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Multi-objective optimisation of stent dilation strategy in a patient-specific coronary artery via computational and surrogate modeling

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Abstract

Although contemporary stents have been shown to improve short and long term clinical outcomes, the optimum dilation protocol is still uncertain in challenging cases characterised by long, highly calcified and tortuous anatomy. Recent clinical studies have revealed that in these cases, sub-optimal delivery can result in stent thrombosis (ST) and/or neointimal thickening as a result of stent malapposition (SM) and/or severe vessel trauma. One of the major contributors to vessel trauma is the damage caused by balloon dilation during stent deployment. In the present work, a Kriging based response surface modelling approach has been implemented to search for optimum stent deployment strategies in a clinically challenging, patient specific diseased coronary artery. In particular, the aims of this study were: i) to understand the impact of the balloon pressure and unpressurised diameter on stent malapposition, drug distribution and wall stresses via computer simulations and ii) obtain potentially optimal dilation protocols to simultaneously minimise stent malapposition and tissue wall stresses and maximise drug diffusion in the tissue. The results indicate that SM is inversely proportional to tissue stresses and drug deliverability. After analytical multi-objective optimisation, a set of "non-dominated" dilation scenarios was proposed as a post-optimisation methodology for protocol selection. Using this method, it has been shown that, for a given patient specific model, optimal stent expansion can be predicted. Such a framework could potentially be used by interventional cardiologists to minimise stent malapposition and tissue stresses whilst maximising drug deliverability in any patient-specific case.

1. Introduction

Clinical studies have revealed that contemporary devices, especially DES, demonstrate better short and long term outcomes than bare metal stents (BMS) (Stefanini and Holmes, 2013) and the second and third generation DES are critically superior to first generation DES. However, clinical complications have been reported which are associated with the recent advances in stent design, the implantation protocol and the complexity of the treated vessel (Cook et al., 2007; Hanratty and Walsh, 2011; Hong et al., 2006; van der Hoeven et al., 2008; Williams et al., 2012). One of the adverse outcomes in such anatomies is stent malapposition (SM) in which the stent is insufficiently expanded resulting in further unwanted events such as delayed neointimal healing, incomplete endothelialisation and higher levels of both neointimal proliferation and thrombus deposition, which give rise to clinical sequence in the form of restenosis and ST, respectively (Cook et al., 2007; Ozaki et al., 2010).

SM is largely dependent on multiple factors including the "reference diameter"[1] and the balloon inflation pressure (Cook et al., 2007; van der Hoeven et al., 2008). Depending on the vessel length and its anatomy, reference diameter is normally calculated in the distal end of the target lesion. This often results in malapposed struts in the proximal end of the stented segment particularly in a longer lesion, which has a diameter discrepancy between the proximal and distal end. When SM is detected, a non-compliant balloon is inflated in the malapposed region to reshape the stent and increase the stent area. However, such post-stenting procedures may trigger further clinical complications including vessel wall dissection or stent fracture (Hanratty and Walsh, 2011). Therefore, it is preferable to limit stenting to a single step approach resulting in i)

[1] Reference diameter is defined as the diameter of a healthy arterial cross section along the length of the intervened segment. Interventional cardiologists size the stent which is to be implanted according to the non-diseased diameter in the distal part of the segment.

maximum stent strut apposition, ii) minimum vessel stress and iii) maximum drug diffusion to the vessel walls.

In this study, the optimal dilation strategy in a patient-specific right coronary artery (RCA) has been investigated by finite element analysis (FEA) and surrogate modelling. Firstly, twenty different dilation protocols were parameterised with respect to the balloon unpressurised diameter and the balloon pressure. For each dilation protocol FEA simulations were performed for the deployment of a representative Xience stent model (Abbott Laboratories, IL, USA) into the reconstructed RCA. Performance was measured by three figures of merit (objective functions) representing i) tissue stresses, ii) stent malapposition and iii) drug delivery. Surrogate models were constructed for each objective function to describe the functional relationship between the input parameters and the performance. Then, based on a dedicated population based algorithm, non-dominated designs (optimum dilation scenarios) were obtained. Three update points were taken along the Pareto front and further computer simulations were carried out to improve the surrogates. This process was repeated until a stopping criterion was met.

