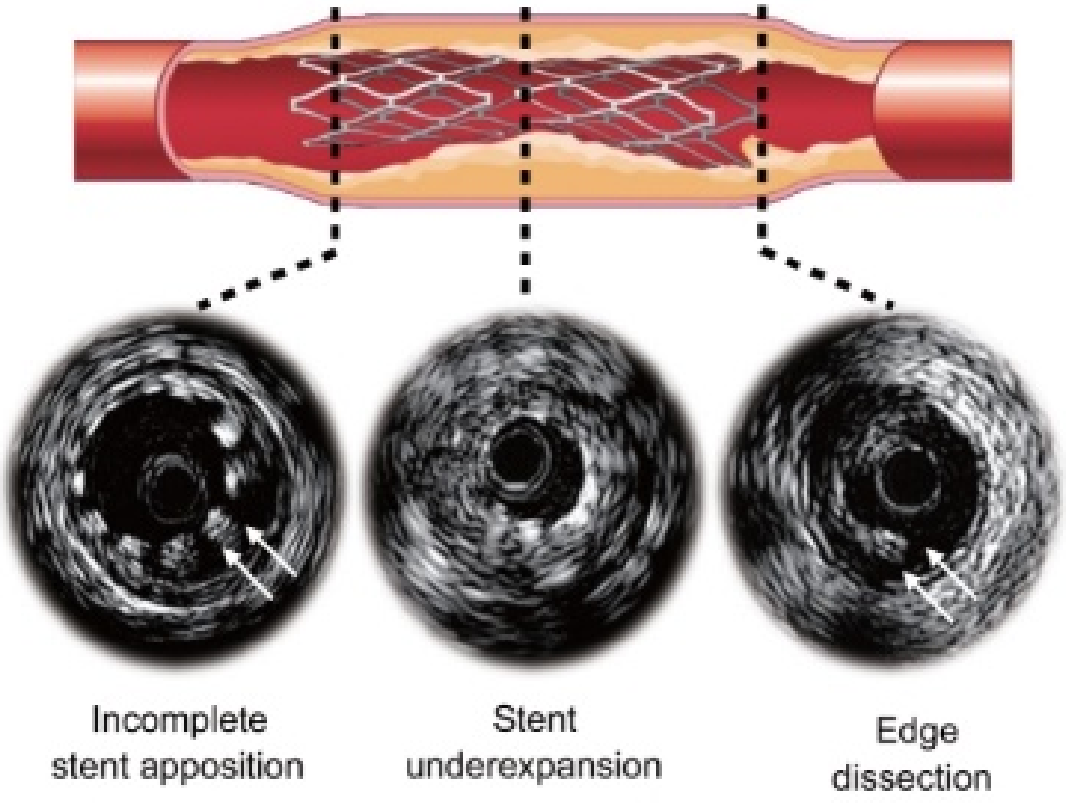

Figure 1. (Figure 2 in Yoon and Hur) Stent-related complications after stent deployment. Reprinted with permission from the Korean Association of Internal Medicine.

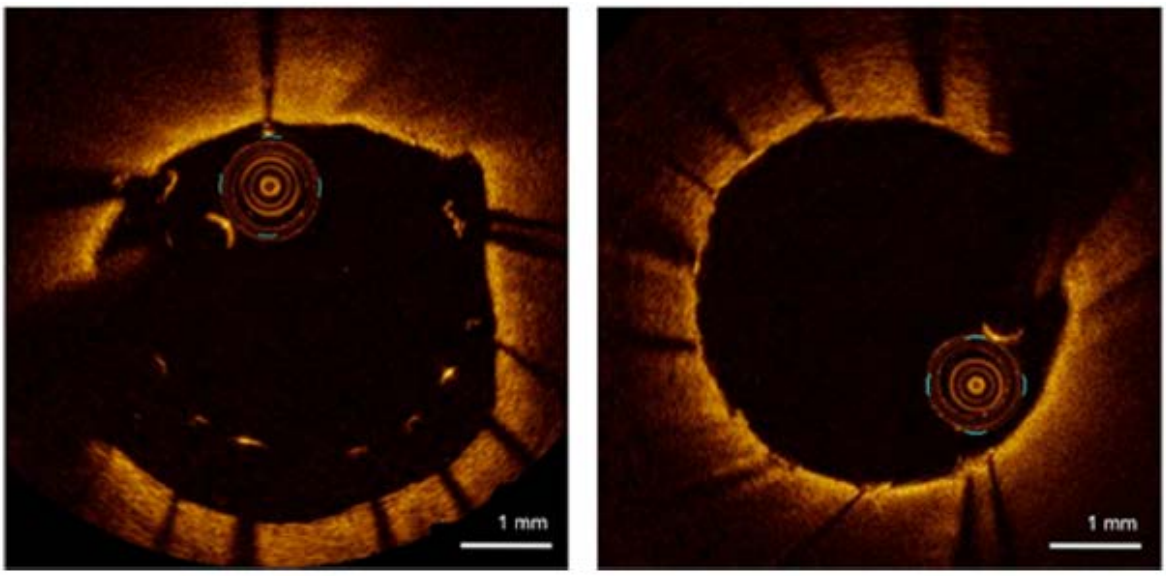

Figure 2. (Figure 1C in Johnson et al.) OCT image of an under-expanded stent (left). The same stent segment seen after post-dilatation, now completely apposing the vessel wall (right). Reprinted with permission from Springer.

