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Vascular Stent Design Optimisation Using Numerical Modelling Techniques

Houman Zahedmanesh, Paul A. Cahill and Caitríona Lally
Dublin City University
Ireland

1. Introduction

Since their first introduction in 1985 by Palmaz et al. (1985), balloon-mounted vascular stents have revolutionised the treatment of atherosclerosis, and in particular coronary artery disease. Vascular stents were developed to restore blood flow in stenosed arteries of the body, thereby preventing ischemia and myocardial infarction in peripheral and coronary arteries, respectively. A modification to these first stents by Schatz et al. (1987) led to the development of the first commercially successful stent, the Palmaz–Schatz stent. This redesign of the very first stent led the way in a new era of vascular medical device design, with a vast range of new stent designs, materials and adjunct drug therapies subsequently emerging at an ever increasing pace. Now over 25 years on, stents have undeniably become the gold standard in the non invasive treatment of atherosclerosis with 3 million implanted worldwide each year (van Beusekom & Serruys, 2010). To-date, vascular stents have been developed using an extensive range of high grade metals, from tantalum and titanium to the more common medical grade stainless steel, and more recently high yield strength materials such as cobalt chromium and platinum chromium alloys have also been used (Lally et al., 2006; Gopinath et al., 2007; Huibregtse et al., 2011). Self-expanding stents have been developed from shape memory alloys for peripheral anatomies to eliminate the need for expansion using angioplasty balloons (Gopinath et al., 2007). Biodegradable stents have been developed to allow for removal of the stent following successful revascularisation, whilst stents have also been developed to incorporate complementary drug, gene and radiation therapies and even pre-seeded with endothelial cells to lower thrombosis and encourage re-endothelialisation (Serruys et al., 2006; Sharif et al., 2004; Kay et al., 2001; Van der Giessen 1988; Dichek et al., 1989).While many of these new stent designs have offered improvements on their predecessors, no single design has successfully incorporated all of the characteristics of the ideal stent and one significant limitation in the long-term success of stents still remains, namely in-stent restenosis.

In-stent restenosis, which ultimately results in re-occlusion of a stented artery, is effectively an over-zealous wound healing response. It has been identified to comprise mainly of neointimal growth, composed principally of proliferating smooth muscle cells (SMC) and extracellular matrix (Lowe et al., 2002). Stent induced injury to the vessel wall is believed to be a determining factor in the onset and progression of in-stent restenosis (Hoffmann & G. S. Mintz, 2000) and consequently there is increasing evidence that stent design influences restenosis. While the biocompatibility of the metal or surface coating may affect long-term

healing in stented vessels, studies have shown that stent geometry designed to optimize expansion and lower recoil is a prerequisite for favourable clinical outcomes (McLean & Eigler 2002). Strut thickness also appears to be an important risk factor, but changing one parameter, such as strut thickness, requires altering other design characteristics, thus altering the overall stent design (McLean & Eigler 2002). Computational models of stent deployment, such as finite element (FE) models, are a very cost effective means of optimising stent designs and can be used to carry out parameterisation studies, whereby the influence of alterations in several stent parameters on the overall stent performance are systematically investigated (Bedoya et al., 2006). Materials changes can be analysed quickly and effectively using numerical modelling techniques such that even the influence that material degradation has on the scaffolding offered by a biodegradable stent can be assessed (Grogan et al., 2011).

FE models of stent expansion enable quantification of the stress-strain field in stents and the vessel wall following stent deployment and therefore provide insights into the various aspects of stent design that are critical in terms of arterial injury (Lally et al., 2005; Holzapfel et al., 2005a). More importantly, however, numerical modelling also provides a means to model the biological response to an implant using mechanobiological models whereby the mechanical environment may be used to dictate the growth and remodelling of vascular cells (Boyle et al., 2011; Zahedmanesh & Lally, 2011). With the emergence of Drug Eluting Stents (DES) and gene delivery stents, however, comes a need to include not only the growth and remodelling of the vessel wall but also the temporal and spatial distribution of such therapeutic agents and their influence on cell growth. Mechanobiological models offer the possibility of including such factors and therefore have the potential to enable future stent designs to be developed such that they combine the best features of conventional bare metal stent designs with the modifications required to facilitate biodegradation or optimum multi-agent drug or gene elution for a variety of vascular applications.

2. The mechanism of in-stent restenosis

Following stent deployment, a healing biological response initiates within the arterial wall which can ultimately lead to renarrowing of the vessel due to excessive migration and proliferation of medial vascular smooth muscle cells (VSMC) towards the vessel lumen. This biological response known as in-stent restenosis consists of four main phases, namely (i) thrombosis (ii) inflammation (iii) proliferation and (iv) remodelling (Edelman et al., 1998). Biomechanical factors which are dictated by the mechanical design of stents have been found to play a key role in all of the aforementioned phases in the development of in-stent restenosis.