2. Materials and methods

2.1. Geometry & mesh discretisation

2.1.1. Artery, plaque, dilation catheter, stent platform

Detailed information on the artery reconstruction process, the stent and balloon models, material properties, mesh discretisation and the stability of the numerical simulations can be found in previous work (Ragkousis et al., 2015; Ragkousis et al., 2014).

2.1.2. Dilation strategy parameterisation

The balloon profile and the inflation pressure were taken as the design variables of this optimisation problem. All the balloons were six-folded. However, depending on the parameterised balloon-profile length (unpressurised diameter), the folding configuration was

varied to fit in the semi-crimped stent. The design space was defined by: i) the initial diameter sampled around ± 20% of the baseline model and ii) the inflation pressure varying between 0.6-1.5 MPa, a range widely used in stenting practice.

2.2. Simulations

2.2.1. Stent expansion

The expansion simulations were carried out in the commercially available FEA solver, Abaqus/Explicit v.6-12 (Simulia Corporation, USA). The events were simulated as quasi-static, therefore, the time period of the simulations were defined by running frequency analysis in ABAQUS/Standard to extract the first fundamental frequency of the stent structure (Ragkousis et al., 2014). For the baseline model, the parameters were chosen according to the reference diameter measured in the distal part of the reconstructed segment. Then, a virtual balloon was generated and calibrated according to a compliance chart given by the manufacturer (De Beule et al., 2008; Ragkousis et al., 2015).

2.2.2. Drug release

After stent deployment, the deformed artery and stent geometry was used to simulate drug release in the walls of the vessel. A heat transfer solution scheme was used as an analogue of the drug delivery process similarly to the work presented by Hose et al. (2004). The release of the drug was simulated as a steady state event by using the forced heat convection analysis capability of ABAQUS/Standard. The boundary conditions for the transport simulation were defined as in other studies (Feenstra and Taylor, 2009; Hose et al., 2004; Pant et al., 2012; Zunino, 2004).

2.3. Objective functions

Three objective functions were considered in this study. Two objectives were extracted after the stent expansion and one after the drug release simulation (see Appendix A).

2.3.1. Volume average stress (VAS)

The VAS metric represents the induced mechanical environment after the stent expansion. It is an index indicating the average stress change within a fixed volume (intima-media wall). VAS has been presented by Holzapfel et al. (2005b) and successfully implemented in recent studies (Pant et al., 2012; Pant et al., 2011; Ragkousis et al., 2015).

2.3.2. Area average stent malapposition (AASM)

Ragkousis et al. (2015) proposed AASM to calculate the average stent malapposition after stent expansion in reconstructed arterial segments. This index expresses the area of malapposed struts within the fixed outer area of the stent surface.

2.3.3. Volume average drug (VAD)

Similarly to the VAS index, a volume average index for drug release was proposed by Pant et al. (2012) to measure the amount of drug transported into the tissue. VAD expresses the average drug diffusion within a fixed volume (intima-media wall).

2.4. Optimization problem & solution methodology

The multi-objective optimisation problem considered in this study was formulated as:

$Minimise\ VAS(d,p)$	(1.1)
$Minimise\ AASM(d,p)$	(1.2)
$Minimise\ -VAD(d,p)$	(1.3)

such that

$2.672 \leq d \leq 4.008$	(1.4)
$0.6 \leq p \leq 1.5$	(1.5)

where $d\ and\ p$ are the diameter and the pressure parameters, respectively. Note that VAD index should be maximised. However, the negative sign was included so that lower values of -VAD indicate better performance. Therefore, the aim was to minimise –VAD.