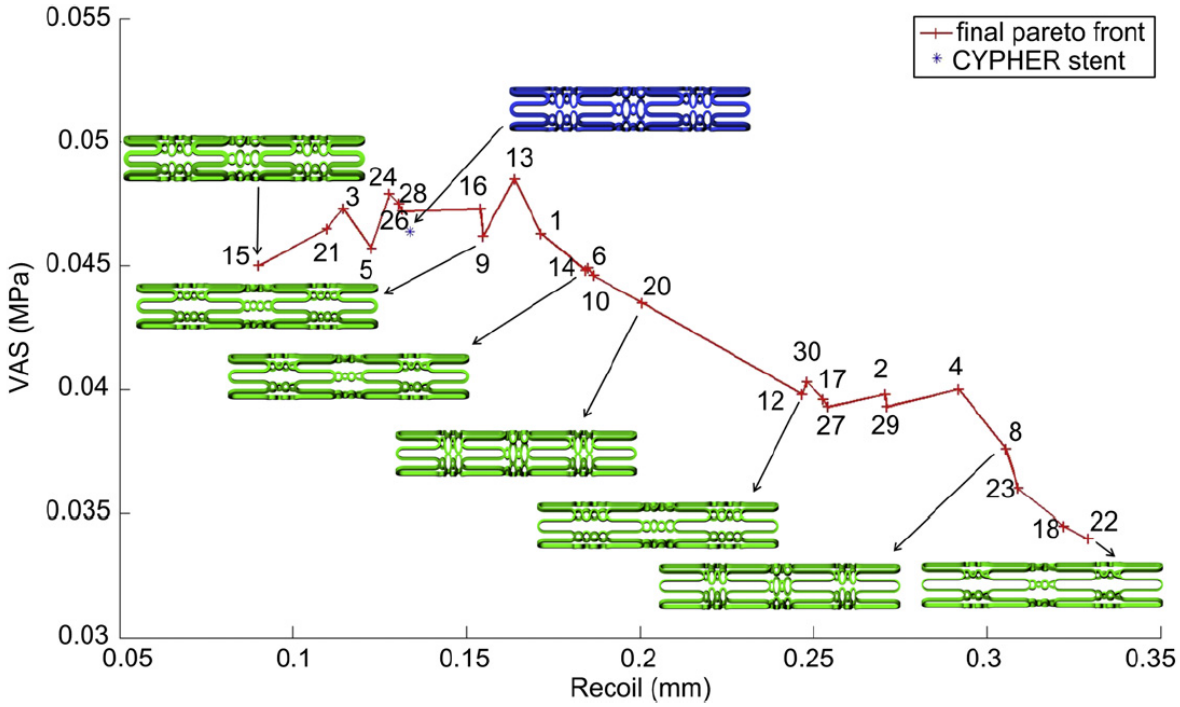

Fig. 18. Final Pareto front slice showing the trade-off between volume average stress (*VAS*) and acute recoil (*Recoil*).

Figure 3. (Fig. 18 in Pant et al. (2011)). Final Pareto front slice showing the trade-off between volume average stress (VAS) and acute recoil (Recoil). Reprinted with permission from Elsevier.

