3D modelling of in-stent restenosis

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Summary:

Coronary artery disease is one of the most widespread causes of mortality in industrialized countries. Coronary artery stenosis, or abnormal narrowing, can lead to ischemia and potentially fatal heart attacks. This narrowing is often corrected by deploying a metal mesh called a stent in the affected artery to keep it open and maintain blood flow. After stenting, cells in the wounded vessel wall start growing and proliferating. Excessive proliferation can lead to a repeat narrowing, or restenosis, which adversely affects coronary blood supply. Computational models can be used to better understand this process.

In this thesis a fully-coupled 3D multiscale computational model of in-stent restenosis is developed, which describes the process of post-stenting tissue growth, and is validated against *in vivo* and *in vitro* data. Also, the model's uncertainties and the assumed boundary conditions are studied.

This multiscale model includes single-scale models for stent deployment, blood flow, and tissue growth in the stented vessel, including smooth muscle cell (SMC) proliferation and extracellular matrix (ECM) production. The blood flow model is fully coupled to the tissue growth model. The model is validated using data from porcine *in vivo* experiments, first by comparing growth in a simulated vessel to growth in a similarly injured porcine vessel, and then by simulating stent deployment using data obtained from micro computed tomography (micro-CT) and directly comparing the simulation results of neointimal growth to histological sections taken at the same locations. To the best of our knowledge, this is the first time that such a detailed validation of a fully coupled three-dimensional model of ISR against detailed histological data has been performed.

Uncertainty quantification and sensitivity analysis is performed on a simplified 2D model of in-stent restenosis to determine the effect of the model's parameters and variances in physiology on neointimal growth. The sensitivity analysis suggests that two major factors that affect restenosis are the wall shear stress in the stented segment and post-operational endothelium recovery. Because of this, two other separate *in silico* models are developed to study the effects of flow boundary conditions and variances in coronary anatomy on cell proliferation in a simplified 2D stented vessel, and also endothelial cell (EC) migration *in vitro* under flow conditions, which can clarify the details of endothelial recovery *in vivo*.

The model of EC migration is particle-based. Cell movement in the model is a combination of random walks and directed movement along the local flow velocity vector. For model calibration and validation, a set of experimental data for cell migration in a rectangular ridged channel has been used. We have first calibrated the model for a baseline case of a channel with no obstacles, and then applied it to the case of a channel with ridges on the bottom surface, representative of stent strut geometry. The modelling results support the hypothesis that EC movement is strongly affected by local wall shear stress direction and magnitude, and also explain the behaviour reported in an earlier work, where the authors attributed cell migration to minimization of shear stress gradient. Our results show that this hypothesis is not required to reproduce *in vitro* observations of cell migration.

The study of flow boundary conditions was done by coupling a 2D model of ISR to a 1D model of an entire human coronary tree. The restenosis dynamics for the assumptions of a constant flow and a constant pressure drop across the coronary tree were considered. The simulations showed no significant difference in neointimal growth between the two assumptions for most locations in the coronary tree, and the differences can only be observed at the locations where a strong alternative flow pathway is present.

On the other hand, the difference between locations is significant, which is consistent with small vessel size being a clinical risk factor for restenosis. These results also suggest that assumption of constant flow is a good approximation for ISR models dealing with the typical progression of ISR in the most often stented locations such as the proximal parts of LAD and LCX.

For the detailed validation study, metrics for comparison are per-strut neointimal thickness and per-section neointimal area. The neointimal area predicted by the model demonstrates a good agreement with the detailed experimental data. For 14 days post-stenting the relative neointimal area, averaged over all vessel sections considered, was 20±3% *in vivo* and 22±4% *in silico*. For 28 days, the area was 42±3% *in vivo* and 41±3% *in silico*.

The model was able to closely match both validation datasets with a single set of parameters. It should be noted that including vessel curvature and ECM production in the model was paramount to obtain a good agreement with the experimental data. Based on these results, we now consider the model validated for the case of BMS implantation in a healthy porcine coronary artery.