In Fig. 1, a flow chart detailing the optimisation process followed in this study is depicted. The process commenced with an optimal distribution of the initial sampling points in the design space, followed by structural and drug simulations for each design configuration. Discrete values of the performance metrics were extracted to construct Kriging response surface models for each metric. The models were then searched by a population-based algorithm to obtain optimum solutions for surrogate model improvement. From the optimum set, three points were selected as infill points to the initial sampling plan or the previous optimisation step. The process stopped when the stopping criterion was met (see section 2.4.2).

2.4.1. Sampling plan

The initial two-dimensional design space consisted of twenty points optimally distributed as a function of balloon unpressurised diameter and balloon pressure. This sampling plan, or *Design of Experiment* (DoE), was constructed by an optimized *Latin-hypercube* (LHC) (Morris and Mitchell, 1995).

2.4.2. Surrogate modelling, NSGA-II & infill strategy

The pyKriging package (http://www.pykriging.com/) (Paulson and Ragkousis, 2015) was used to construct the surrogates and guide the multi-objective optimization study. A validation of the algorithms that were used in this study is presented in Supplementary material S1. A non-sorting genetic algorithm (NSGA-II) (Deb, 2001), as implemented in pyOpt (http://www.pyopt.org) (Perez et al., 2012) was used to extract the optimal Pareto Front after each optimisation phase.

Surrogate models

To model the response of each objective function to variations in balloon pressure and unpressurised diameter a Gaussian Process (GP) methodology, known as Kriging, was used. Appendix B contains the basic equations for Kriging model construction. For detailed derivation, consult the work by Jones (2001) and Forrester et al. (2008). Kriging models have been also

implemented successfully in previous studies on stent optimisation, such as in Pant et al. (2011) and Gundert et al. (2012). For a detailed overview in recent optimisation and surrogate modelling studies, consult the review paper by Bressloff et al., 2015, including reference to early studies such as the one by Timmins et al 2007.

Validation of surrogates

Once the surrogates were built, validation was performed using the *standardised cross validated residual* (Jones et al. 1998), expressed as

$\mathrm{SCVR_i} = \frac{\mathrm{y}(\mathrm{x}^{(\mathrm{i})}) - \hat{\mathrm{y}}_{-\mathrm{i}}(\mathrm{x}^{(\mathrm{i})})}{\sqrt{\mathrm{C}_{-\mathrm{i}}(\mathrm{x}^{(\mathrm{i})}, \mathrm{x}^{(\mathrm{i})})}},$	(2)

where y is the observed value at the *i-th* point (point that is left out), $\hat{\mathrm{y}}_{-\mathrm{i}}$ denotes the prediction of the *i-th* leave out point and $\mathrm{C}_{-\mathrm{i}}$ is the posterior variance of the prediction at the left out point. Validity of each model was tested against the target to have each point within plus or minus three standard errors (99.7% confidence). Further, a "*leave-one-out*" method was used to test for model reliability (Jones et al., 1998). Again, for each surrogate model, one point of the DoE was left out and a surrogate model with constant parameters constructed for the remaining sampling points. Then, a prediction was made at the point that was left out and compared to the actual value. This process was repeated for all the points that comprise the DoE and a correlation residual was calculated for each model.

NSGA-II

The superiority of Gaussian models is the fact that such surrogates contain the estimation of model uncertainty, expressed by the mean square error (MSE). This is very useful for the so-called "exploration" of the design space by adding infill points in regions where the uncertainty is the maximum. Additionally, a highly attractive tool in stochastic optimisation is the expected improvement (EI) (Jones et al., 1998), which indicates the magnitude of improvement towards

the optimum solution. Both the MSE and the EI are defined in Appendix B. Since the EI can be evaluated for each objective function, NSGA-II was used to search the Pareto Front for maximisation of the multi-objective EI.