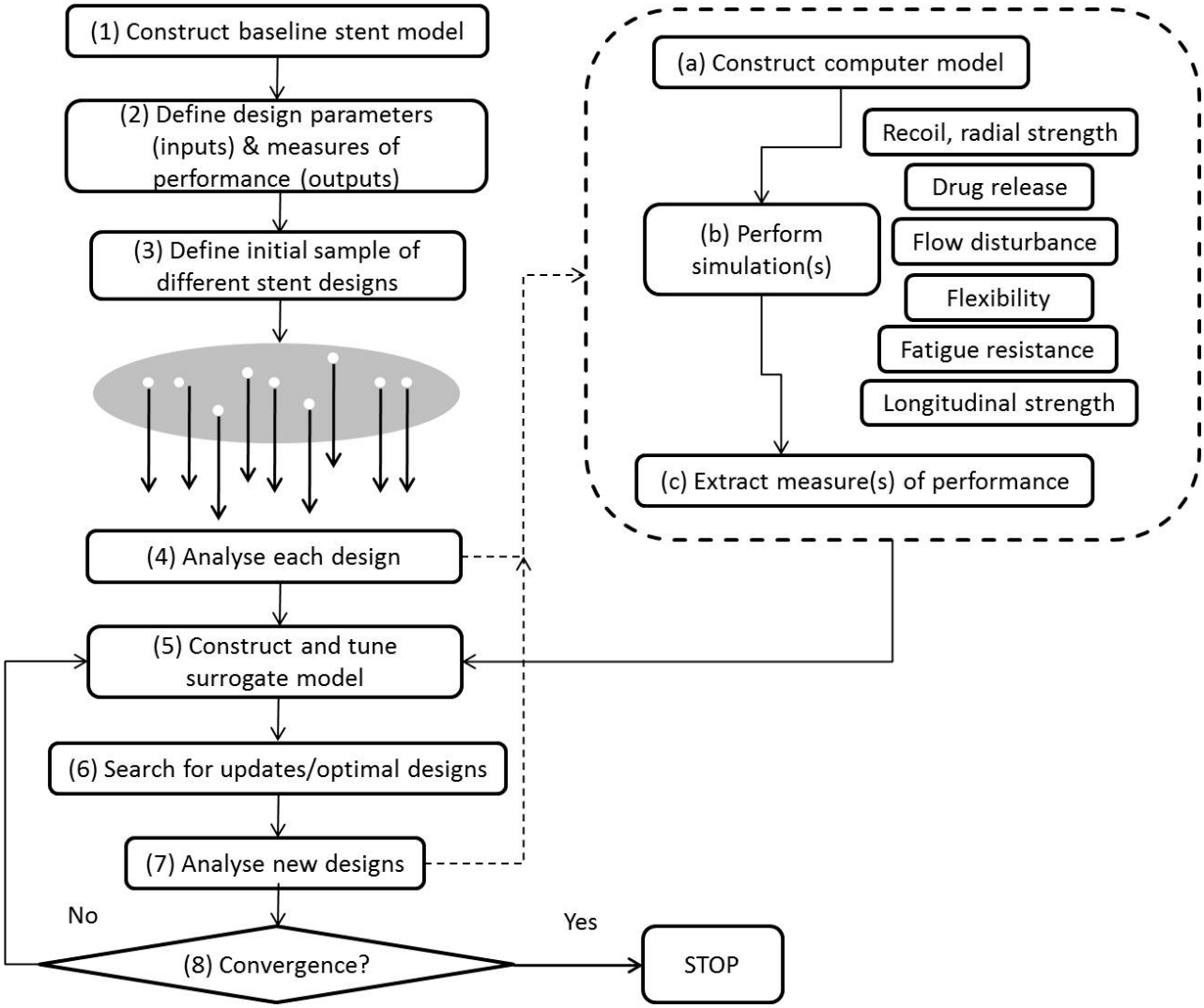

Figure 4. Flow-chart of the response surface modelling approach to coronary artery stent optimisation.

Supplementary material A

FEA and structural optimality

Radial (and longitudinal) strength, recoil, flexibility and fatigue resistance can be calculated using FEA simulations. It's worth noting that these structural metrics can also be determined experimentally and that, before computing power and software capability made it feasible to run computational experiments, laboratory testing provided the only means of obtaining these metrics.

Radial strength can be obtained by applying an additional step at the end of a deployment simulation. An inward pressure can be applied to the outer surface of the deformed stent, isolated from the arterial model, such that node displacements are measured and the radial strength is determined as the pressure at which a critical displacement gradient is generated (equivalent to the FDA's definition of irrecoverable deformation). Elastic recoil and stent foreshortening should be mentioned here, as well, since both of these metrics can be evaluated during the expansion step of a simulation. The FDA recommends that recoil should be calculated as the change in diameter from peak balloon inflation pressure to post balloon deflation, as a percentage of the expanded diameter. While it also recommends to check the recoil along the length of a stent, numerically, single values are needed for optimisation. Therefore, average recoil or maximum recoil should be used. Recoil (and foreshortening) can also be measured clinically using quantitative coronary angiography.

Longitudinal strength can be quantified by applying a compressive force to the crowns at the end of a stent so as to determine the force needed to displace the stent a certain distance. This is the approach adopted experimentally *in vitro* by Ormiston et al. in response to the issue of longitudinal stent deformation (Hanratty and Walsh). Ragkousis

et al. set up similar computational models and then applied FEA to validate their results against the laboratory experiments. They could then asses the effects of point loads applied to the malapposed struts of stent models deployed in a patient-specific diseased vessel. Although longitudinal strength has not yet appeared in any stent optimisation studies, it should appear in due course as a constraint on design variation if designers again push the envelope of feasible designs towards compromised longitudinal strength.

Interestingly, fatigue resistance has been neglected in many of the optimisation studies that have appeared to date, despite the fact that it was the focus of one of the earliest reported FEA studies of a peripheral stent by Whitcher. The two articles that have sought to optimise stent strut design with respect to fatigue resistance, *FR*, Azouazi et al. and Clune et al., have simulated the cyclic loading of a stent unit from which the amplitude and mean variations of stress and strain were extracted for each element. Seeking to maximise *FR*, Azouazi et al. employed a constraint on strain amplitude to keep it below a value of 0.4% whilst Clune et al. evaluated fatigue resistance directly according to the Goodman number.

Many of the early closed cell stent designs, including the Cypher platform (Cordis Corp., Johnson & Johnson Co.), were relatively rigid. Despite the overall strength of such designs, the accompanying lack of flexibility meant that they were superseded by more flexible open cell configurations. Flexibility is an important clinical metric both in terms of deliverability and conformability. In 2012, Pant et al. quantified flexibility by measuring the area under the graph of an applied moment versus a curvature index following application of a moment to a single stent unit. The curvature index was calculated from the ratio of the bending angle to the length of the single stent unit. In contrast, Clune et al. calculated flexibility from the average outward deflection of all nodes under an outward radial force (equivalent to 40mmHg) applied to the stent’s inner surface.

Tissue damage during PCI occurs due to contact pressure from balloons used for angioplasty, stent expansion and post-dilatation, as well as from contact and lacerations caused by stent struts embedded in the arterial wall. The resulting inflammation is the major trigger for restenosis, recognition of which led to the development of DES. However, a definitive definition of tissue damage doesn't exist. Consequently, researchers (c.f. Pant et al.) have largely defined volume average quantities for von Mises stress that can be evaluated by summing the stresses in all elements following FEA simulations of stent deployment (Holzapfel et al.). Volume averaged stress can then be defined as

$$VAS = \frac{\sum_{i=1}^{i=n} \sigma_i dV_i}{\sum_{i=1}^{i=n} dV_i} \qquad \text{(A1)}$$

where von Mises stress, σ_i and element volume, dV_i, are combined for all n elements of the relevant domain. In an optimisation framework, designs are sought that minimise *VAS*.

Hanratty, C., and S. Walsh. Longitudinal compression: a new complication with modern coronary stent platforms-time to think beyond deliverability. EuroIntervention 7:872–877, 2011.

Holzapfel, G. A., M. Stadler, T. Gasser. Changes in the mechanical environment of stenotic arteries during interaction with stents: computational assessment of parametric stent designs. J Biomech. Eng. 127:166–180, 2005.