Samenvatting:

Coronaire hartziekte is een van de meest voorkomende doodsoorzaken in geïndustrialiseerde landen. Vernauwing van de kransslagader kan leiden tot ischemie en mogelijk fatale hartaanvallen. Deze vernauwing wordt vaak gecorrigeerd door het gebruik van een metalenbusje, een stent genaamd, om deze open te houden en de bloedstroom in stand te houden. Na het plaatsen van een stent beginnen de cellen van de beschadigde vaatwand te groeien en zich te vermenigvuldigen. Overmatige proliferatie kan leiden tot een herhaalde vernauwing, of restenose, die een negatieve invloed heeft op de coronaire bloedtoevoer. Computermodellen kunnen worden gebruikt om dit proces beter te begrijpen.

In dit proefschrift wordt een volledig-gekoppeld 3D multi-schaal rekenmodel van in-stent restenose (ISR) ontwikkeld, dat het proces van weefselgroei na het plaatsen van een stent beschrijft, en gevalideerd wordt aan de hand van in vivo en in vitro data. Ook worden de onzekerheden van het model en de veronderstelde randvoorwaarden bestudeerd.

Dit multi-schaal model omvat enkel-schaalmodellen voor de plaatsing van de stent, de bloedstroom en de weefselgroei in het bloedvat, met inbegrip van de proliferatie van gladde spiercellen (SMC) en de productie van extracellulaire matrix (ECM). Het bloedstrommodel is volledig gekoppeld aan het weefselgroeimodel. Het model wordt gevalideerd aan de hand van gegevens uit in vivo experimenten, eerst door de groei in een gesimuleerd vat te vergelijken met de groei in een gelijkaardig beschadigd varkensvat, en vervolgens door het simuleren van de plaatsing van de stent met behulp van gegevens verkregen uit microcomputertomografie (microCT) en het direct vergelijken van de simulatieresultaten van de neo-intimale groei met histologische secties genomen op dezelfde locaties. Voor zover bij ons bekend, is dit de eerste keer dat een dergelijke gedetailleerde validatie van een volledig gekoppeld driedimensionaal model van ISR aan de hand van gedetailleerde histologische gegevens is uitgevoerd.

Onzekerheidskwantificering en sensitiviteitsanalyse wordt uitgevoerd op een vereenvoudigd 2D model van in-stent restenose om het effect van de parameters van het model en variaties in de fysiologie op de neo-intimale groei te bepalen. De sensitiviteitsanalyse suggereert dat twee belangrijke factoren zijn die restenose beïnvloeden: de afschuifspanning in het segment met de stent en het postoperatieve

endotheelherstel. Om deze reden worden twee afzonderlijke in silico modellen ontwikkeld om de effecten van grensvoorwaarde en varianties in de coronaire anatomie op de celproliferatie in een vereenvoudigd 2D bloedvat te bestuderen, en ook endotheelcel (EC) migratie in vitro onder flow condities, wat de details van endotheelherstel in vivo kan verduidelijken.

Het model van EC migratie is gebaseerd op deeltjes. De celbeweging in het model is een combinatie van willekeurige wandelingen en gerichte beweging langs de lokale snelheidsvector. Voor de kalibratie en validatie van het model is gebruik gemaakt van een set van experimentele gegevens voor celmigratie in een rechthoekig geribbeld kanaal. We hebben het model eerst gekalibreerd voor een kanaal zonder obstakels, en vervolgens toegepast op een kanaal met ribbels op de bodem, representatief voor de geometrie van de stentstang. De modelleringsresultaten ondersteunen de hypothese dat de EC beweging sterk beïnvloed wordt door de richting en grootte van de lokale afschuifspanning en verklaren ook het gedrag dat gerapporteerd werd in een eerder werk, waar de auteurs de celmigratie toeschreven aan het minimaliseren van de afschuifspanningsgradiënt. Onze resultaten tonen aan dat deze hypothese niet nodig is om in vitro observaties van celmigratie te reproduceren.

De studie naar de randvoorwaarden werd door uitgevoerd her koppelen van een 2D model van ISR aan een 1D model van een volledig menselijk coronair vaatstelsel. De restenose dynamiek voor de aannames van een constante flow en een constante drukval over het coronair vaatstelsel werden overwogen. De simulaties toonden geen significant verschil in neo-intimale groei tussen de twee aannames voor de meeste plaatsen in het coronair vaatstelsel, en de verschillen kunnen alleen worden waargenomen op de plaatsen waar een sterke alternatieve stroomroute aanwezig is.