Infill strategy and convergence criterion

In each optimisation phase, two steps were performed to select update points. In the first step, three points were selected with two of the points positioned at the ends and a third point located in the middle of the Pareto Front. The second step comprised the mapping of these points to the design space to check their shortest distance with respect to the initial/previous sampled points. Around each update point, a circle with radius equal to 1% of the variable range (0.01 here since the variables were normalised in the range $[0\text{-}1]^2$) was constructed and if there was no point already sampled in this circle, the selection was approved. Otherwise, the point was rejected and the next Pareto point was selected. The first step ensures exploitation while the second step contributes to the exploration (very essential in a mathematical optimisation routine). In this study, due to the high computational cost for each simulation (average point simulation duration was approximately 160 hours on a 32GB RAM node, split over 32 domains), a convergence criterion was set to avoid a large number of optimisation iterations. In particular, in each step, updated surrogates were constructed containing the infill points from the previous iteration and a second NSGA-II search (this time on the updated response surfaces of the prediction) were carried out. Then, an optimum point was calculated as the Pareto Front point with the minimum Euclidean distance from the ideal vector/"utopia" point. More specifically, the obtained Pareto Front was normalised with respect to the utopia (ideal vector) and the nadir (maximum objective function vector) point as

$\bar{f}_i(x) = \frac{f_i(x) - z_i^*}{n_i^* - z_i^*}$	(3)

where $f_i(x)$, z_i^*, and n_i^*, the non-normalised objective function value, the minimum objective function value and the maximum objective function value of the i^{th} model, respectively (Miettinen, 1998). Then, the minimum Euclidean distance was expressed by the weighted $l_2 - \text{metric}$ proposed by Miettinen (1998) as

minimise $d(f, z) = \left(\sum_{i=1}^{k} w_i \lvert f_i(x) - z_i^* \rvert^2\right)^{1/2}$	(4.1)
subject to $x \in S$,	(4.2)

with S being the entire search space and $\sum_{i=1}^{k} w_i = 1$. When the predicted optimum point (with $w_1, w_2, w_3 = 1/3$) was the same in two subsequent iterations, the optimisation process was terminated.

3. Results and discussion

3.1. Baseline and DoE point simulations and Kriging interpolation

The results for the baseline model are reported in the first row of Table 1. From the second to the last row of Table 1, the discrete objective function evaluations of the initial DoE are reported. Surrogate models were constructed for each objective function. The response surfaces along with the MSE and the EI of the surrogates are depicted in Fig. 2. The x-axis and the y-axis represent the normalised balloon diameter and pressure, respectively. It can be noted that the diameter parameter has a stronger effect than the pressure for all models. In the first column of Fig. 2, the model predictions indicate that stent malapposition is inversely proportional to tissue stress and drug diffusion (note that drug diffusion contours or +VAD, would have the opposite behaviour from -VAD). Consequently, VAS is competing against both AASM and -VAD. This can be explained by the fact that when SM decreases, more stent struts interact with the vessel walls and higher tissue stresses are imposed by the stent, especially when using higher balloon pressures. Moreover, since more struts interact with the wall, the drug diffusion is increased. In contrast, when malapposition increases, the drug diffusion is decreased (-VAD is increased) as a result of

the reduced wall-stent interaction. In the second column of Fig. 2, MSE error indicates that high uncertainty exists in the corners for all the surrogates. This is expected as, in this optimisation study; LHC was used to generate the initial DoE leaving the corners and the edges of the design space un-sampled. Finally, in the third column, the EI indicates where model improvement can be obtained via infilling the design space in regions where EI is maximum. In general, the EI tends to be large in regions where the predicted value is larger than the minimum actual value (extracted by the simulations) and/or there is a high level of uncertainty associated with the prediction.

3.2. Validation of the surrogates

On the left column of Fig. 3, the $SCVR_i$ values for all the Kriging models are reported. It can be observed that all points lie within the interval $[-3, +3]$ for all the surrogate models. The *leave-one-out* plots are depicted in the right column of Fig. 3. As can be observed, all the surrogate models predict close function values to their corresponding "actual" values (extracted by the computational analyses). This is evident by the fact that the *leave-one-out* plot has approximately linear behaviour with in all cases (R^2 was 0.97, 0.92 and 0.95 for VAS, AASM and VAD, respectively).

