In vitro and in silico testing of partially and fully bioresorbable vascular scaffold

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Abstract

Coronary artery disease (CAD), one of the leading causes of death globally, occurs due to the growth of atherosclerotic plaques in the coronary arteries, causing lesions which restrict the flow of blood to the myocardium. Percutaneous transluminal coronary angioplasty (PTCA), including balloon angioplasty and coronary stent deployment is a standard clinical invasive treatment for CAD. Coronary stents are delivered using a balloon catheter inserted across the lesion. The balloon is inflated to a nominal pressure, opening the occluded artery, deploying the stent and improving the flow of blood to the myocardium.

All stent manufacturers have to perform standard *in vitro* mechanical testing under different physiological conditions. In this study, partially and fully bioresorbable vascular scaffold (BVS) from Boston Scientific Limited have been examined in vitro and in silico for three different test methods: inflation, radial compression and crush resistance.

We formulated a material model for poly-L-lactic acid (PLLA) and implemented it into our in-house software tool. A comparison of the different experimental results is presented in the form of graphs showing displacement-force curves, diameter – load curves or diameter - pressure curves. There is a strong correlation between simulation and real experiments with a coefficient of determination (R^2)>0.99 and a correlation coefficient (R)>0.99.

This preliminary study has shown that *in-silico* tests can mimic the applicable ISO standards for mechanical *in vitro* stent testing, providing the opportunity to use data generated using *in-silico* testing to partially or fully replacing the mechanical testing required for regulatory submission.

Keywords: In vitro mechanical test, bioresorbable stent, PLLA, finite element analysis

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Introduction: 569

Methodology for the mechanical simulations: 640

Results: 1728

Conclusions: 451

1 INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death in the world. CAD occurs due to the growth of atherosclerotic plaques in the coronary arteries. Percutaneous transluminal coronary angioplasty (PTCA) was introduced as a minimally invasive treatment for CAD. The catheter balloon is inflated to a nominal pressure, compressing the atherosclerotic plaque against the arterial wall and deploying the stent. This restores the vessel patency and improves the flow of blood to the myocardium. PTCA generally results in high clinical success rates, although a percentage of patients redevelop the initial symptoms over 6–12 months. This re-narrowing of the treated artery is caused by restenosis, which is the principal limitation of this procedure (Martin and Boyle, 2011).

Migliavacca et al. (2002) investigated the effect of the geometrical parameters (artery surface ratio, strut thickness, cell length) of the Palmaz-Schatz stent on deployment characteristics. Results for this stent were compared to the Carbostent and Multi-Link Tetra stent (Migliavacca et al., 2002). The expansion of each stent was obtained through a pressure load applied to the inner surface. The results showed that geometrical parameters had a significant influence on the deployment characteristics. When the metal to artery surface ratio is lower, this is associated with higher rates of radial and longitudinal recoil and also lower rates of dog-boning. This study demonstrated the potential of the finite element method in optimization of stent designs.

The design of biodegradable stents would be greatly improved if one were to predict how a given structure degrades over time in response to cyclic loading. This coupled contact mechanics problem, while difficult under typical physiologic conditions, is manageable with many FEM packages. In papers (Soares et al., 2007; Soares et al., 2008; Soares et al., 2010a; Soares et al., 2010b) a description of material properties that include the effects of mechanical deformation in conditions of accelerating biodegradation is proposed. This is a basic model in which the material, at fixed degradation, is characterized with a neo-Hookean, purely elastic model. The energy density function for neo-Hookean material is dependent on shear modulus and the first principal invariant of the right Cauchy-Green deformation tensor. Shear modulus is typically a material constant that is

estimated from load-deformation experiments, but in the case of biodegradable material, this material property varies with time as material degrades. The parameter of degradation is 3D spatially and time dependent degradation field, and for undegraded material it has value 0, and for completely degraded material it has value 1. Soares et al. (2008) proposed a function for rate of deformation in the case of uniaxial extension.

As mentioned above, using biodegradable materials for implantable stents brings numerous advantages. Unfortunately, their performance is not sufficiently well characterized, either in vivo or in silico.