Aan de andere kant is het verschil tussen de locaties significant, dit is consistent met het feit dat de kleine vaatgrootte een klinische risicofactor voor restenose is. Deze resultaten suggereren ook dat de aanname van een constante stroming een goede benadering is voor ISR modellen die de typische progressie van ISR in de meest voorkomende locaties van een stent zoals de proximale delen van LAD en LCX beschrijven.

Voor de gedetailleerde validatiestudie zijn de vergelijkingsmaatstaven per-steun neo-intimale dikte en per sectie neo-intimal gebied. Het door het model voorspelde neo-intimal gebied toont een goede overeenkomst aan met de gedetailleerde experimentele gegevens. Gedurende 14 dagen na het plaatsen van de stent bedroeg het relatieve neo-intimal gebied, gemiddeld over alle betrokken vaatdelen, 20±3% in vivo en 22±4% in silico. Gedurende 28 dagen was het gebied 42±3% in vivo en 41±3% in silico.

Het model was in staat om beide validatiedatasets met één enkele set parameters nauw op elkaar af te stemmen. Opgemerkt moet worden dat het opnemen van de kromming van de vaten en de ECM-productie in het model van het grootste belang was om een goede overeenstemming met de experimentele gegevens te verkrijgen. Op basis van deze resultaten beschouwen we het model nu als gevalideerd voor het geval van BVK-implantatie in een gezonde kransslagader van varkens.

Краткое содержание:

Заболевания коронарных артерий являются одной из самых распространенных причин смерти в индустриализованных странах. Стеноз — это аномальное сужение коронарных артерий, которое может привести к ишемии и к потенциально смертельным сердечным приступам. Такое сужение артерий часто корректируется установкой металлической сетки – стента – в пораженную артерию для увеличения просвета артерии и восстановления кровотока. После стентирования клетки в поврежденной стенке артерии начинают процесс роста и пролиферации. Чрезмерная пролиферация клеток может привести к повторному сужению, или рестенозу, который отрицательно влияет на кровоснабжение сердечной мышцы. Для лучшего понимания этого процесса могут быть использованы компьютерные модели.

В данной диссертации разработана полностью сопряженная трехмерная компьютерная модель внутристентового рестеноза (ВСР), которая описывает процесс роста ткани после стентирования, и которая валидируется с помощью данных экспериментов in vivo и in vitro. Кроме того, изучаются имеющиеся в модели неопределенности и используемые граничные условия.

Данная многомасштабная модель включает в себя модели раскрытия стента, кровотока и роста ткани в стентированном сосуде, при этом модель роста ткани включает пролиферацию гладкомышечных клеток (ГМК) и секрецию внеклеточного матрикса (ВКМ). Модель кровотока полностью сопряжена с моделью роста ткани. Многомасштабная модель валидируется с помощью данных экспериментов на свиньях in vivo, вначале путем сравнения роста в модельном сосуде с ростом в так же поврежденном сосуде in vivo, а затем путем моделирования раскрытия стента с помощью данных, полученных путем микро-компьютерной томографии (микро-КТ) стента и прямого сравнения результатов моделирования роста неоинтимы с гистологическими срезами тех же участков сосуда. Насколько нам известно, это первое настолько детальное валидационное исследование трехмерной компьютерной полностью сопряженной модели ВСР на основе подробны гистологических данных.

Оценка неопределенности и анализ чувствительности проводятся на упрощенной двумерной модели ВСР, для того чтобы определить эффект модельных параметров и

вариаций физиологии на рост неоинтимы. Анализ чувствительности указывает на два основных фактора, которые влияют на рестеноз: сдвиговое напряжение на стенке сосуда и послеоперационное восстановление эндотелия. По этой причине, две отдельные компьютерные модели были разработаны для изучения эффектов граничных условий кровотока и вариаций коронарной анатомии на пролиферацию в упрощенной двумерной версии стентированного сосуда, а также миграции клеток эндотелия (ЭК) in vitro в условиях течения в сосуде, что поможет прояснить детали восстановления эндотелия in vivo.