During the expansion of the stent, high stresses induced by the stent cause injury to the artery which leads to thrombosis formation in the arterial wall and a cascade of inflammatory events. Close correlation has been observed between the degree of inflammation and neo-intimal thickness which suggests that inflammation caused by the arterial injury plays a central role in the formation of in-stent restenosis (Wieneke et al., 1999; Welt et al., 2002; Mitra et al., 2006). After stent deployment, vessel injury by the stent struts leads to the activation of thrombocytes and the formation of mural thrombus at the injury site. These thrombocytes produce mitogenic factors which contribute to dedifferentiation of medial VSMC, which are in a quiescent and contractile phenotype in the uninjured artery, to a synthetic phenotype. This change of phenotype is followed by a chemotactic migration and proliferation of dedifferentiated medial VSMC towards the lumen and lesion formation, see Figure 1.
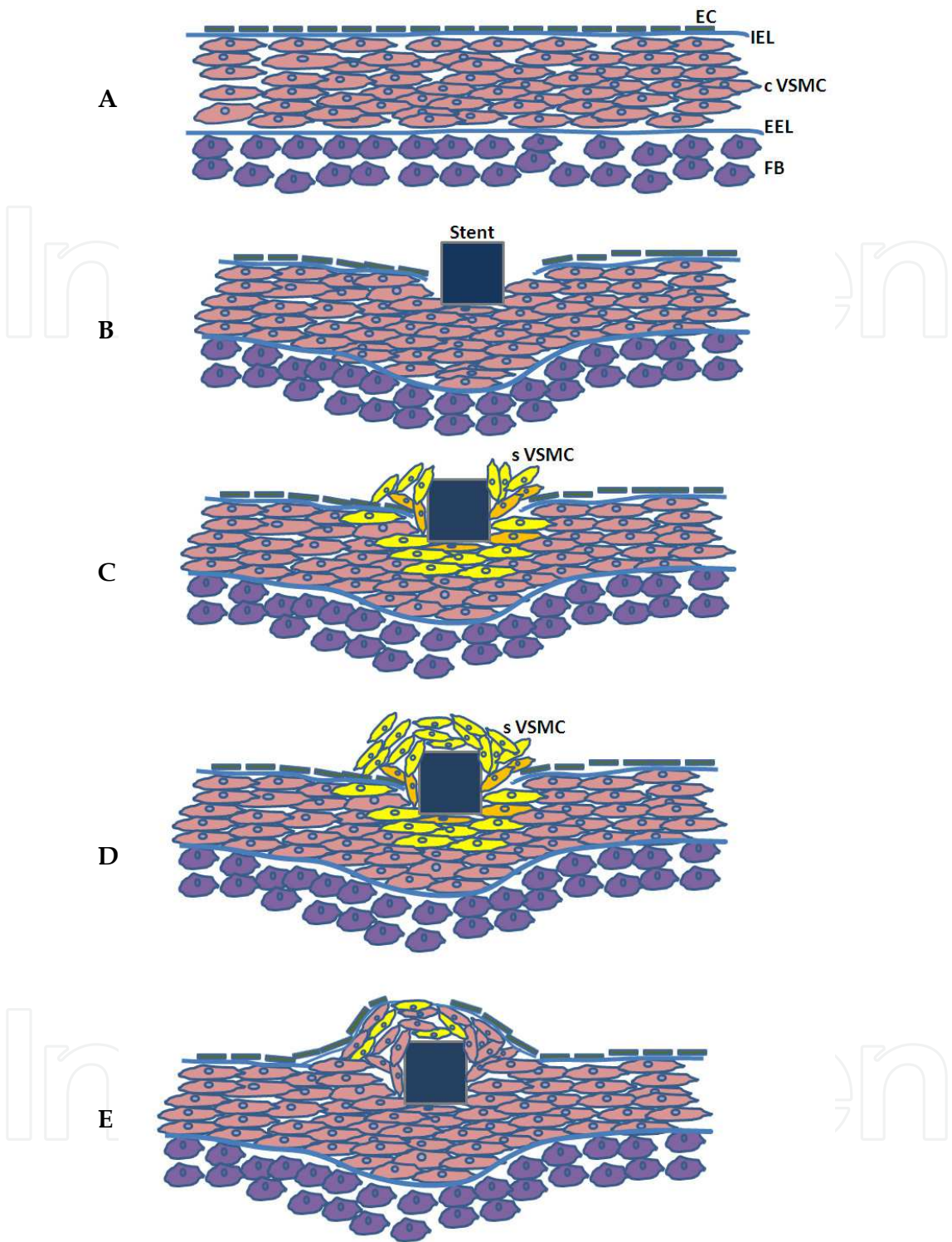
Fig. 1. Development of in-stent restenosis following stent deployment. (A) normal artery (B) de-endothelialisation and injury of the media (C) modulation of medial VSMC phenotype and their migration and proliferation towards the lumen (D) development of in-stent restenosis (E) re-endothelialisation and differentiation of VSMC back to the quiescent phenotype. (EC) endothelial cells, (IEL), internal elastic lamina, (s VSMC) synthetic vascular smooth muscle cell, (c VSMC) contractile vascular smooth muscle cell, (EEL), external elastic lamina.

The cytokines produced by the inflammatory cells not only serve as mitogens for VSMC but also upregulate synthesis of extracellular matrix by the synthetic VSMC (Wieneke et al., 1999; Babapulle and Eisenberg, 2002; Welt et al., 2002; Mitra et al., 2006).

In addition to the stresses induced within the arterial wall and the resulting mechanical injury, flow field perturbations due to stent implantation have also been found to influence the degree to which thrombocytes are recruited and their adhesion to the arterial wall. Specifically, it has been shown that a higher degree of thrombocyte aggregation occurs in locations where the flow field is directed toward the arterial wall rather than away from the wall (Duraiswamy et al., 2005). In addition, stagnant flow patterns adjacent to stent struts, particularly low shear stress, has been found to trigger the recruited inflammatory cells into their activated states (Kroll et al., 1996; Moazzam et al., 1997).

The altered solid mechanical environment following stent deployment also governs the inflammatory and remodelling response. The stent induced lesions are invaded by VSMC with mainly a synthetic phenotype. These cells produce extracellular matrix (ECM) components such as collagen, elastin and proteoglycans which constitute the neointimal tissue and the process usually takes up to 6 months, after which further luminal loss is minimal (Wieneke et al., 1999, Sousa et al., 2005). Intimal hyperplasia is found to be present at increasing thicknesses following injury and lacerations to the internal elastic lamina (IEL), the media, external elastic lamina (EEL) and adventitia (Wieneke et al., 1999; Lowe et al., 2002). An experimental study carried out in pigs identified the degree of injury caused by the implantation of a stent as an independent determinant for estimating the thickness of restenotic growth (Schwartz & Holmes 1994). Consistently, Gunn defined an Injury Score system that determined the degree of injury according to the angle of the IEL at the point of strut contact, the rupture of the IEL or, for extreme cases, rupture of EEL. Gunn applied this scoring system to categorize injury arising from the deployment of a stent in a porcine model (Gunn et al., 2002). The degree of vessel injury is therefore a major determining factor for in-stent restenosis and consequently a key design consideration for stents. In the context of stent optimisation using numerical modelling techniques, the design objective must therefore be to minimise the stress level in the arterial wall following stent deployment (Lally et al., 2005, Holzapfel et al., 2005a).