In this study we initially created a finite element model for a partially BVS stent (SYNERGY™ BP (Bioabsorbable Polymer) Everolimus-Eluting Platinum Chromium Coronary Stent – Boston Scientific Limited) and then for a fully BVS stent (prototype polymeric bioresorbable stent made from PLLA – Boston Scientific Limited). Then we introduced our specific material model based on experimental curves implemented on the PLLA material model. The PLLA experimental curves were available referring to three different strain rates: 0.001 s^{-1}, 0.01 s^{-1} and 0.1 s^{-1}. In the Results section inflation, radial compression and crush resistance tests are presented. A comparison of the results between simulation and real experiments is given with coefficient of determination and correlation coefficient.

2 METHODOLOGY FOR THE MECHANICAL SIMULATIONS

2.1 Finite element model for SYNERGY™ BP

The SYNERGY™ BP Everolimus-Eluting Platinum Chromium Coronary Stent is a partially Bioresorbable Vascular Scaffold (BVS) produced by Boston Scientific Limited (Galway, Ireland). The geometrical model of the SYNERGY™ BP stent in pre-crimping configuration is presented in the Figure 1a. The strut section has 89 µm width and 79 µm thickness (Figure 1b). After crimping and expansion, the stent obtained has a nominal expanded inner diameter of 3 mm and a nominal length of 16.17 mm.

Figure 1

Since the aim of the study is to perform structural analyses of the device, it is of primary importance to build a representative discretized model of the stent. The whole model was discretized with 36786 hexahedral elements (Figure 1c).

2.2 Material model of SYNERGY™ BP stent

The SYNERGY™ BP stent is made of a platinum-chromium alloy (Pt-Cr) which exhibits bi-linear elastoplastic behaviour.

For this device, the following material parameter values were used (O'Brien et al., 2010). The values for the material density, Young's modulus, Poisson's ratio and yield stress were provided by Boston Scientific Limited.

2.3 Finite element model of a polymeric prototype of a bioresorbable stent implantation system

The device is a **BVS prototype polymeric bioresorbable** stent made from PLLA, supplied by Boston Scientific Limited. Analogous to the SYNERGY™ BP case, the geometrical model of the polymeric prototype of a bioresorbable stent was provided by Boston Scientific Limited (Figure 2a). It has a length of 16 mm, an

internal diameter of 3 mm, the same as the tube used for laser-cutting the stent, with 184 μm strut width and strut thickness of 115 μm.

Figure 2

The whole model was discretized with 49464 hexahedral elements (Figure 2b).

This polymeric device is made of poly-L-lactic acid (PLLA), an elasto-visco-plastic polymer, which exhibits a non-trivial mechanical behaviour dependent on both the strain rate and the operating temperature.

2.4 Material model of BVS material

The model used in PAK solver (Kojic and Filipovic) is based on experimental curves provided by manufacturer (Boston Scientific Limited), Figure 3a.

Figure 3

The manufacturer provided the average results of uniaxial tensile tests performed on a number of dog-bone samples with a gauge length L = 5 mm, width W = 2 mm and a thickness t = 0.105 mm. Tests were conducted at three different temperatures: 25°C, 37°C and 48°C. For each temperature, three different curves were available referring to three different strain rates: 0.001 s^{-1}, 0.01 s^{-1} and 0.1 s^{-1}. Results are in accordance with typical PLLA behavior (Figure 3b): at each temperature, the three curves show a common initial elastic response, a strain rate dependent yield point and plastic behavior ending with a strong hardening. At higher temperature or lower velocity, stress values decrease despite the increasing final strains.