Модель миграции ЭК представляет отдельные клетки в виде частиц. Движение клеток в этой модели – это комбинация случайных блужданий и направленного движения под действием локального течения. Для калибровки и валидации модели используется набор экспериментальных данных о миграции клеток в прямоугольном канале с препятствиями. Вначале модель была откалибрована для базового случая канала с плоским дном, а затем применена к случаю канала с ребрами на нижней поверхности, соответствующими геометрии волокон стента. Результаты моделирования поддерживают гипотезу того, что движение ЭК в значительной степени определяется направлением и величиной локального сдвигового напряжения, и также объясняет поведение клеток, описанное в более ранней работе, где авторы объясняли миграцию клеток минимизацией градиента сдвигового напряжения. Наши результаты показывают, что данная гипотеза не обязательна для воспроизведения в компьютерной модели движения клеток in vitro.

Исследование граничных условий проводилось путем сопряжения двумерной модели ВСР с одномерной моделью тока крови в коронарных сосудах. Была рассмотрена динамика рестеноза для предположений постоянного потока и постоянного давления в аорте. Моделирование показало отсутствие значимых различий в росте неоинтимы для большей части рассмотренных сосудов, и различия наблюдаются только в тех местах, где присутствует крупный обходной канал течения.

С другой стороны, различия между разными точками коронарных артерий весьма значительны, что согласуется с тем, что малый размер сосуда является клиническим фактором риска рестеноза. Эти результаты также указывают на до, что приближение постоянного потока является хорошей аппроксимацией для моделей ВСР, рассматривающих типичное развитие рестеноза в наиболее часто стентируемых местах, таких как проксимальные части передней межжелудочковой артерии (ПМЖА) и огибающей артерии (ОА).

Для детального валидационного исследования в качестве метрик для сравнения были выбраны толщина неоинтимы поверх отдельных волокон стента и площадь неоинтимы на срезах. Предсказанная моделью площадь неоинтимы хорошо соотносится с экспериментальными результатами. Для 14 дней после стентирования относительная площадь неоинтимы, усредненная по всем рассмотренным срезам, составила 20±3% *in vivo* и 22±4% *in silico*. Для 28 дней площадь составила 42±3% *in vivo* и 41±3% *in silico*.

Модель смогла достаточно точно воспроизвести оба набора валидационных данных с использованием одного набора параметров. Надо отметить, что включение в модель секреции ВКМ и изогнутой геометрии сосуда оказалось необходимым для хорошего воспроизведения экспериментальных данных. На основе этих результатов модель мы считаем модель валидированной для случая здоровой коронарной артерии свиньи, стентированной металлическим стентом.

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The work described here builds upon earlier studies by a number of people. I thank Hannan Tahir, David Evans, Joris Borgdorff, Carles Bona-Casas and Bernd Stahl for their contributions to the initial 2D ISR model and to the 3D prototype.

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Valeria, Grace, thank you for your help with the more formal side of preparing my thesis.

I would like to end this thesis with a quote from Michael Faraday: "Nothing is too wonderful to be true, if it be consistent with the laws of nature; and in such things as these, experiment is the best test of such consistency".

List of publications

Journal papers:

1.   Zun PS, Anikina T, Svitenkov A, Hoekstra AG. A Comparison of Fully-Coupled 3D In-Stent Restenosis Simulations to In-vivo Data // Front Physiol 2017. №8. P. 284.

DOI: http://dx.doi.org/10.3389/fphys.2017.00284

Contributions: PSZ implemented the current version of the model, designed and performed the simulations for variable injury score and variable reendothelization speed, analysed the results and wrote the manuscript.

2.   Zun PS, Hoekstra AG. On the Possible Interaction Mechanism between Collateral Vessels and Restenosis // Procedia Comput Sci 2015. №66. P. 412–8.

DOI: http://dx.doi.org/10.1016/j.procs.2015.11.047

Contributions: PSZ designed and implemented the model, performed the analytical estimation and wrote the manuscript.