Several factors are involved in the modulation of VSMC phenotype from a quiescent to synthetic phenotype, including endothelial damage and denudation during stent deployment which is followed by adhesion of thrombocytes which express mitogenic chemokines and result in the chemotactic migration and proliferation of VSMC towards the lumen. Nevertheless, mitogens are not the only factor involved in the phenotypic modulation and activation of medial VSMC. For example, exogenously added fibroblast growth factor (FGF) increases VSMC proliferation in injured arteries, whereas it does not influence VSMC proliferation in uninjured arteries (Lindner & Reidy, 1991; Reidy & Lindner 1991). This observation suggests that other changes related to injury within the vessel may also be involved in the regulation of VSMC activation. In this context, the extracellular matrix (ECM) changes following vessel injury seem to be key regulators of VSMC phenotype and activation. Thyberg et al. (1997) showed that the medial VSMC in injured rat carotid arteries with a synthetic phenotype were enclosed by an incomplete basement membrane compared to normal arteries. These cells were found to migrate into the intima via holes in the internal elastic lamina and to form the neointimal tissue. Ultimately the

VSMC resumed a contractile phenotype as the neointima reached its final size with development of a complete basement membrane. Based on these observations Thyberg et al., (1997) suggested that laminin and other basement membrane components promote differentiation of VSMC towards a quiescent and contractile phenotype whereas their degradation leads into VSMC dedifferentiation and activation. Consistently, several studies have shown the role of collagen type IV, a major component of ECM representing 50% of all basement membrane proteins, in promoting restoration of VSMC to a contractile and quiescent phenotype (Hirose et al., 1999; Aguilera et al., 2003). In addition, exposing VSMC to mechanical loading has been shown to upregulate matrix metalloproteinase (MMP) synthesis by VSMC and mechanical injury upregulates MMP-2 production which is a major proteinase of the basement membrane (James et al.; 1993; Bendeck et al. 1994; Southgate et al., 1996; George et al., 1997) and so does mechanical stretch (Asanoma et al., 2002; Grote et al., 2003). By degrading ECM, MMPs are therefore key regulators of the onset and progression of in-stent restenosis, since they can regulate VSMC phenotype and consequently their behaviour i.e. migration and proliferation.

Finally, it should be noted that the origin of VSMC that accumulate in the neointima in vascular diseases such as in-stent restenosis remains controversial. These cells are a highly heterogeneous cell population with different characteristics and markers, and distinct phenotypes in physiological and pathological conditions. Although, early research on the pathophysiology of in stent-restenosis presents evidence indicating that these cells originate in the host artery (Edelman et al., 1998), several more recent studies have reported a role for bone marrow-derived progenitor cells in vascular maintenance and repair. Moreover, bone marrow-derived smooth muscle progenitor cells have been detected in human atherosclerotic tissue as well as in *in vivo* mouse models of vascular disease. However, it is not clear whether smooth muscle progenitor cells can be regarded as a 'friend' or 'foe' in neointima formation (van Oostrom er al., 2009). The relationship of circulating progenitor cells during stent deployment to the subsequent development of in-stent restenosis has also been evaluated. Bone-marrow- and neural-crest-derived cells, the most dendritic cells, have been found to be consistently present in in-stent restenosis, whilst α-smooth muscle actin positive cells constitute the largest intimal cell pool (Skowasch et al., 2003). Patients with restenosis also have higher numbers of subpopulations of endothelial progenitor cells incorporated into endothelial cells when compared with controls (Pelliccia et al., 2010). Cleary the role of intimal cells and progenitor cells in in-stent restenosis remains to be further elucidated and numerical modelling, and in particular mechanobiological modelling, may provide insights in this area.

3. Numerical modelling as a means to reduce stent induced injury

3.1 Stress/strain analyses of stenting

In addition to being cost effective, computational models often offer the only solution to address some of the important challenges influencing stent design, such as the estimation of stresses induced in the vessel wall and therefore the degree of vascular injury. Several different computational models of stent deployment have been developed in recent years. These models have improved our knowledge on the mechanics of stent-artery interaction (Migliavacca et al., 2002; Wang et al., 2006; Zahedmanesh et al., 2010) and the influence of several different variables of stent geometry such as the influence of stent strut thickness

(Timmins et al., 2007; Zahedmanesh & Lally 2009), plaque composition (Pericevic et al., 2009) and bending in stented peripheral arteries (Early et al., 2009). Balloon expandable stents and self expandable stents have been compared in terms of the level of stresses they induce within the arterial wall and hence the risk of arterial injury using finite element (FE) models (Migliavacca et al., 2004) whilst a number of studies have also been dedicated to investigating hemodynamic related factors in stent design and performance (Wentzel et al., 2000; Wentzel et al., 2001; LaDisa et al., 2006; Duraiswamy et al., 2007; Pant et al., 2010).

One important advantage of computational models of stent deployment over *in-vivo* studies is that they enable the influence of the mechanical parameters of interest to be studied in isolation. Due to the several complex and intertwined biological, chemical and mechanical factors involved *in-vivo*, it is often difficult to associate the outcome of an *in-vivo* trial with one specific mechanical factor. A good example of this is the influence of stent strut thickness on in-stent restenosis. In recent years, several clinical trials have identified stent strut thickness as an independent predictor of restenosis (Kastrati et al., 2001; Briguori et al., 2002; Pache et al., 2003). A clear conclusion from the many clinical studies on stent strut thickness is that stents with thinner struts have a lower restenosis rate, consequently, most of the current generation of stents are produced with thinner struts using high strength materials such as cobalt–chromium alloys (Morton et al., 2004). The ISAR-STEREO clinical trial focussed on the influence of stent strut thickness and compared the restenosis outcome for two stents with the same design but different strut thickness (Kastrati et al., 2001). Although the study highlights the importance of stent strut thickness, it does not clearly elucidate the role and significance of the mechanism by which stent strut thickness could lead to the higher restenosis rate.

From a mechanical perspective the effect of stent strut thickness can be twofold: (i) from a solid mechanical viewpoint strut thickness would influence the stresses induced in the artery during stent deployment and recoil, and (ii) from a hemodynamic viewpoint strut thickness could influence blood flow perturbations. *In-vitro* studies cannot address each of these factors in isolation whilst *in vivo* several biological factors are also involved, such as the higher metal surface exposed to blood flow in thicker strut stents to which platelets can adhere and produce mitogenic growth factors. In contrast, computational models enable each different parameter involved in such a complex process to be studied in isolation. For instance, Duraiswamy et al., (2007) studied the influence of stent strut thickness from a hemodynamics perspective and quantitatively showed that thicker stent struts lead to significantly larger recirculation zones and altered shear stress patterns in the vicinity of struts which can contribute to restenosis. In this context, to further elucidate the influence of stent strut thickness on the vessel wall stresses Zahedmanesh & Lally developed FE simulations of stent deployment procedures and showed that stents with thicker struts induce higher chronic stresses within the vessel wall and also pose a higher risk of injury in the vessel during expansion (Zahedmanesh & Lally 2009). Together, these results elucidate the role of the mechanical environment in the lower restenosis rates observed when using thin strut stents compared to thick strut stents as reported by such clinical trials as the ISAR-STEREO, (Kastrati et al., 2001).