3.3. Infill point simulations, update Kriging construction and selection criteria

The nine infill point parameter values along with the objective function evaluations at each point are reported in Table 2. The corresponding updated surrogates in each optimisation iteration are depicted in Fig. 4. It can be noted that the maximum and minimum values of all the surrogates appear to be close to convergence from the second optimisation iteration. In Fig. 5, the EI of each model from the initial step (first row), to the last optimisation step (last row) are depicted. The implemented algorithm selects points on the Pareto Front where the EI is the maximum. Since two of the objectives (AASM and VAD) have relatively similar behaviour, the first update

is chosen based in an average of both maximum EI values. The second update is selected where the EI for VAS is the maximum and the third update is selected in the middle part of the Pareto front. As discussed in section 2.4.2, the optimisation process is stopped when the convergence criterion is met. In the last two optimisation steps the Pareto Front obtained by NSGA-II run using the prediction surfaces is not significantly changed. Consequently, the same optimum point is predicted.

3.4. Visualisation of the simulated sampling points

In Figs. 6 and 7, spatial SM and wall circumferential stress contours, respectively, are mapped to the deformed simulated models. It is evident that models with reduced SM result in higher tissue stresses (c.f. Tables 1 and 2), for instance DoE_08, DoE_11, DoE_12, DoE_16, DoE_18, UPD_12, and UPD_22. This is expected from the fact that luminal gain leads to higher stresses in the arterial wall. Especially in DoE_08, DoE_11, UPD_12 and UPD_22, the increased VAS index is as a result of stent over-expansion. Interestingly, while DoE_11 and DoE_12 have similar strut apposition results, the VAS index for the DoE_11 is 12.66% higher. Such stress differences between models may lead to biomechanical responses which in turn may result in different restenosis rates in the dilated segment. This has been shown in recent studies (Keller et al., 2014; Timmins et al., 2011) reporting localised biological response as a result of mechanical forces imposed by the stent system during deployment and, consequently, the radial compression of the arterial wall. On the other hand, models with low induced mechanical environment are as a result of suboptimal stent and wall interaction or stent under-expansion. This is well demonstrated in models DoE_02, DoE_09, UPD_11 and UPD_21 where, especially for the proximal parts, severe stent malapposition is observed which, in clinical practice, would likely necessitate post-operational manoeuvrings to restore the malapposed struts. These findings

suggest that a dilation protocol should be used that balances lumen gain and the imposed mechanical stress environment for a given specific case.

3.5. Post-optimisation point selection

Generally, once a final Pareto Front is obtained, the weighted $l_p - metric$ can be implemented to locate optimum points according to a user's preference. This post-optimisation technique, which is also known as "compromise programming", picks a solution which is minimally located from a given reference point (Deb, 2001). Then, according to the user's judgment and the given patient-specific case, corresponding weights to each objective function can be applied and, by minimising the weighted $l_2 - metric$, the optimum point can be located. In the current study, the reference point was the ideal vector (utopia point). The first point selected was the closest Pareto Front point to the ideal vector. To locate this point, equal weights were used in Eq. 4. In Fig. 8, the final Pareto Front obtained by a NSGA-II search of the prediction models is depicted. The Pareto Front is normalised according to the nadir and utopia point (c.f. Eq. 3). The minimum Euclidean distance or, alternatively, the weighted $l_2 - metric$ is the same in the last two iterations. Consequently, the same optimum point is predicted. In Fig. 8a, the sphere represents equal weighted $l_2 - metric$ (with w_1, w_2, w_3 = 1/3), and its radius is tangent to the Pareto Front point which, in turn, is the closest point to the utopia point. In Fig. 8b, the elliptical sphere represents a non-equal weighted $l_2 - metric$. By way of example, the weights that were applied to the minimisation problem were $w_1 = 0.15, w_2 = 0.8, w_3 = 0.05$. Its long axis is equal to the Euclidean distance between the ideal vector and the point for which the weighted $l_2 - metric$ is the minimum. Its short axes are equal to the minimum weighted $l_2 - metric$. Therefore, with this method, a Pareto Front point can be easily located in which an objective function is made to have higher importance than the others. In Fig. 8b, AASM has been assigned a greater weight to locate a dilation protocol for which stent malapposition is of greater importance.