3.   Hoekstra AG, Alowayyed S, Lorenz E, Melnikova N, Mountrakis L, Rooij B van, Svitenkov A, Zavodszky G, Zun P. Towards the Virtual Artery: a Multiscale Model for Vascular Physiology at the PCB Interface // Phil Trans R Soc A 2016. №374. P. 20160146.

DOI: http://dx.doi.org/10.1098/rsta.2016.0146

Contributions: PZ contributed to the research on the ISR, drafted and revised that part of the manuscript and created figure 2. He also contributed to the conception of the concept of the virtual artery and revised those sections of the manuscript.

4.   Nikishova A, Veen L, Zun P, Hoekstra AG. Uncertainty Quantification of a Multiscale Model for In-Stent Restenosis // Cardiovasc Eng Technol 2018. №9. P. 761–74.

DOI: http://dx.doi.org/10.1007/s13239-018-00372-4

Contributions: PZ adapted the ISR2D model for uncertainty quantification, designed the study, implemented a new flow model, and helped draft the manuscript.

5.   Nikishova A, Veen L, Zun P, Hoekstra AG. Semi-intrusive multiscale metamodelling uncertainty quantification with application to a model of in-stent restenosis // Philos. Trans. R. Soc. A Math. Phys. Eng. Sci. 2019. Vol. 377, № 2142. P. 20180154.

DOI: http://dx.doi.org/10.1098/rsta.2018.0154

Contributions: PZ helped to design the study, adapted the ISR2D model, and helped to draft the manuscript.

6.   Svitenkov A, Zun P, Rekin O, Hoekstra AG. Partitioning of Arterial Tree for Parallel Decomposition of Hemodynamic Calculations // Procedia Comput Sci 2016. №80. P. 977–87.

DOI: http://dx.doi.org/10.1016/j.procs.2016.05.393

Contributions: PZ implemented the spectral graph partitioning algorithms, set up the computational experiments and helped draft the manuscript.

Planned:

1.   Zun P, Narracott AJ, Chiastra C, Gunn J, Hoekstra AG. Location-specific comparison between a 3D in-stent restenosis model and micro-CT and histology data from porcine *in vivo* experiments // Accepted for publication in Cardiovasc Eng Technol, 2019.

DOI: http://dx.doi.org/10.1007/s13239-019-00431-4

Contributions: PZ implemented the current version of the model, designed and performed the simulations, analysed the results and drafted the manuscript.

2.   Zun P, Narracott AJ, Evans P, Hoekstra AG. A model for endothelial cell migration under flow conditions // Under review at Biomech. and Mod. Mechanobiol., 2019.

Contributions: PZ designed and implemented the model, designed and performed the simulations, analysed the results and drafted the manuscript.

3.   P.S. Zun, L.E. Veen, A.I. Svitenkov, A.G. Hoekstra. Effects of Local Coronary Blood Flow Dynamics on the Predictions of a Model of In-stent Restenosis // Paper under preparation.

Contributions: PZ adapted the 2D ISR model for the study, designed and implemented the 1D-2D coupling, designed and performed the simulations, analysed the results and drafted the manuscript.

Appendix A.
Parameters used in the model

#	Name	Value porcine	Value human	Comments
1	Inner diameter	2.8 mm [131]	3.6±0.4 mm [136,137]	Porcine data is what is currently used in the simulation (Yorkshire minipig RCA); human value based on the middle of LAD segment before the first bifurcation for balanced hearts
2	Outer diameter	3.3 mm [131]	4.5±0.3 mm [66]	Human value includes adventitia; porcine does not
3	Wall thickness	0.25 mm [138]	0.85 mm A+M+I; 0.3 mm M only; 0.5 mm M+I; (calc. from [66])	Holzapfel et al.: "The ratio of outer diameter to total wall thickness was 0.189 ± 0.014; ratios of adventitia, media, and intima thickness to total wall thickness were 0.4 ± 0.03, 0.36 ± 0.03, and 0.27 ± 0.02" A – adventitia, M – media, I – intima. NB: Most arteries were diseased.