Stent strut thickness is just one of the many factors involved in stent design and the use of finite element method (FEM) is not limited to this factor. FEM can be utilised to study a wide range of design parameters in order to reduce arterial injury. Several studies have

investigated the mechanical response of stents using FEM and have suggested different strategies for their simulation (Lee et al., 1992, Rogers et al., 1999, Auricchio et al., 2001, Prendergast et al., 2003, Holzapfel et al., 2005a, Lally et al., 2005, Migliavacca et al., 2002, 2005, 2007, Wang et al., 2006, Gijsen et al., 2008). Given the difficulties involved in construction of the model geometry and the complex contact problem involved in the interaction of a balloon, stent and artery, many simplified methods have been used to model the complex mechanics of stent deployment. Balloons used for stent deployment are initially in a folded configuration. As the balloon unfolds it appears highly compliant, however, as its unfolded shape is reached the balloon becomes highly noncompliant. This complex procedure of balloon unfolding is difficult and very computationally expensive to model. Four main strategies have been used in the literature for numerically modelling balloon expansion of stents which include, (i) direct application of a uniform pressure to the stent luminal surface (Dumoulin & Cochelin 2000; Migliavacca et al., 2005; De Beule et al., 2006; Early et al., 2008), (ii) a rigid cylinder expanded by application of radial displacement (Hall & Kasper, 2006; Takashima et al., 2007; Wu et al., 2007), (iii) stent deployment using a folded balloon model (De Beule et al., 2008; Gervaso et al., 2008; Mortier et al., 2010) and (iiii) pressurisation of simple elastic cylinders with hyperelastic material properties neglecting the balloon folds (Ju et al., 2008; Kiousis et al., 2009).

In a recent study using FE simulation Zahedmanesh et al. (2010) presented a method to create a folded balloon model and utilised the method to numerically model the accurate deployment of a stent in a realistic geometry of an atherosclerotic human coronary artery. Stent deployment is commonly modelled by applying an increasing pressure to the stent, thereby neglecting the balloon and reducing the computational cost and complicated contact between the balloon, stent and artery. This method was compared to the realistic balloon expansion simulation to fully elucidate the limitations of this more simplified procedure. The results illustrated that inclusion of a realistic balloon model is essential for accurate modelling of stent deformation and stent stresses. An alternative balloon simulation procedure was also presented however, which overcame many of the limitations of the applied pressure approach by using elements which restrained the stent as the desired diameter was achieved (Zahedmanesh et al., 2010). This study showed that direct application of pressure to the stent inner surface may be used as an optimal modelling strategy to estimate the stresses in the vessel wall using these restraining elements and hence offer a very efficient alternative approach to numerically modelling stent deployment within complex arterial geometries.

The aforementioned advances in computational modelling when applied to the analysis of the mechanical interaction between stents and the vessel wall provide a robust and efficient tool for stent design optimisation. The models can quantitatively assess the risk of vessel injury by different stents in the early design phase and hence minimise in-stent restenosis in the longer term.

3.2 Mechanobiological models and stenting

The global biological response of vessels to the biomechanical perturbation caused by stent implantation emerges at the tissue level as excessive luminal ingrowth. However, the tissue level response stems from the dynamic changes which occur in the micro-environment of cells deep at the cell level. Cellular behaviours such as differentiation, proliferation, migration, protein and chemokine synthesis and cell death are influenced by the changes in

the micro-environmental factors such as extracellular matrix, chemicals, and forces and combine to result in complex responses at the tissue level. This intrinsic multi-scale behaviour of biological systems necessitates a multi scale modelling approach. Therefore, multiscale approaches utilising discrete methods such as cellular automata (CA) (Masselot & Chopard 1998, Ilachinski 2001) and agent based models (ABM) (Wooldridge 2002; Walker et al., 2004) have recently received particular attention for modelling in-stent restenosis.

One prominent example is the multiscale modelling platform developed within the COAST (complex automata simulation technique) project (www.complex-automata.org) which is funded by the European Commision (Evans et al., 2008). The project takes a multiscale and discrete approach towards modelling in-stent restenosis where the growth response of VSMC within the arterial wall is modelled based on the value of wall shear stress (WSS) due to blood flow, the stress level experienced by VSMC within the arterial wall and the concentration of the anti-proliferative drugs diffused from drug eluting stents (Caiazzo et al., 2009). Their model has also been applied to investigate the influence of stent strut size and shape where their simulation results suggest that the growth of the restenotic lesion is strongly dependent on the stent strut cross-sectional profile consistent with the outcome of clinical and animal models (Tahir et al., 2011).

In addition to the approach adopted by the COAST project which is mainly based on discrete methods, a hybrid approach can also be adopted by combining continuum methods such as FEM and discrete methods. FEM is particularly advantageous given that it has proved to be a robust method for quantification of arterial stresses and has been successfully utilised for patient specific modelling of stent-artery interaction (Zahedmanesh et al., 2010, Gijsen et al., 2008). As an example, Boyle et al., (2010) used FE simulations of stent deployment to quantify damage within a stented artery and subsequently used a CA approach to simulate the biological response of the artery to this stent induced damage quantified by the FE model (Boyle et al., 2010, Boyle et al., 2011).

Although the differences between CA and ABM are marginal, the main difference is that a lattice needs to be defined for CA while ABM can be lattice free, meaning that cells can be at any location in the computational domain. This location is usually determined by solving either kinematic or dynamic equations of motion for each individual cell. Hence ABM can yield more realistic results given that no restriction is imposed on the location of the cells in comparison to CA where the cells can only move through certain predefined lattice points and results can therefore be highly dependent on the lattice structure and lattice point density. As a result, a hybrid model utilising ABM, as opposed to CA, and FEM can potentially provide greater simulation capabilities and produce more realistic results. Therefore, a novel hybrid model to simulate in-stent restenosis, using coupled ABM and FEM, will now be presented by the authors. This novel approach has recently been applied to model vascularisation in tissue engineered blood vessels (Zahedmanesh et al., 2011) and is adapted and applied here to model in-stent restenosis.

4. A multi-scale mechanobiological model of in-stent restenosis using coupled agent based models and the finite element method

4.1 Model background

As previously discussed, changes occurring within the arterial wall, particularly ECM changes and degradation of basement membrane around VSMC, play a key role in the

dedifferentiation and activation of medial VSMC. Here, a novel mechanistic model is presented which quantitatively captures the processes involved in the degradation and activation of VSMC following stent implantation. The model enables quantitative investigation of the role of stent induced stresses, ECM degradation by MMPs and the subsequent response of VSMC. It can therefore provide insight into the mechanisms involved in the development of in-stent restenosis and it can also be used as a robust and efficient tool to improve the mechanical behaviour of stents in the design cycle. A significant novelty of the presented model is the combination of the FEM with a lattice free ABM which holds significant advantages over the lattice based CA models.