3.6. Model limitations

The main limitations of this work are associated with the constitutive material models characterising i) the walls of the vessel and ii) the balloon models. The vessel walls were assumed to be hyper-elastic and isotropic, modelled by reduced polynomial strain energy functions (Gastaldi et al., 2010; Pant et al., 2011). In reality, the wall deformation is characterised by hyper-elastic anisotropic behavior and has been successfully modelled by more advanced constitute laws such as the model proposed by Holzapfel et al. (2005a). With respect to the balloon, inflation behavior was considered to be linear elastic and isotropic where, in reality, the balloon behaves as a non-linear cylindrically orthotropic membrane (Kiousis et al., 2009). However, the balloon models were calibrated according to actual compliance charts. Therefore, the virtual expansion behavior closely matches that which occurs in clinical practice, especially at nominal pressures. Due to the comparative nature of the current work along with the fact that there is no clinical record of the investigated performance indices, the implemented constitutive models can still provide valuable and reliable results.

4. Conclusion

The presented work investigated the optimisation of a dilation protocol in a patient-specific RCA using balloon pressure and unpressurised balloon diameter as variables. In particular, the mechanical performance of a modest number of protocol realisations was predicted for metrics that quantify tissue stress, stent strut malapposition and drug delivery. Due to the expense of FEA simulations for each realisation, a Kriging surrogate modelling approach was employed using updates selected from the multi-objective Pareto front derived from the expected improvement of each objective function. Then, a post-optimisation method was used to demonstrate how, for a given patient specific case, optimum interventional protocols can be derived, balancing the competing objectives of tissue stress and strut malapposition. The

proposed approach thus provides a tool for dilation system selection (e.g. alternative size balloons and compliance charts could be supplied for a given stent) and design optimization of lesion-specific dilation systems, a process that will become realizable in non-urgent cases with increases in computer power.

Conflict of interest statement

Prof. Curzen has received unrestricted research funding from Medtronic, Haemonetics, St Jude Medical and Boston Scientific. He has received speaking and/or consultancy fees from Boston Scientific, St. Jude Medical, Medtronic, Abbott Vascular, Lilly/DS, Heartflow and Haemonetics. Prof. Bressloff and Mr. Ragkousis have no conflict of interest to declare.

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Figure 1. Flow chart on the description of the adopted optimisation methodology of this study

Figure 2. Surrogate models interpolated to the objective function evaluations after the initial DoE. From up to bottom, surrogates for VAS, AASM, and VAD are depicted. From left to right, Kriging interpolation surface of the prediction, MSE and EI for each model.

Figure 3. Surrogate model validation: On the left panel, SCVR values for all models (rows). On the right panel, *leave-one-out* plots for all models (rows).

Figure 4. GP interpolation surfaces for the three models (columns) after each optimisation

iteration (rows).

Figure 5. NSGA-II search in the EI of the GP models (columns) in the initial DoE and each optimisation iteration (rows). The Pareto non-dominated solutions along with the update points are also mapped onto the design space to ensure exploitation and exploration.

Figure 6. Spatial SM superimposed on the deformed stent models after balloon deflation: the spatial SM was calculated as the Euclidean distance between triangulated vertex points on the external surface of the deformed stent and their normal projections to the deformed lumen surface after the virtual stent expansion.