2.5 Representation of the 3D stress-strain state by uniaxial experimental curves

The principle of equivalence of virtual work in 1D and 3D stress-strain conditions is implemented. The following equivalent stress $\bar{\sigma}$ and equivalent strain $\bar{e}$ are adopted (Kojic and Bathe, 2005):

$$\bar{\sigma} = \left\{ \frac{1}{2} \left[\left(\sigma_{11} - \sigma_{22} \right)^2 + \left(\sigma_{22} - \sigma_{33} \right)^2 + \left(\sigma_{33} - \sigma_{11} \right)^2 + 6 \left(\sigma_{12}^2 + \sigma_{23}^2 + \sigma_{31}^2 \right) \right] \right\}^{1/2} \quad (1)$$

123 $$\bar{e} = \left[\frac{2}{3}\left(e_{11}^2 + e_{22}^2 + e_{33}^2\right) + \frac{1}{3}\left(\gamma_{12}^2 + \gamma_{23}^2 + \gamma_{31}^2\right) \right]^{1/2} \quad (2)$$

124 where σ_{ij} stress components; e_{ij} are strains, with γ_{ij} being engineering strains. The uniaxial constitutive
125 relationships obtained experimentally are used with these equivalent stress and strain, evaluated at each
126 integration points within the finite element model.

127 ## 2.6 Interpolation of experimental curves

128 Uniaxial stress-strain curves for different strain rates and two temperatures are schematically shown in Figure
129 3b.

130 We interpolate the equivalent stress for the current strain, stain-rate and temperature as

131 $$\sigma_{T1} = \left(\sigma_1 + \frac{\sigma - \sigma_1}{\sigma_2 - \sigma_1} \right)_{T1}, \qquad \sigma_{T2} = \left(\sigma_1 + \frac{\sigma - \sigma_1}{\sigma_2 - \sigma_1} \right)_{T2} \quad (3)$$

132 and then interpolate for temperature,

133 $$\sigma_T = \sigma_{T1} + \frac{T - T_1}{T_2 - T_1}\left(\sigma_{T2} - \sigma_{T1}\right) \quad (4)$$

134 where it is assumed that $\sigma_1 < \sigma < \sigma_2$, $T_1 < T < T_2$; the curves 1 and 2 correspond to strain rates
135 $\dot{e}_1 < \dot{e} < \dot{e}_2$ and temperatures T_1 and T_2. In the case of $\dot{e} < \dot{e}_{\min}$ we use

136 $$\sigma_{T1} = \frac{\dot{e}}{\dot{e}_{\min}}\sigma_1 \quad \text{or} \quad \sigma_{T2} = \frac{\dot{e}}{\dot{e}_{\min}}\sigma_2 \quad (5)$$

137 In the case of $\dot{e} > \dot{e}_{\min}$ we use

138 $$\sigma_{T1} = \sigma_{\max} + \frac{\dot{e} - \dot{e}_{\max}}{\dot{e}_{\max} - \dot{e}_{\max-1}}\left(\sigma_{\max} - \sigma_{\max-1}\right) \quad (6)$$

3 RESULTS

3.1 Inflation test

The purpose of this test is to determine the diameter required to inflate the balloon to the nominal recommended pressure, analyzing the outer diameter (measured in three positions: proximal, middle, distal) and length. The test provides results for recoil, foreshortening, dog boning. Foreshortening test determines the length to diameter relationship of the stent, the unconstrained length of a self-expanding stent and the wall thickness of a stent. Dog boning test evaluates the difference between the diameter of the implant and those of the proximal and distal ends of the balloon, when the implant is released under the maximum recommended inflation pressure. This test also provides information that might be useful for planning of clinical treatment. The results from the test are diameter/pressure curves. The testing occurs at 37° C temperature in pH 7.4 phosphate-buffered saline. For the test environment, pH and temperature are selected to simulate a clinically relevant environment.

For the in vitro experiment, a computer-controlled Nexus 5000 with 99.96% accuracy syringe pump was used for inflation. A pressure sensor with 0.1% measurement error and a Keyence laser optical micrometer was used for the measurement of diameter (Figure 4a). The sample is fixed in a specially designed fixator. At the start of the inflation process, on every increase of 50kPa the pump temporarily stops and performs the stent outer diameter measurement with the laser micrometer, and then the process continues. Stent manufacturers use a variety of methods to determine the optimal rate of stent inflation. Making the compromise between the rate of inflation and internal stress in the stent material. The aim is to perform the surgical procedure as quickly as possible without compromising the integrity of the stent too much. Finding this limit is a very demanding process and very much depends on the experience of the manufacturer. To obtain consistently test results the inflation speed used is around 3kPa/s which is much less than the manufacturer's suggestion to provide the balloon material more time to adapt to new pressure and avoid possible inflation speed impact on the balloon material deformation.