4.2 Materials and methods

4.2.1 Model overview

A mechanobiological modelling framework was developed which comprises of two main coupled modules, (i) a module based on FEM that quantifies von Mises stress to determine the level of arterial damage due to stent deployment and (ii) a biological modelling module based on a lattice free ABM that simulates the key responses of VSMC growth, i.e. migration, proliferation, and ECM degradation and synthesis, in the arterial wall in response to the stent induced damage quantified using the FE analysis, see Figure 2.
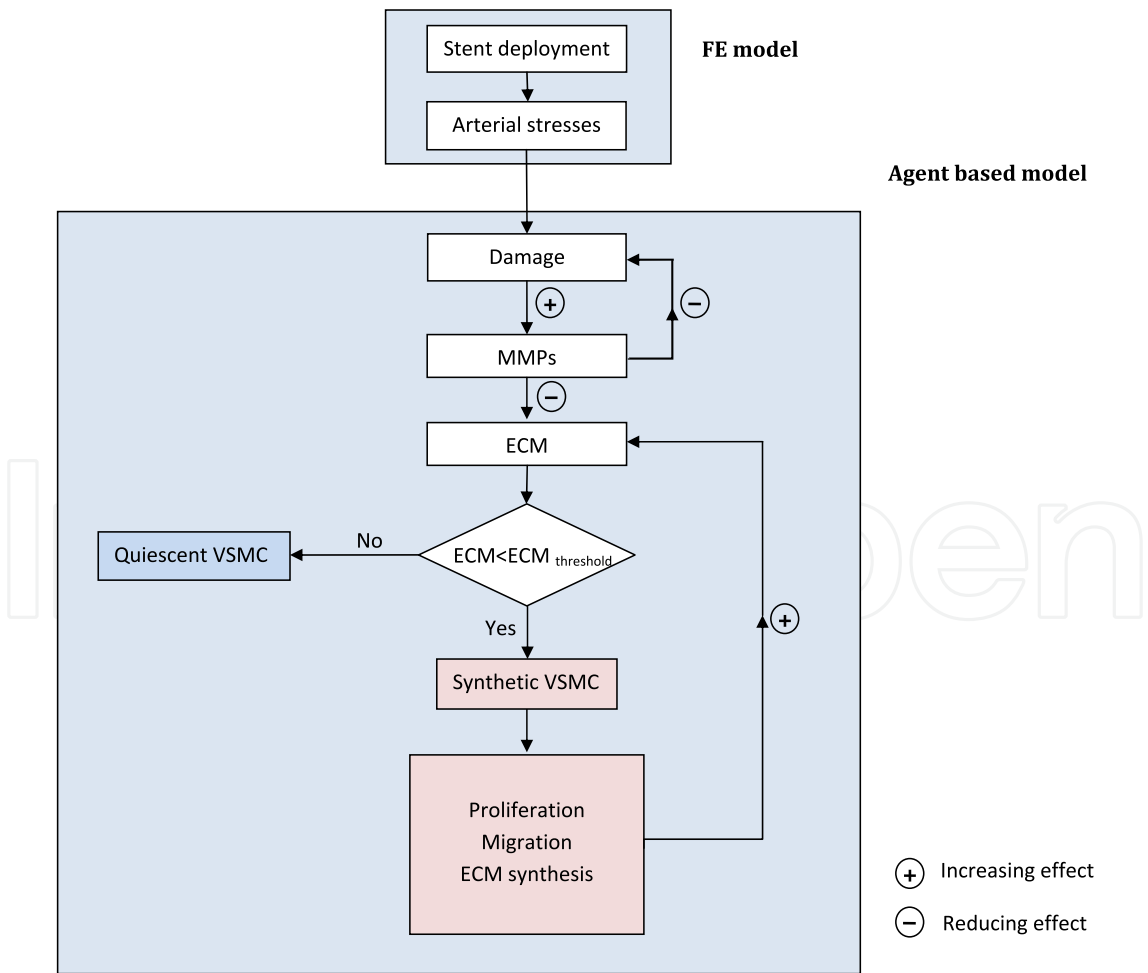

Fig. 2. Overall schematic of the mechanobiological model of in-stent restenosis

The simulation starts in the FE module where the value of the initial stent induced damage is quantified and is transferred to the ABM where the growth of VSMC is simulated. A custom-written routine was developed using python programming language to enable communication between the FE software Abaqus (Simulia, Providence, RI, USA) and the agent-based modelling framework BREVE (www.Spiderland.org). The ABM was programmed using the STEVE language specific to the BREVE agent-based modelling framework.

4.2.2 Finite element model

An axisymmetric hyperelastic FE model of an artery was developed and the influence of stent struts was modelled by application of a radial displacement of 1mm to the luminal surface of the artery where the stent strut contacts the artery, see Figure 3. A pressure of 120 mmHg was applied to the luminal surface to take the systolic arterial blood pressure into account while the two ends of the artery were longitudinally tethered. The model is composed of 3,040 equilateral rectangular axisymmetric elements (Abaqus type CAX4RH). The artery geometry was modelled as 8mm long with a thickness of 0.673mm and a luminal diameter of 4.18mm and was discretised by 190 elements longitudinally and 16 elements radially. This mesh density was chosen based on mesh sensitivity studies.
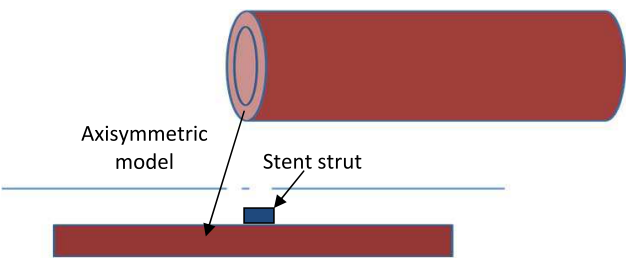

Fig. 3. Axisymmetric representation of the model

The following Ogden hyperelastic equation was used to model the stress-strain response of the artery (Ogden, 1972).

$$\overline{U} = \sum_{i=1}^{3}\frac{2\mu_i}{\alpha_i^2}(\lambda_1^{-\alpha_i} + \lambda_2^{-\alpha_i} + \lambda_3^{-\alpha_i} - 3) \qquad (1)$$

Where, $\overline{U}$ is the deviatoric strain energy density, λ_i denotes the deviatoric principle stretches and μ_i and α_i are the hyperelastic constants, see table 1.