#	Name	Value porcine	Value human	Comments
4	Blood velocity	0.15 m/s [139]	0.40±0.19 m/s [93]	Average velocity at the center of the vessel Ofili et al.: 6 LMA, 7 LAD, 4 LCX Huo et al.: 5-14 cm/s in porcine RCA during cardiac cycle
5	Endothelium regeneration time	14 days [72,73] Healthy vessels See comment section for details	Early BMS, implanted in 1995-97 [116] Diseased vessels Up to 16 days: complete destruction 6 weeks: continuous SMC-rich neointima 61 days: no recovery yet; 12 weeks (84, 96 days): recovery	Porcine: 53±36% after 2 days, 95±2% after 5 days, 99±2% after 14 days – EC coverage 59±25% after 3 days, 96±7% after 14 days (data over struts, used in porcine model) – PECAM-1 (platelet endothelial cell adhesion molecule) aka CD31 Between struts: 81±14%, 100±0% respectively [72]. Data for Genous stent was used instead of BMS. The reasoning was that the Genous stent accelerates reendothelization, but does not reduce the hyperplasia, hence it is assumed extra ECs are dysfunctional, and PECAM-1 expression is the same as BMS

#	Name	Value porcine	Value human	Comments
6	Curvature radius	28-36 mm [131] Degree of the curve ~39-51° for a 25 mm segment	Calculated, see comment. For average values, radius is $\frac{180\cdot10.2}{\pi\cdot52} = 11\ cm$ (whole RCA) For proximal RCA, R is up to $57.3 \cdot \frac{4.7}{55} = 5\ cm$ (or less)	Degree of curve: 30-66°, avg. 52°±9 Length: 10.2±1.7 cm (5.7-14.5 cm) [130]
7	SMC cell cycle	32 hours [138]	Similar	The doubling time in human arterial SMCs in vitro ranges between 24-48 hours for different setups [140–142]. Some SMCs in the cultures are likely inhibited; low doubling time requires a load of PDGF
8	SMC agent radius	0.015 mm [29,138]		Radius is an estimation (SMCs are not round in reality) Probably the same radius is a good approximation
9	NO production rate	See [138,143] for NO in relation to WSS		For more detailed data see source; porcine data for pig hind limbs of varying size

#	Name	Value porcine	Value human	Comments
10	NO growth inhibition threshold	1000 nM [65,144]	Similar	In vitro cell cultures, murine and human mostly

Appendix B.
Vessel slices *in vivo* and *in silico*

In silico slices are rotated so that the outer curvature of the vessel is on top. Stent explanted (a) 14 days; (b) 28 days post-stenting. Slides order from proximal to distal. Letters denote strut IDs, see Figure 37. Blue areas show neointima estimation, as described in the paper. If the lumen is outside the area enclosed by the struts (see e.g. EF in the 1st *in vivo* slide), the area is taken as negative.