Figure 4

For in silico simulations, the stent is positioned in the way that the central stent axis is collinear with Z axis. Node movement at one end of the stent is fixed in Z direction. Lower inflation speed provides numerical stability. The pressure is set on the internal surface of the balloon, which is placed inside the stent. The contact boundary condition is set between the stent internal surfaces and the balloon outer surfaces. Boundary conditions for mimicking the test are presented in the **Error! Reference source not found.** Figure 4b.

3.1.1 Computed results

The stress distribution from the simulation of the inflation test for the SYNERGY™ BP device and BVS prototype device are presented in Figure 5a and Figure 5b, respectively. In the case of the SYNERGY™ BP device, the inflation test starts from a crimped device form without any residual stress and strain (material is Pt-Cr alloy so residual stress and strain it is negligible and therefore was disregarded). But in the case of the BVS prototype device (material PLLA), to preserve residual stress and strain, the crimping process is simulated first (Figure 5b, top), then the inflation simulation is performed.

Figure 5

Comparison of diameter-pressure curve results, between real experimental data and simulations for the SYNERGY™ BP and BVS devices are presented in Figure 6a and Figure 6b, respectively. In the real inflation test 14 SYNERGY™ BP units and 9 BVS prototype units were tested, but only two representative diameter-pressure curves from actual tests are presented in Figure 6a and Figure 6b. However, the data from all SYNERGY™ BP; n=14 curves, and BVS prototype; n=9 curves were used in the calculation of the R^2 results reported in Table 1.

Figure 6

The simulation of the inflation test also generates results for several different tests (Table 1):

- Foreshortening
- Dog boning
- Stent-free Surface Area.

Stent-free Surface Area (SAR) is easily measured from the CAD model and ISO 25539 part 2 does not require this parameter to be measured on a real test article. The simulation cannot provide a result for the Profile/diameter test that can be compared with the data generated from bench testing of an actual stent. During manufacturing process, a test article can be generated with different dimensions within the acceptable range of the profile/diameter specification. . However, the test can provide information about stent opening and the simulation can be programmed to expand the stent to a pre-defined diameter.

3.2 Radial compression test (radial force)

The purpose of this test is to determine the load/deformation characteristics of the stent, while a circumferentially uniform radial load is applied. The stent is compressed using a uniform rate of compression, starting with a diameter equal to the maximum indicated vessel diameter. In this simulation, the stent is positioned in such a way that the central stent axis is collinear with Z axis. Node movement at one end of the stent is fixed in the Z direction. The radial force is set on the outer surface of the cylinder placed outside of the stent with the purpose of simulating the “Mylar” loop crimping device. The contact boundary condition is set between the stent outer surfaces and the cylinder internal surfaces. Boundary conditions for mimicking the test are presented in Figure 7a (right).

Figure 7

3.2.1 Computed results

The stress distribution from the simulation of crimping the SYNERGY™ BP device and BVS prototype device have been presented in Figure 7b and Figure 7c, respectively.

Comparison of the diameter-load curve results, between real experimental data and the simulation is presented in the Figure 7d and Figure 7e. In the real compression test 5 SYNERGY™ BP and 4 BVS prototype device units were tested. The data from all SYNERGY™ BP: n=5 curves and BVS prototype device n=4 were used in the calculation of the R^2 results reported in Table 1.

Comparison of the real experimental data for stent recoil and the results of the simulation required simplification in order to allow interpretation to take place. A comparison of the mean values between the real test and the simulation is presented in Table 1.