Ormiston, J. A., B. Webber and M. W. I. Webster. Stent longitudinal integrity: bench insights into a clinical problem. JACC: Cardiovascular Interventions. 4:1310–7, 2011.

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Supplementary material B

It is useful to specifically focus on the nature of the Kriging predictor and on the MSE with respect to the advantages described in the main article.

At a prescribed set of *n* design points, the Kriging predictor can be written as

$$\hat{\mathrm{v}}(\mathbf{z}^*) = \hat{\mu} + \sum_{\mathrm{i}=1}^{\mathrm{n}} \mathrm{b_i}\varphi(\mathbf{z}^* - \mathbf{z_i}) \quad \text{(B1)}$$

representing the combination of a mean response, $\hat{\mu}$, given by the equation

$$\hat{\mu} = \frac{\mathbf{1'R^{-1}v}}{\mathbf{1'R^{-1}1}} \quad \text{(B2)}$$

and a summation of the predicted influences of each known design point, $\mathbf{z_i}$, on the new point, $\mathbf{z}^*$, at which a prediction is to be obtained. $\mathbf{z_i}$ and $\mathbf{z}^*$ are *d*-dimensional vectors, where *d* signifies the number of design parameters. In Eq. B2, $\mathbf{1} = \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}$ is an n x 1 vector of ones, $\mathbf{v} = \begin{pmatrix} \mathrm{v_1} \\ \vdots \\ \mathrm{v_n} \end{pmatrix}$ is a vector of the values of the simulated data points and **R** is the n x n correlation matrix with each element (i, j) given by the Gaussian basis function

$$\exp\left(-\sum_{l=1}^{\mathrm{d}} \theta_l \left|\mathbf{z}_{\mathrm{i}l} - \mathbf{z}_{\mathrm{j}l}\right|^{\mathrm{p}_l}\right) \quad \text{(B3)}$$

The ability to tune the Krig derives from the hyper-parameters, $\mathrm{p_l}$ and θ_l which, respectively, control the smoothness and response activeness for each one of the *d* design parameters. Jones notes that this tuning capability is “the main reason Kriging often outperforms other basis-function methods in terms of prediction accuracy”. Usefully, it’s possible to automatically tune the hyper-parameters by maximising the concentrated log-likelihood function (CLF), a simplified version of the likelihood function which is only a

function of **R**. In other words, a search can be performed on the CLF to find the optimal set of hyper-parameters that maximises the CLF.

Returning to Eq. B1, each term in the summation of the predicted influences of the known design points on the design point to be predicted, is given by the weighted basis function

$$b_i \varphi(\mathbf{z}^* - \mathbf{z}_\mathrm{i}) = b_i \exp\left(-\sum_{l=1}^{\mathrm{d}} \Theta_l \, |\mathbf{z}_l^* - \mathbf{z}_{\mathrm{i}l}|^{\mathrm{p}_l}\right) \tag{B4}$$

where the weight, $\mathrm{b_i}$, denotes the *i*th element of $\mathbf{R}^{-1}(\mathbf{v} - \mathbf{1}\hat{\mu})$**.**

From the Kriging predictor, it is possible to derive a range of functions that can be used to improve the accuracy of the predictor and/or the search for optimum designs. Since the mean error features in these functions and it can be used directly to identify update points to improve predictor accuracy, the mean error is detailed here. Since Kriging is based on a Gaussian Process Model, the mean squared error (MSE) is given by

$$\hat{s}^2(\mathbf{x}) = \hat{\sigma}^2 \left[1 - \mathbf{r}'\mathbf{R}^{-1}\mathbf{r} + \frac{(1 - \mathbf{r}' \mathbf{R}^{-1}\mathbf{r})^2}{\mathbf{1}' \mathbf{R}^{-1}\mathbf{1}}\right] \tag{B5}$$

as derived by Sacks et al., where

$$\mathbf{r} = \begin{pmatrix} \exp\left(-\sum_{l=1}^{\mathrm{d}} \Theta_l \, |\mathbf{x}_l - \mathbf{x}_{1l}|^{\mathrm{p}_l}\right) \\ \vdots \\ \vdots \\ \exp\left(-\sum_{l=1}^{\mathrm{d}} \Theta_l \, |x_l - \mathbf{x}_{\mathrm{n}l}|^{\mathrm{p}_l}\right) \end{pmatrix} = \begin{pmatrix} \exp(-\Theta_1 |\mathrm{x} - \mathrm{x}_1|^{\mathrm{p}_1} - \Theta_2 |\phi - \phi_1|^{\mathrm{p}_2}) \\ \vdots \\ \vdots \\ \exp(-\Theta_1 |\mathrm{x} - \mathrm{x}_\mathrm{n}|^{\mathrm{p}_1} - \Theta_2 |\phi - \phi_\mathrm{n}|^{\mathrm{p}_2}) \end{pmatrix} \tag{B6}$$

and

$$\hat{\sigma}^2 = \frac{(\mathbf{v} - \mathbf{1}\hat{\mu})' \mathbf{R}^{-1} (\mathbf{v} - \mathbf{1}\hat{\mu})}{\mathrm{n}} \tag{B7}$$

signifies the optimal variance of the predictor; optimal in the sense that it has been determined following maximisation of the concentrated log-likelihood function.

By combining the Kriging predictor and the mean error in a normal density function for the expectation of improving the prediction of an optimal point, it's possible to derive a function for the expected improvement. Both the mean error and the EI can be used to configure convergence criteria but they are most useful when exploited for the specification of update points during search and optimisation.