Figure 7. Maximum principal stress plots superimposed on the deformed lumen surface after balloon deflation

Figure 8. Final PF obtained by NSGA-II search in the updated surrogates (third iteration step): a) the optimum point is selected according to the minimum distance from utopia criterion, by applying equal w_i to the weighted $l_2 - metric$. b) optimum point selected by setting $w_1 = 0.15, w_2 = 0.8, w_3 = 0.05$.

Table 1. Baseline and DoE point parameters and objective function evaluations

Design	Diameter X_1 (0 - 1)	Pressure X_2 (0 - 1)	Diameter X_1 (mm)	Pressure X_2 (MPa)	VAS	AASM	VAD
Baseline	0.532	0.268	3.383	0.842	0.0199895	0.0531295	-0.0785628
DOE_01	0.625	0.525	3.507	1.0725	0.0264650	0.0400620	-0.0859427
DOE_02	0.474	0.025	3.306	0.622	0.0172700	0.0849213	-0.0672303
DOE_03	0.275	0.174	3.039	0.757	0.0153593	0.0885886	-0.0630614
DOE_04	0.174	0.775	2.905	1.297	0.0147054	0.0969262	-0.0610030
DOE_05	0.325	0.925	3.106	1.432	0.0196714	0.0632130	-0.0757653
DOE_06	0.925	0.125	3.907	0.712	0.0385187	0.0246679	-0.0927742
DOE_07	0.074	0.574	2.772	1.117	0.0115248	0.1412866	-0.0463872
DOE_08	0.974	0.724	3.974	1.252	0.0452974	0.0233686	-0.0926703
DOE_09	0.025	0.275	2.705	0.847	0.0088470	0.2035017	-0.0310349
DOE_10	0.125	0.074	2.838	0.667	0.0102840	0.1660097	-0.0377240
DOE_11	0.824	0.875	3.774	1.387	0.0398379	0.0265523	-0.0912732
DOE_12	0.724	0.675	3.640	1.207	0.0347925	0.0265455	-0.0914798
DOE_13	0.525	0.824	3.373	1.342	0.0274498	0.0394250	-0.0873315
DOE_14	0.574	0.225	3.440	0.802	0.0248069	0.0443346	-0.0833497
DOE_15	0.375	0.625	3.173	1.162	0.0197208	0.0646653	-0.0746734
DOE_16	0.775	0.325	3.707	0.892	0.0338754	0.0291174	-0.0906493
DOE_17	0.424	0.375	3.239	0.937	0.0174558	0.0744635	-0.0690409
DOE_18	0.875	0.474	3.841	1.027	0.0391969	0.0238637	-0.0924370
DOE_19	0.225	0.424	2.972	0.982	0.0138717	0.1115204	-0.0552826

DOE_20	0.675	0.974	3.573	1.477	0.0325380	0.0308955	-0.0907502

Table 2. Infill point parameters and objective function evaluations

Design	Diameter X_1 (0 - 1)	Pressure X_2 (0 - 1)	Diameter X_1 (mm)	Pressure X_2 (MPa)	VAS	AASM	VAD
UPD_01	0	0	2.672	0.6	0.0087020	0.2116110	-0.0291556
UPD_02	0.935	0.176	3.921	0.758	0.0380468	0.0243901	-0.0923420
UPD_03	0.715	0	3.627	0.6	0.0276499	0.0394574	-0.0861582
UPD_11	0.028	0	2.710	0.6	0.0089423	0.2058367	-0.0304440
UPD_12	0.897	0.767	3.870	1.291	0.0466347	0.0227087	-0.0929400
UPD_13	0.262	0.761	3.022	1.285	0.0172374	0.0837953	-0.0679390
UPD_21	0	0.367	2.672	0.931	0.0087822	0.2133572	-0.0294927
UPD_22	0.901	0.617	3.876	1.156	0.0425773	0.0226643	-0.0920894
UPD_23	0.651	0.145	3.541	0.731	0.0268951	0.0405922	-0.0851674