3.3 Crush resistance / Crush test with two plates (force / distance)

The purpose of this test is to determine the load required to cause clinically relevant buckling or a deflection equivalent to a diameter reduction of at least 50%. In this test method, it is also necessary to determine the load/deformation characteristics of the stent while a uniform axial load is applied. The stent is compressed between two plates and a load force applied at a uniform rate. In this simulation, the stent is positioned in such a way that the central stent axis is collinear with Z axis, between the two plates (top and bottom). Node movement at one end of the stent is fixed in the Z direction. All stent nodes located in the XZ coordinate plane are bounded in the Y direction and all stent nodes located in the YZ coordinate plane are bounded in the X direction. The axial force is set on the top plate. The bottom plate is fixed. The contact boundary condition is set between the stent outer surfaces and the surfaces of the plates. Boundary conditions for mimicking the test are presented in Figure 8a.

Figure 8

3.3.1 Computed results

The stress distribution from the crush test of SYNERGY™ BP and BVS prototype device have been presented in Figure 8b and Figure 8c, respectively.

Comparison of the diameter-load curve results, between real experimental data and the simulation is presented in Figure 9a for SYNERGY™ BP devices and in Figure 9b for BVS prototype devices. In the real crush test 5 SYNERGY™ BP units and 3 BVS prototype units were tested. The data from all SYNERGY™ BP: n=5 curves and BVS prototype device n=3 were used in the calculation of the R^2 results reported in Table 1.

Figure 9

By comparing diameter-pressure curves (Inflation test: Figure 6a, Figure 6b) and diameter-load curves (Radial compression test: Figure 7d, Figure 7e; Crush test: Figure 9a, Figure 9b) created from the simulation with data from real experiments, it can be concluded that the simulation mimics the real inflation test with very high precision. The precision of simulation is quantified by the coefficient of determination (R^2) and correlation coefficient (R) calculated between the simulation curve and all points from all experimental curves.

- From the obtained inflation test results there is a strong correlation for SYNERGY™ BP (R^2=0.999, R=0.9955) and BVS (R^2=0.9973, R=0.9925) for the proximal/distal stent positions. At the central position for the SYNERGY™ BP stent, the coefficient of determination (R^2=0.777) and correlation coefficient (R=0.8815) show a little “deviation”, because the speed of process transition is different between the real test and the simulated test.
- In the case of the radial compression test it can be observed that the coefficient of determination (R^2=0.8099) and correlation coefficient (R = 0.9) are lower in the case of the SYNERGY™ BP device. The difference is due to the setup for the radial mechanical test for a very small stent diameter. In the “Mylar loop” device setup if the stent diameter is decreasing, the measurement “noise” increases. In the real test measurements, when the diameter is less than 2mm, the load value is decreased. This directly produces lower results in the coefficient of determination (R2) and the correlation coefficient (R).
- Results from crush test present a strong correlation between the simulation and real experiments for the SYNERGY™ BP device, quantified with R^2=0.9957 and R=0.9979 and for the BVS device quantified with R^2=0.9986 and R=0.9993.

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4 CONCLUSIONS

In this study, we presented in vitro and in silico mechanical tests with two different types of stent devices - SYNERGY™ BP representing a partially BVS device and a prototype bioresorbable stent from Boston Scientific Limited representing fully BVS devices. A comparison between the results of the real test and the simulation are presented in the form of comparable curves. We presented inflation, radial compression and crush resistance tests. Comparison of the tests results interpreted in form of graphs (diameter – load curves or pressure – diameter curves) for the partially BVS SYNERGY™ BP (device already approved for commercialization) and the fully BVS devices (polymeric prototype of a bioresorbable vascular scaffold) show very good correlation with results from real mechanical tests. A newly developed material model for simulation of PLLA or other similar polymer materials shows very satisfying performance and results. We proposed a material model for PLLA in our program PAK (Kojic and Filipovic) for experimental curves which used original experimental curves. This material model includes average results of uniaxial tensile tests performed on a number of dog-bone samples and conducted at three different temperatures. The experimental curves show an initial elastic response, a strain rate dependent yield point and plastic behavior ending with a strong hardening. Any kind of experimental curves available for the stent material can be used, which is a significant benefit in comparison with commercial software where that is not possible. For most of the results, there are strong correlations between simulation and real experiments for the coefficient of determination (R^2>0.99) and the correlation coefficient (R>0.99).