By way of example, the exact distribution of the Branin test function is shown in Fig. B1 and a Krig prediction of the function is shown in Fig. B2 for an optimised Latin Hypercube initial sample of eight points. With less than eight points, the predictor fails to capture the valleys in a recognisable form.

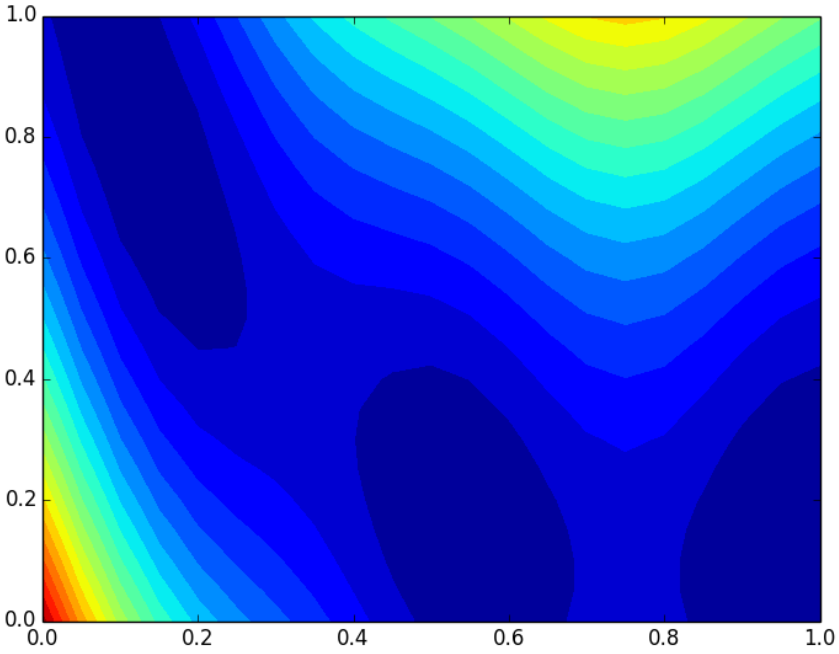


Fig. B1 Exact Branin function

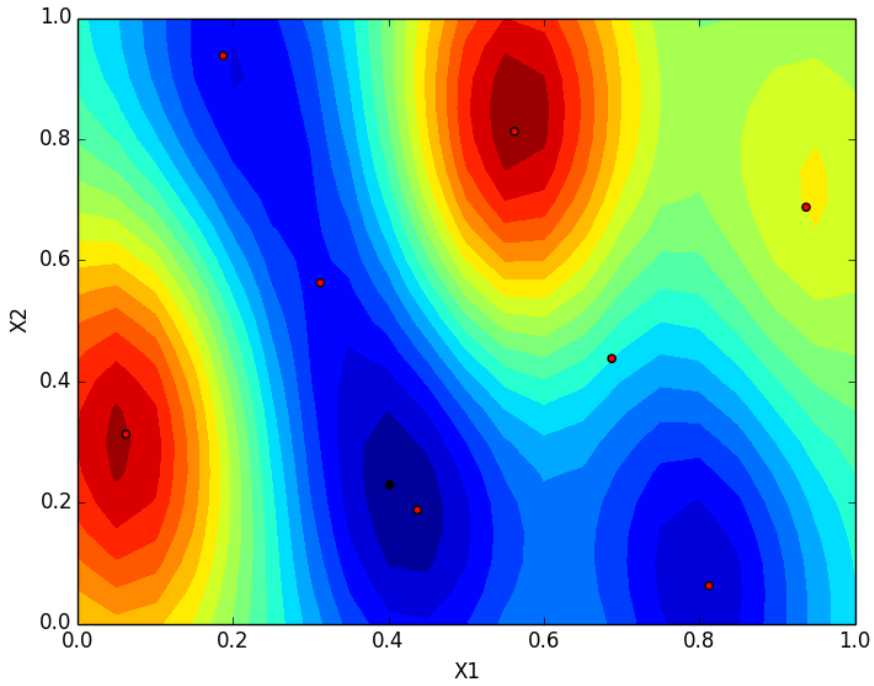


Fig. B2 Krig prediction of the Branin function using eight points (shown coloured red and the black point is the predicted minimum).

The MSE and EI functions for the prediction shown in Fig. B2 are depicted in Figs. B3 and B4, respectively. As expected, the MSE is zero at the predictions and increases in the spaces between them. Recalling that the EI combines exploration and exploitation (i.e. finding favourable locations), the “strongest” region of EI is located in the space between the predictions close to the minima. In both cases, update points could be selected at points that maximise the respective functions. When the initial sample size approaches twenty points, both MSE and EI become very small throughout the domain and are largest in the corners, something to be expected for an optimised Latin hypercube sample.