Hyperelastic constants	Value
μ_1 (Pa)	-1,231,144.96
μ_2 (Pa)	785,118.59
μ_3 (Pa)	453,616.46
α_1	16.59
α_2	16.65
α_3	16.50

Table 1. Coefficients of the Ogden hyperelastic constitutive models (Zahedmanesh & Lally 2009, Zahedmanesh et al., 2011)

4.2.3 Damage/injury quantification

As a first approach, damage/injury level within the stented artery was quantified with a continuous linear range of 0 to 1. A value of 1 was assigned for the damage in the elements where von Mises stresses exceeded 150kPa. This is a simplified assumption which represents a very first approach to modelling damage accumulation within the artery. This value was chosen given that the intimal layer in human coronary arteries has been reported to have an ultimate tensile strength of 394±223 kPa in the circumferential direction whilst the human medial layer has an ultimate tensile strength of 446±194kPa (Holzapfel et al., 2005b). Therefore, 150kPa represents the lowest value of ultimate tensile strength of these tissues before failure, i.e. one standard deviation below the mean for intimal tissue, and it is therefore deemed a suitable stress level for maximal injury. The authors are currently developing a more sophisticated damage model which will provide a more accurate measure of damage accumulation by defining damage as a continuous function of stent induced stress rather than simply using a threshold stress value. It should be noted that the ABM-FE model presented here can incorporate any range of damage models, with damage accumulation calibrated against clinical or experimental data, such as that proposed by Boyle et al, 2011.

4.2.4 Agent based model

An agent based model of an artery was constructed with VSMC randomly distributed throughout the artery domain. Following the FE analysis the values of the arterial damage at each element of the FE model were exported to the ABM module where the response of VSMC to damage was modelled similar to the approach previously outlined in Zahedmanesh et al., (2011).

The damage induced in the vessel wall due to high stresses upregulates MMP synthesis by VSMC which consequently causes degradation of the ECM. Initially VSMC are in a quiescent and contractile phenotype, degradation of ECM modulates their differentiation toward a synthetic phenotype at the site of damage which ultimately triggers their migration and proliferation, i.e. cells are only allowed to migrate and proliferate when their ECM is degraded to lower than half of the value of ECM in the healthy arteries which for collagen is a value of approximately 3.1×10^{-4} µg/cell (Hahn et al., 2007). In the meantime ECM cleavage and degradation due to MMP upregulation reduces the value of the initially accumulated damage, and hence functions as a negative feedback mechanism leading to recession of the neointimal growth rate. In addition, the proliferating VSMC synthesise ECM and gradually switch back to the contractile phenotype once their value of ECM reaches normal values, see Figure 1. A summary of the relevant parameters used in the ABM and their values is provided in Table 2.

Parameter	Value	Reference
MMP synthesis by VSMC	$MMP(\frac{(pg/cell)}{6hour}) = \frac{0.0006}{1 + 3462 \times e^{(-16.3 \times dmg)}}$ where dmg is damage value with a range of 0 to 1.	(Kim et al., 2009; Okuno et al., 2002)
ECM degradation rate	50 pg collagen/pg MMP/hour	(Welgus et al., 1980, 1981)

Parameter	Value	Reference
Damage removal by MMPs	0.1/ pg MMP/hour	Set to ensure damage will be fully remove in 15 days
MMP Removal	0.0001pg MMP/element/hour	(Mass balance constraint)
ECM synthesis by VSMC	0.00899 pg collagen/hour/cell	(Kim et al. 1988; Schlumberger et al., 1991; Absood et al., 2004)
Doubling time of synthetic VSMC	35 hours	(Zahedmanesh et al., 2011)
Maximum VSMC migration Speed:	0.001 mm/hr	(Zahedmanesh et al., 2011)

Table 2. Parameters used in the ABM module and their values.

4.3 Results

The mechanobiological model captured the characteristic S-shaped neointimal growth response of arteries to stent deployment previously reported in *in-vivo* studies (Schwartz et al., 1996), see Figure 4. The growth curve comprised a dramatic increase in VSMC number shortly after stent deployment and a plateau region following stabilisation of the healing response. The value of arterial von Mises stresses due to stent deployment was quantified showing high stress concentrations where the stent strut contacted the artery, see Figure 5.
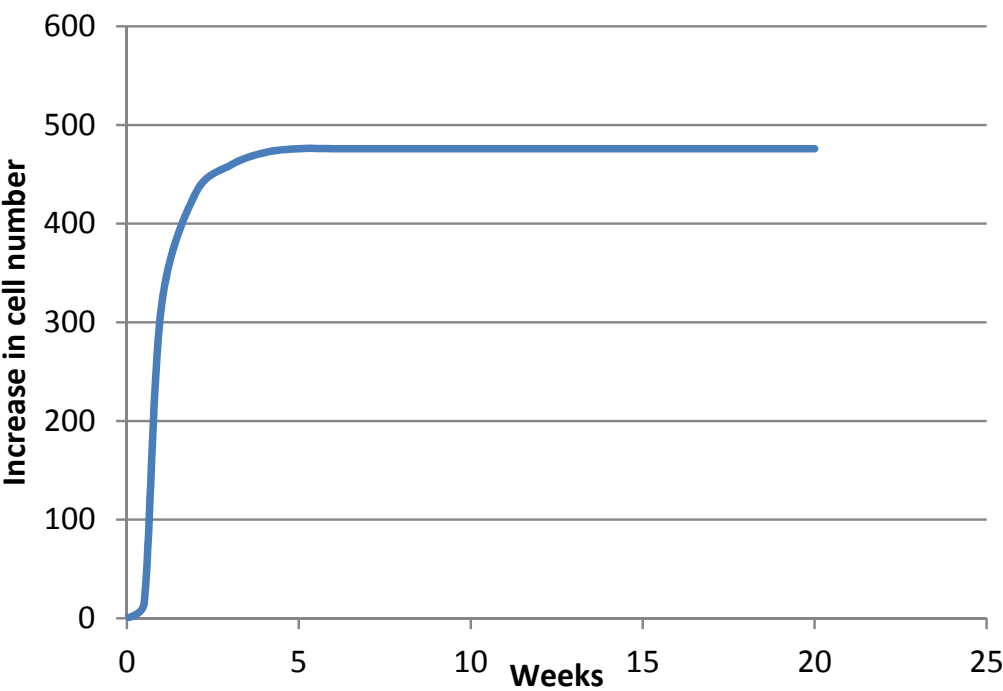

Fig. 4. Increase in the VSMC count in the model due to in-stent restenosis.