In the inflation test for the SYNERGY™ BP stent, the coefficient of determination (R^2=0.777) and the correlation coefficient (R=0.8815) show a little “deviation” at the central stent position. This can be attributed to the speed of process transition between the real test and the simulation. In the radial compression test, the coefficient of determination (R^2=0.8099) and the correlation coefficient (R = 0.9) are lower in the case of the SYNERGY™ BP device due to the setup of the radial mechanical test for a small stent diameter.

All simulations need several hours of preparation for boundary conditions, prescribing material models, material properties and nonlinear contact. The execution of the simulation takes a few hours which is attributed to the complexity of most of the tests. The residual stress and initial geometry for different tests derive directly from the previous running tests like crimping and expanding.

Up to our knowledge there is no similar study for comparison of partially and fully BVS. In addition, a newly developed material model for simulation of PLLA that uses experimental curves has shown a very good agreement with experimental test results. It has been shown that in-silico tests can mimic most of the appropriate ISO standards for mechanical in vitro stent devices testing. It opens a new avenue for in silico tests which can partially or fully replace the real mechanical testing required for submission to a regulatory body.

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References

Auricchio F., Di Loreto M., Sacco E., 2001. Finite element analysis of a stenotic artery revascularisation through a stent insertion. Computer Methods in Biomechanics and Biomedical Engineering 4: 249–263, DOI: 10.1080/10255840108908007

Bathe K. J., Finite Element Procedures, Prentice-Hall, Englewood Cliffs, N. J., 1996.

Bergstrom, J. S., Boyce M. C., 1998. Constitutive modeling of the large strain time-dependent behavior of elastomers. Journal of the Mechanical and Physics of Solids 46:931–954, DOI: 10.1016/S0022-5096(97)00075-6.

Balossino R., Gervaso F., Migliavacca F., Dubini G., 2008. Effects of different stent designs on local hemodynamics in stented arteries. Journal of Biomechanics 41(5):1053-1061, DOI: 10.1016/j.jbiomech.2007.12.005

Capelli C., Gervaso F., Petrini L., Dubini G., Migliavacca F., 2009. Assessment of tissue prolapse after balloon-expandable stenting: influence of stent cell geometry. Medical Engineering and Physics 31(4):441-447, DOI: 10.1016/j.medengphy.2008.11.002

Chua D., MacDonald B., Hashmi M., 2004a. Finite element simulation of slotted tube (stent) with the presence of plaque and artery by balloon expansion. Journal of Materials Processing Technology 155–156:1772–1779, DOI: 10.1016/j.jmatprotec.2004.04.396

Chua D., MacDonald B., Hashmi M. 2004b. Effects of varying slotted tube (stent) geometry on its expansion behaviour using finite element method. Journal of Materials Processing Technology 155–156:1764–1771, DOI: 10.1016/j.jmatprotec.2004.04.395

De Beule M., Mortier P., Carlier S.G., Verhegghe B., Van Impe R., Verdonck P., 2008. Realistic finite element-based stent design: the impact of balloon folding. Journal of Biomechanics 41(2):383-389, DOI: 10.1016/j.jbiomech.2007.08.014

Djukic T., Saveljic I., Pelosi G., Parodi O., Filipovic N., 2019. Numerical simulation of stent deployment within patient-specific artery and its validation against clinical data. Computer Methods and Programs in Biomedicine 175: 121-127, DOI: 10.1016/j.cmpb.2019.04.005

Dumoulin C., Cochelin B., 2000. Mechanical behaviour modelling of balloon-expandable stents. Journal of Biomechanics 33:1461–1470. DOI:10.1016/S0021-9290(00)00098-1