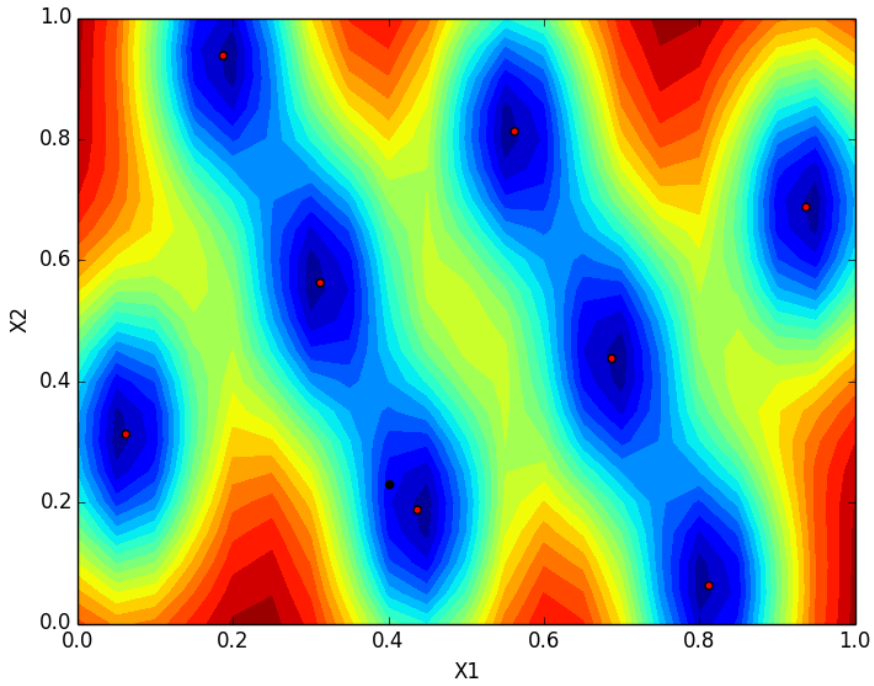


Fig. B3 Mean square error for eight point Krig predictor.

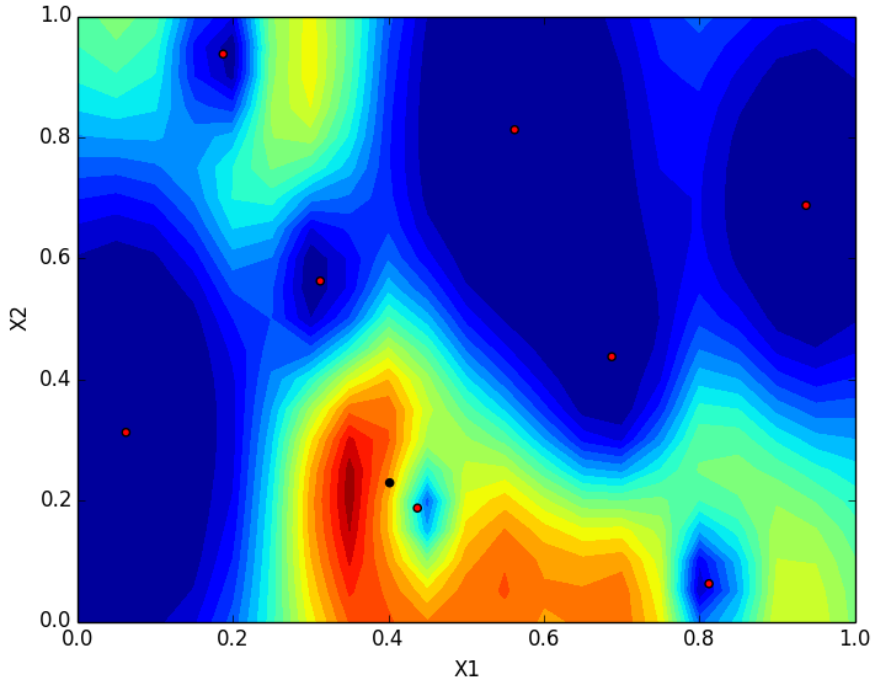


Fig. B4 Expected improvement for eight point Krig predictor.

In Grogan et al., convergence may have been compromised by a mesh induced noisey objective function. There are a number of ways in which noise can be generated in

objective function data and meshing issues are often responsible. When this is the case, it is possible to introduce regression into the Kriging model by adding a regression constant to the leading diagonal of the correlation matrix as described in Forrester et al. Care has to be taken when performing updates but this can be addressed as well (Forrester et al.).

Optimisation software resources

Within this review, the most commonly used software for optimisation appears to be the MATLAB DACE toolkit used, for example, by Clune et al., Gundert et al. and Li et al. (2013). Others (e.g. Li et al. 2009) have used the response surface models in ANSYS (for which further information is available online[1]). The surrogate management framework (Booker et al.) has been used by Gundert et al. and Bozsak et al. Grogan et al. used the open-source DAKOTA optimization toolkit (Sandia National Laboratories, USA). Another popular open source toolkit is pyOpt[2]. In-house toolkits were used by Pant et al. (2011 & 2012). Commercially available dedicated optimisation software includes modeFrontier[3] that focusses on multi-objective and multi-disciplinary optimisation and Isight and the SIMULIA Execution Engine (formerly Fiper)[4] containing a wide range of DoE, approximation and optimisation methods.

Forrester, A. I. J., A. J. Keane, and N. W. Bressloff. Design and Analysis of "Noisy" Computer Experiments.,AIAA Journal, 44(10): 2331-2339, 2006.

Sacks, J., W. J. Welch, T. J. Mitchell and H. P. Wynn. Design and analysis of computer experiments. Stat. Sci. 4(4):409-423, 1989.

[1] http://www.ansys.com/Products/Workflow+Technology/ANSYS+Workbench+Platform/ANSYS+DesignXplorer
[2] http://www.pyopt.org
[3] http://www.esteco.com/modefrontier
[4] http://www.3ds.com/products-services/simulia/products/isight-simulia-execution-engine/

Supplementary material C

Future challenges and opportunities

In certain respects, the relatively small body of coronary artery stent optimisation could be viewed as opportunistic and/or backwards-facing since state of the art coronary stents were developed before the related findings had been published. Also, many of the conclusions have simply reinforced what was already known. For example, it is not unexpected to discover that various performance metrics are in competition: tissue stress and elastic recoil; flexibility and fatigue resistance. Nor is it surprising that strut width has been shown to have a dominant effect on stent performance. As a counter to this negative perspective, a number of interesting findings have been reported including those related to haemodynamic disturbance, fatigue resistance and drug kinetics and, most positively, the research to date has laid the foundations for a number of notable future opportunities.