A significant area in the vicinity of stent strut showed stresses higher than the threshold stress value for damage and hence a damage value of 1 was automatically assigned to the associated elements. This damage was fully removed following two weeks due to upregulation of MMPs, see Figure 6.
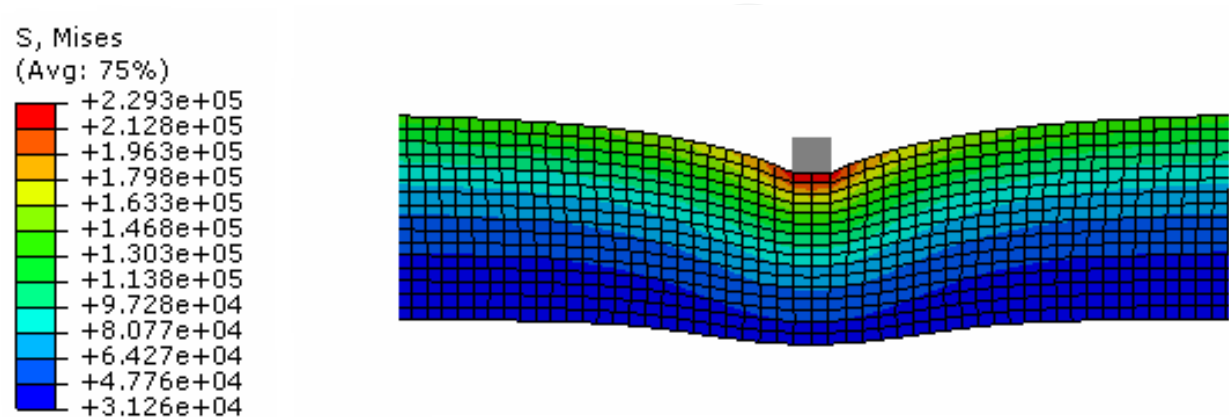

Fig. 5. Distribution of von Mises stresses (Pa) in the arterial wall following stent deployment.
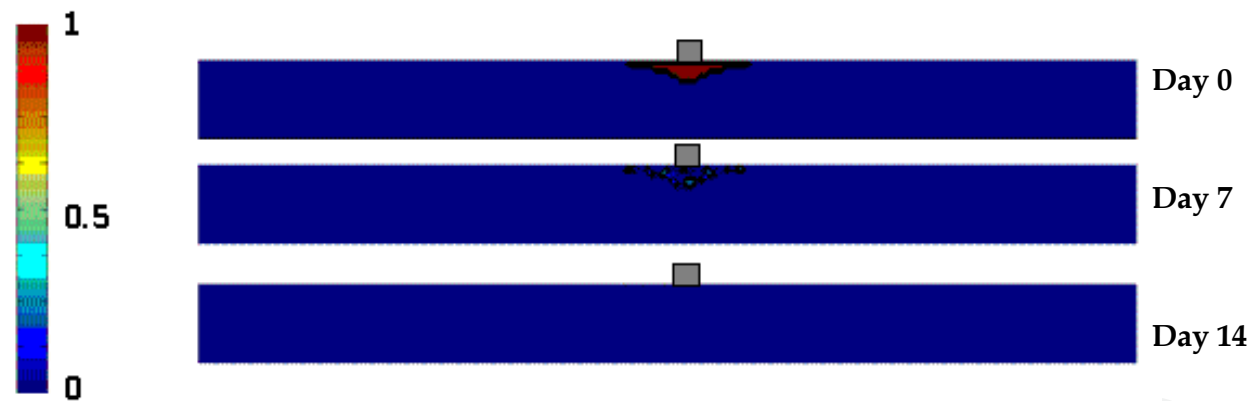

Fig. 6. Damage accumulation in the artery following stent deployment and its reduction due to the healing response.

Following stent deployment, neointimal growth started due to degradation of ECM by MMPs which were upregulated due to the damage accumulation. Neointimal growth reached its maximum following 35 days when the stenosis size reached steady state, see Figures 4 & 7.

The alteration in the ECM distribution and value with time post stent deployment is shown in Figure 7 where ECM is initially degraded due to the damage accumulation and upregulation of MMPs. With the removal of damage and recession of the inflammation, new ECM is synthesised by VSMC, reaching the normal values of ECM in the healthy arteries following 100 days.
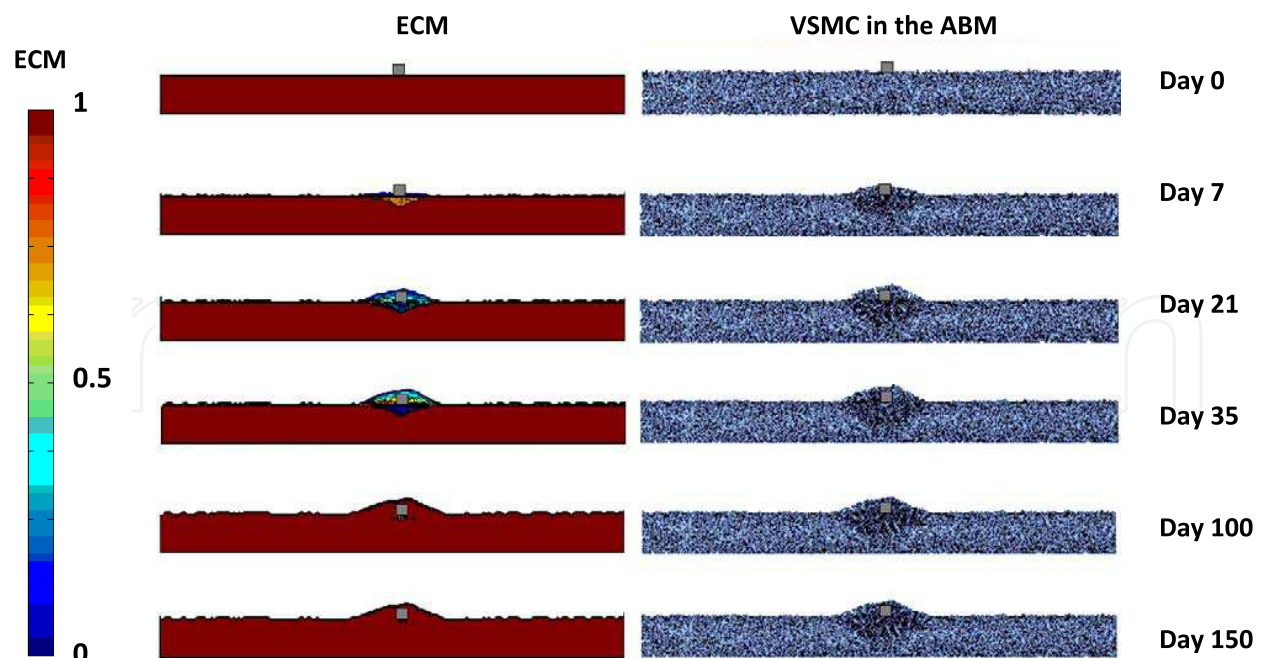
Fig. 7. The development of neointimal tissue with time, (left) alterations of ECM due to degradation and also synthesis by activated VSMC, (right) VSMC growth and distribution.