Etave F., Finet G., Boivin M., Boyer J.C., Rioufol G., Thollet G., 2001. Mechanical properties of coronary stents determined by using finite element analysis. Journal of Biomechanics 34(8):1065-1075, DOI: 10.1016/s0021-9290(01)00026-4

Hayman, D., Bergerson C., Miller S., Moreno M., Moore J. E., 2014. The effect of static and dynamic loading on degradation of PLLA stent fibers. Journal of Biomechanical Engineering 136:081006, DOI: 10.1115/1.4027614

Holzapfel G.A., Stadler M., Gasser T.C., 2005. Changes in the mechanical environment of stenotic arteries during interaction with stents: computational assessment of parametric stent designs. Journal of Biomechanical Engineering 127(1):166-180. DOI:10.1115/1.1835362

Isailovic V., Kojic M., Milosevic M., Filipovic N., Kojic N., Ziemys A., Ferrari M., 2014. A computational study of trajectories of micro- and nano-particles with different shapes in flow through small channels. Journal of the Serbian Society for Computational Mechanics, 8(2): 14-28 DOI: 10.5937/jsscm1402014I

Jovicic G., Vukicevic A., Filipovic N., 2014. Computational Assessment of Stent Durability Using Fatigue to Fracture Approach. Journal of Medical Devices, 8(4): 041002, DOI: 10.1115/1.4027687

Karanasiou G.S. et al., In Silico analysis of stent deployment- effect of stent design, 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Honolulu, HI, 2018, pp. 4567-4570, DOI: 10.1109/EMBC.2018.8513205.

Kojic M., Bathe K. J., 2005. Inelastic Analysis of Solids and Structures, Springer, Berlin-Heidelberg-New York.

Kojic M., Filipovic N., Stojanovic B., Kojic N., 2008. Computer Modeling in Bioengineering – Theoretical Background, Examples and Software. John Wiley and Sons, 978-0-470-06035-3, England

Kojic M, Filipovic N et al, http://www.bioirc.ac.rs/index.php/software/5-pak (last visited: June 10, 2021)

Krsmanovic D., Filipovic N., Koncar I., Petrovic D., Milasinovic D., Davidovic L., 2014. Computer modelling of maximal displacement forces in endoluminal thoracic aortic stent graft. Computer Methods in Biomechanics and Biomedical Engineering, 17:9, 1012-1020, DOI:10.1080/10255842.2012.735661

LaDisa J., Hettrick D., Olson L., Guler I., Gross E., Kress T., Kersten J., Warltier D., Pagel P., 2002. Stent implantation alters coronary artery hemodynamics and wall shear stress during maximal vasodilation. Journal of Applied Physiology 93:6, 1939–1946, DOI: 10.1152/japplphysiol.00544.2002

LaDisa J., Olson L., Guler I., Hettrick D., Audi S., Kersten J., Warltier D., Pagel P., 2004. Stent design properties and deployment ratio influence indexes of wall shear stress: a three-dimensional computational fluid dynamics investigation within a normal artery. Journal of Applied Physiology 97:1, 424–430, DOI: 10.1152/japplphysiol.01329.2003

Lally C., Dolan F., Prendergast P.J., 2005. Cardiovascular stent design and vessel stresses: a finite element analysis. Journal of Biomechanics 38(8):1574-1581, DOI: 10.1016/j.jbiomech.2004.07.022

Mac Donald B. J. 2007. Practical stress analysis with finite elements. Glasnevin Publishing: Dublin.

Martin D., Boyle F. J., 2011. Computational structural modelling of coronary stent deployment: a review. Computer Methods in Biomechanics and Biomedical Engineering 14:4, 331-348, DOI: 10.1080/10255841003766845

Migliavacca F., Petrini L., Colombo M., Auricchio F., Pietrabissa R., 2002. Mechanical behavior of coronary stents investigated through the finite element method. Journal of Biomechanics 35(6):803-811, DOI:10.1016/s0021-9290(02)00033-7

368 Migliavacca F., Petrini L., Montanari V., Quagliana I., Auricchio F., Dubini G., 2005. A predictive study
369 of the mechanical behaviour of coronary stents by computer modelling. Medical Engineering and
370 Physics 27(1):13-18, DOI: 10.1016/j.medengphy.2004.08.012

371 O'Brien B.J., Stinson J.S., Larsen S.R., Eppihimer M.J., Carroll W.M., 2010. A platinum-chromium steel
372 for cardiovascular stents. Biomaterials 31(14): 3755-3761, DOI:
373 10.1016/j.biomaterials.2010.01.146.