In the survey of the modelling of stented coronary arteries, Morlacchi and Migliavacca concluded with an overview of new frontiers and arising clinical challenges. With respect to optimisation, this featured the suggestion that shape control could be used to improve the mechanical properties and degradation performance of the emerging family of biodegradable stents. Whilst this is certainly an interesting application, a more ambitious role for optimisation exists with respect to patient-specific stenting. Indeed, patient-specificity featured strongly in the Morlacchi and Migliavacca review without being specifically stated in an optimisation framework.

Patient-specific coronary artery stenting

Since 2008, a number of articles have presented patient-specific cases wherein computational models of real diseased vessels have been constructed from segmented

images and then used as the host vessel into which stent deployments have been simulated. A number are featured in Morlacchi and Migliavacca and other recent articles include Morlacchi et al. and Ragkousis et al. Having established this capability, it is now feasible to predict how new designs, existing designs and/or variants of existing designs might perform for a particular patient and disease. This suggests that computational modelling could be used in decision support, helping interventionalists select an appropriate device from those available in the catheter-laboratory. Indeed, the most suitable stent could be selected by using systematic optimisation to design an optimal device which is then compared to the available devices. Extending this notion further, it may be feasible in time to personalise and deploy bespoke stent systems that are manufactured, sterilised, coated and loaded onto catheters having been designed using the design, search and optimisation tools discussed here.

Whilst it is already technically feasible to do this, it is unlikely to be possible to satisfy all necessary regulatory requirements without (a) advances in modelling accuracy, including the representation of arterial tissue and disease, and (b) detailed verification and validation of the modelling strategies that might be used in this way. Also, without marked speed-up in the computational run-times for detailed simulations, the time it takes to generate results will present a significant barrier to clinical acceptance and usability of this technology.

Nonetheless, these issues present significant opportunities for computational engineers to work with clinicians to develop approaches to overcome them. A good starting point concerns clinically challenging cases that may have involved sub-optimal deployment outcomes and/or required remedial intervention (e.g. post-dilatation) to improve apposition and maximise MLA/MSA. Sufficient angiographic and intravascular imaging information will be needed to construct computational models of a patient’s diseased

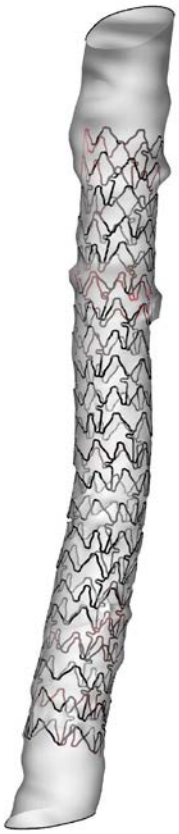
artery. Then, using a model of the stent actually deployed during PCI, a simulation will be performed and validated against the original clinical procedure. Using this simulation as a baseline, it will be possible to undertake optimisation studies to predict what could have been a more optimal outcome. Applied to a cohort of real patient cases, a virtual clinical study could be conducted, potentially leading to opportunities for novel stent characterisations, each one being better suited to certain sub-sets of patient cases.

With a parallel perspective, Conway et al. presented a cogent argument for the development of a computational test-bed for the assessment of coronary stent implantation mechanics and how it could be used to modify and enhance the associated regulatory standards. For example, it was recommended to assess stent performance for a range of stenosis “to see if there is an optimum design for a given stenosis level.”

Delivery system optimisation

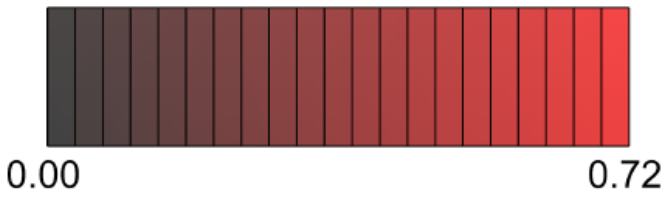
Since modern stents can be efficaciously and safely over-expanded, it may be more appropriate to design and select an optimal delivery balloon as an alternative to optimising a particular stent. Although compliance charts provide target expansion diameters for a range of pressures, based on a nominal target pressure, which can be used to guide procedural outcome, better PCI performance may be achievable for a particular patient by optimising the nominal balloon diameter and inflation pressure, for a given stent. Such a possibility emerged from the work by Ragkousis et al. as a means for minimising stent malapposition. Figs. C1 and C2 depict the final predicted states of a stent model (based on the Xience platform (Abbott Lab., IL, USA)) deployed in a patient-specific case using different delivery systems. The nominal diameters and inflation pressures were *3.383mm* and *8.42bar* for the baseline system depicted in Figs. C1A and C2A, calibrated for a target diameter of *3.50mm* using the AbbottVascular Instructions for Use document.

A)



B)

Figure C1. Stent malapposition (mm) in a patient-specific coronary artery following balloon expandable stent deployment. Nominal diameters and pressures, respectively: A) 3.38mm and 8.42bar; B) 3.87mm and 12.91bar.