4.4 Conclusion

Although in a relatively early stage of development, the mechanobiological model presented here successfully captures the key characteristics of the arterial response to stent deployment, specifically the neointimal growth. *In-vivo* studies on the development of intimal hyperplasia in patients due to vascular injury report an exponential increase in the number of neointimal VSMC with a peak in the proliferation rate occurring about two weeks post injury, followed by a reduction in the cell proliferation rate (Schwartz et al., 1996). This characteristic growth response is captured by the mechanobiological model where the cells initially increase at exponential rate followed by a cessation in the cell proliferation and lesion size, see Figure 4 & 7. Nevertheless, this response also depends on the intensity of the mechanical damage and hence it is necessary to further study how different stent designs and deployment parameters influence the development of in-stent restenosis. In this context, when the extent of vascular injury increases, causing laceration to the external elastic lamina and adventitia, the neointimal thickness significantly increases and could necessitate repeat surgical intervention (Wieneke et al., 1999). In addition, endothelial denudation and disruption is observed following stent deployment which has implications for in-stent restenosis given that endothelial cells synthesise nitric oxide which is directly implicated in inducing and maintaining the contractile and quiescent phenotype in VSMC (Lemson et al., 2000). It is therefore also necessary to study the influence of reendothelialisation following stent deployment and this will be addressed with further development of the model and inclusion of endothelial cells.

The presented model is based on the hypothesis that damage accumulation occurs within the ECM, given that ECM components bear the most significant part of the mechanical load. Clearly therefore, it is feasible to hypothesise that mechanical damage accumulation is most

significant within ECM and specifically collagen matrix which is the most abundant ECM constituent, making up more than 50% of the basement membrane (Monaco et al., 200). This hypothesis is also supported by comparison to *in-vivo* studies on injured arteries, where it has been shown that VSMC with synthetic phenotype in the injured arteries are encapsulated by an incomplete basement membrane (Thyberg et al., 1997). Whether this observed disruption of the basement membrane is caused by direct mechanical injury or it is due to the increased matrix degradation, it is clear from such *in-vivo* findings that ECM, and specifically the basement membrane, plays a key role in regulation of VSMC phenotype as the main mechanism underlying the development of intimal hyperplasia.

The presented model provides a quantitative evaluation of the ECM alterations occurring within the arterial wall following stent deployment and the resulting neointimal growth. In addition the multiscale mechanobiological model provides a platform for understanding the processes underlying the development of in-stent restenosis. The platform enables new hypotheses on the mechanisms of in-stent restenosis to be tested quantitatively and hence helps to generate key knowledge and insights into the pathophysiology of in-stent restenosis. Knowledge creation is a particular advantage of this modelling framework given that ABMs enable a fully mechanistic approach towards modelling the mechanisms involved in the development of in-stent restenosis. This strength of ABM also facilitates direct translation and incorporation of *in-vitro* and clinical data into the *in-silico* models of in-stent restenosis in a manner which is comprehensible for scientists from diverse backgrounds, such as biologists, clinicians and engineers. As such, ABMs facilitate communication and integration of investigators with diverse backgrounds for a more thorough analysis and understanding of biomedial challenges, which is a crucial requirement for today's multidisciplinary research in the biomedical field. In addition, combining the lattice free ABMs with FE simulations of stent deployment gives a new dimension to the ongoing research on modelling in-stent restenosis by integrating the proven capabilities of FEM in capturing the mechanics of stent-artery interaction with the added value of ABM for mechanistic modelling of the biological response of cells within arteries.

This model clearly has the potential to be used as a robust and efficient tool in the design phase of stents and can be developed further to include additional cell populations such as endothelial cells, the influence of various growth factors, and even drug or gene elution from the stent or stent degradation.

5. Future directions

Whilst stent optimisation studies have advanced considerably in the last 20 years by using numerical modelling techniques, the future of such studies lies in their ability to assess the biological response of the artery to the deployed stent along with the mechanical environment changes induced by the stent. The real power of these models will only be fully realised when inter-patient variability can be incorporated into the models, thereby generating similar data to clinical trials where the probability of stent success in a large population is determined rather than simply one clinical outcome. This can be achieved using patient-specific geometry and material properties in numerical models of stents and such data can currently be obtained from non-invasive medical imaging techniques (Creane et al., 2010). Variations in patient growth responses, and even genetic information can be

used to inform such stochastic models (Nowlan & Prendergast, 2005) with advances in computational techniques possibly enabling lesion and patient-specific stents to be designed and manufactured for such patients on the basis of the model results. Ultimately, clinicians may be in a position to prescribe the optimum patient specific stent design, which incorporates drug elution, gene delivery, radiation therapy or a biodegradable stent, to treat a patient specific lesion taking into account the geometry, material properties and growth response of the patient concerned using preclinical predictive models which indicate the best long-term outcome.

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7. References

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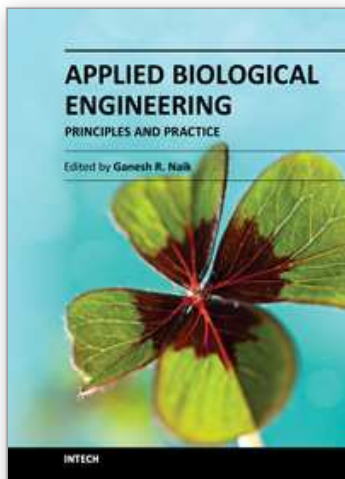
Applied Biological Engineering - Principles and Practice

Edited by Dr. Ganesh R. Naik

Biological engineering is a field of engineering in which the emphasis is on life and life-sustaining systems. Biological engineering is an emerging discipline that encompasses engineering theory and practice connected to and derived from the science of biology. The most important trend in biological engineering is the dynamic range of scales at which biotechnology is now able to integrate with biological processes. An explosion in micro/nanoscale technology is allowing the manufacture of nanoparticles for drug delivery into cells, miniaturized implantable microsensors for medical diagnostics, and micro-engineered robots for on-board tissue repairs. This book aims to provide an updated overview of the recent developments in biological engineering from diverse aspects and various applications in clinical and experimental research.

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