374 Petrini L., Migliavacca F., Auricchio F., Dubini G., 2004. Numerical investigation of the intravascular
375 coronary stent flexibility. Journal of Biomechanics 37:495–501, DOI:
376 10.1016/j.jbiomech.2003.09.002

377 Pontrelli G., de Monte F. 2007. Modelling of mass convectiondiffusion in stent-based drug-delivery. Paper
378 presented at: XXV Congresso Nazionale UIT sulla Trasmssione del Calore; 18–20 May, 2007;
379 Trieste.

380 Soares, J. S., Moore J. E. Jr., Rajagopal K. R., 2007. Modeling of biological materials. Edited by F. Mollica,
381 L. Preziosi, K. R. Rajagopal. Birkhauser Basel, pp. 125– 177.

382 Soares, J. S., Moore J. E. Jr., Rajagopal K. R., 2008. Constitutive framework for biodegradable polymers
383 with applications to biodegradable stents. ASAIO Journal 54(3):295-301, DOI:
384 10.1097/MAT.0b013e31816ba55a

385 Soares, J. S., Moore J. E. Jr., Rajagopal K. R., 2010a. Modeling of deformation-accelerated breakdown of
386 polylactic acid biodegradable stents. Journal of Medical Devices 4:041007, DOI:
387 10.1115/1.4002759

388 Soares, J. S., Rajagopal K. R., Moore J. E. Jr., 2010b. Deformation-induced hydrolysis of a degradable
389 polymeric cylindrical annulus. Biomechenics and Modeling in Mechanobiology 9:177–186, DOI:
390 10.1007/s10237-009-0168-z

391 Soares, J.S., Moore, J.E., 2015. Biomechanical Challenges to Polymeric Biodegradable Stents. Annals of
392 Biomedical Engineering 44, 560–579 (2016), DOI: 10.1007/s10439-015-1477-2

393 Vieira, A. C., Vieira J. C., Ferra J. M., Magalhaes F. D., Guedes R. M., Marques A. T., 2011. Mechanical
394 study of PLA–PCL fibers during in vitro degradation. Journal of the Mechanical Behavior of
395 Biomedical Materials 4:451–460, DOI: 10.1016/j.jmbbm.2010.12.006

396 Vieira, A. C., Guedes R. M., Tita V., 2014. Constitutive modeling of biodegradable polymers: hydrolytic
397 degradation and time-dependent behavior. International Journal of Solids and Structures 51:1164–
398 1174, DOI: 10.1016/j.ijsolstr.2013.12.010

399 Vukicevic A.M., Stepanovic N.M., Jovicic G.R., Apostolovic S.R., Filipovic N.D., 2014. Computer
400 methods for follow-up study of hemodynamic and disease progression in the stented coronary
401 artery by fusing IVUS and X-ray angiography. Medical and Biological Engineering and
402 Computing, 52(6): 539-556, DOI: 10.1007/s11517-014-1155-9

403 www.bostonscientific.com/ (last visited: June 10, 2021)

404 Zienkievich, O. C., 1983. The finite element method, third edition, Published by McGraw-Hill Book Co.,
405 New York, ISBN 10:0070840725 / ISBN 13:9780070840720, (1983)

406 Zunino P., D'Angelo C., Petrini L., Vergara C., Capelli C., Migliavacca F., 2009. Numerical simulation of
407 drug eluting coronary stents: mechanics, fluid dynamics and drug release. Computer Methods in
408 Applied Mechanics and Engineering. 198:3633–3644, DOI: 10.1016/j.cma.2008.07.019

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