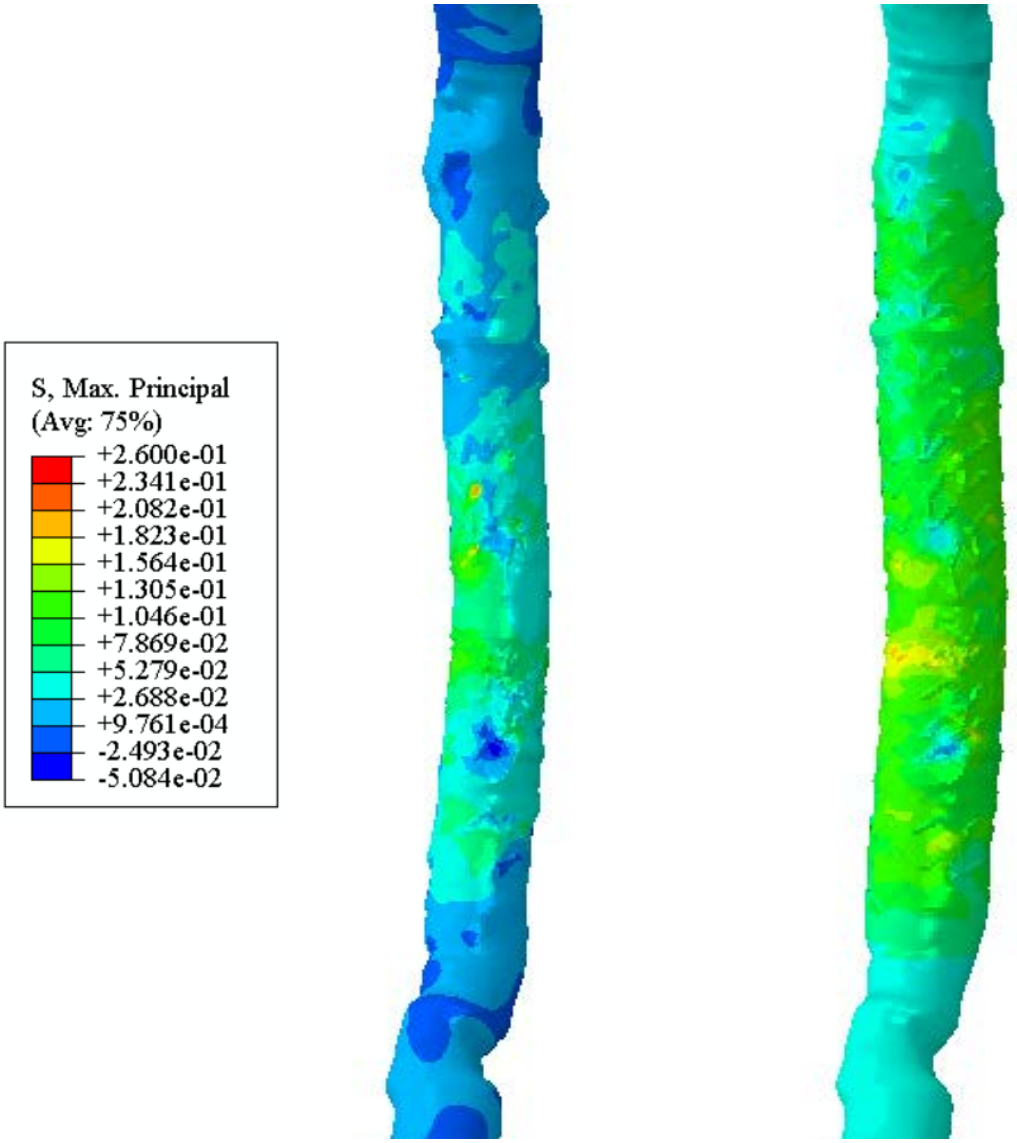


Figure C2. Tissue stress (MPa) in a patient-specific coronary artery following balloon expandable stent deployment. Nominal diameters and pressures, respectively:

A) 3.38mm and 8.42bar; B) 3.87mm and 12.91bar.

For the system shown in Figs. C1B and C2B, the diameter and pressure were *3.870mm* and *12.91bar*, respectively. The larger balloon, inflated at a higher pressure reduced stent malapposition by over 50% as measured using an area-averaged stent malapposition (AASM) index given by

$$AASM = \frac{\sum_{i=1}^{n_s} SM_i \delta A_i}{\sum_{i=1}^{n_s} \delta A_i} \qquad \text{(C1)}$$

where n_s denotes the total number of triangulated elements, SM_i is the malapposition in the *i*th element given by the Euclidean distance between the centre point of the *i*th element and its projection to the lumen surface and δA_i signifies the area of the *i*th element.

However, at the higher pressure, the stress in the tissue increases as shown in Figs. C2A and C2B. Quantitatively, the volume average stress, as defined in Eq. A1, more than doubles. From this comparison, the question emerges as to the optimum combination of un-pressurised balloon diameter and inflation pressure, as determined from the *AASM* and *VAS*, for this model of a diseased coronary artery. A multi-objective optimisation study could be performed in which an optimal combination of un-pressurised balloon diameter and inflation pressure is sought in the expected trade-off between these two metrics. The clinical implication of this approach is that a wider range of delivery system balloon catheters could be needed in the catheter-laboratory.

Surrogate modelling

Although Kriging has become the dominant choice for response surface modelling, it has largely been used with a lack of demonstrable insight into how the technique should be applied most efficiently. In particular, future optimisation studies involving expensive simulations need to employ best practice with respect to initial sample size, update strategies, hyper-parameter tuning and validation. Researchers need to better understand how to efficiently search for design improvement such that optimal designs are found with minimal effort.

Further interest could also develop in novel uses of Kriging in the development of methods to speed-up the design process. Kolandaivelu et al. used Kriging to train a machine learning process that could predict high fidelity mesh solutions from coarse

solutions when applied to the simulation of drug delivery to a coronary artery wall from both a stent and a drug eluting balloon. Drawing on evidence from other disciplines, there are also opportunities in the areas of uncertainty and robust design.

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