(a) 14 days (stent ID: JG929RCA)
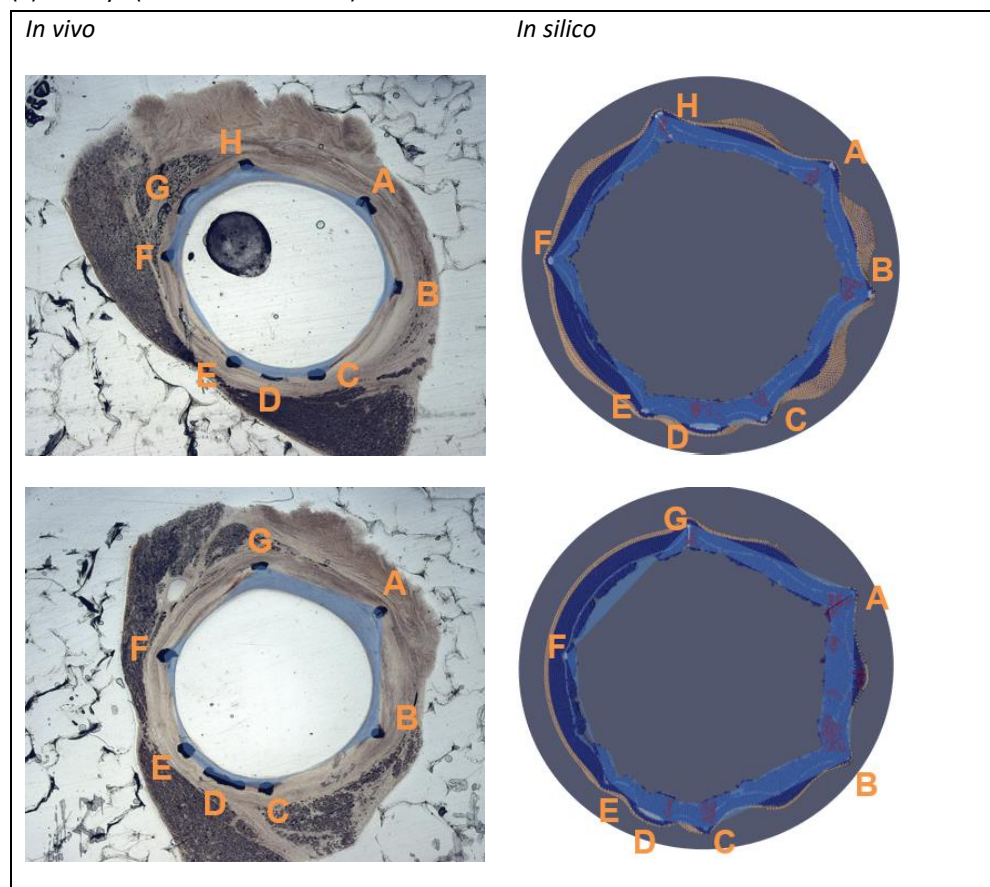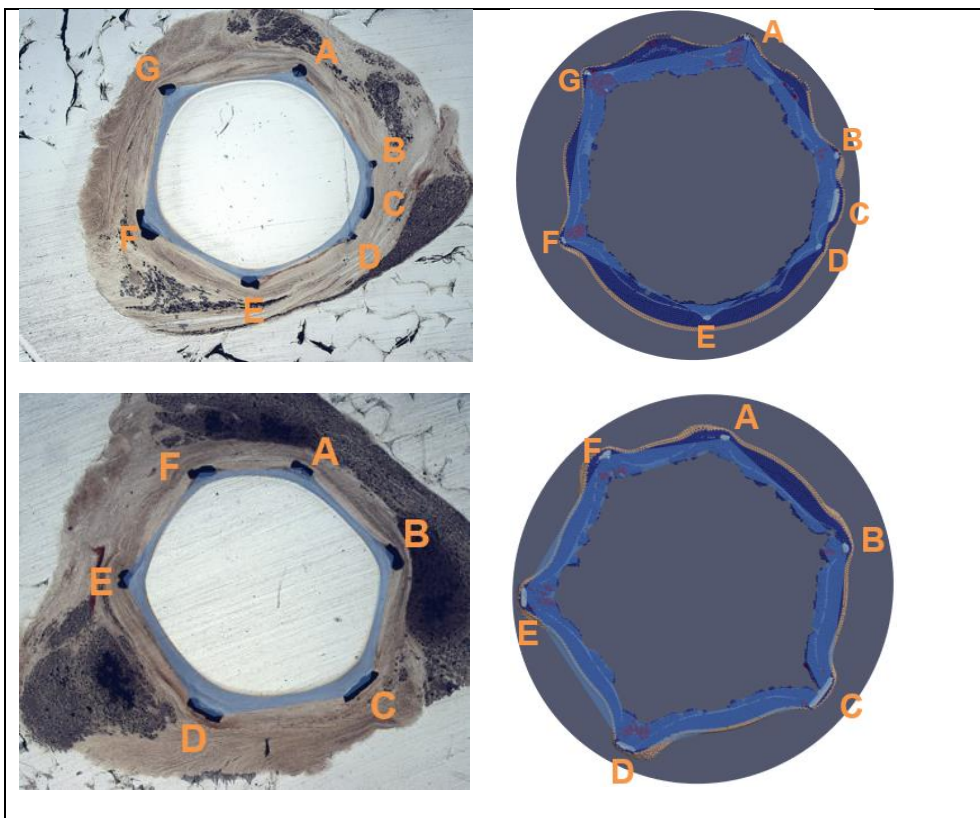
(b) 28 days (stent ID: JG931RCA)

In vivo   *In silico*
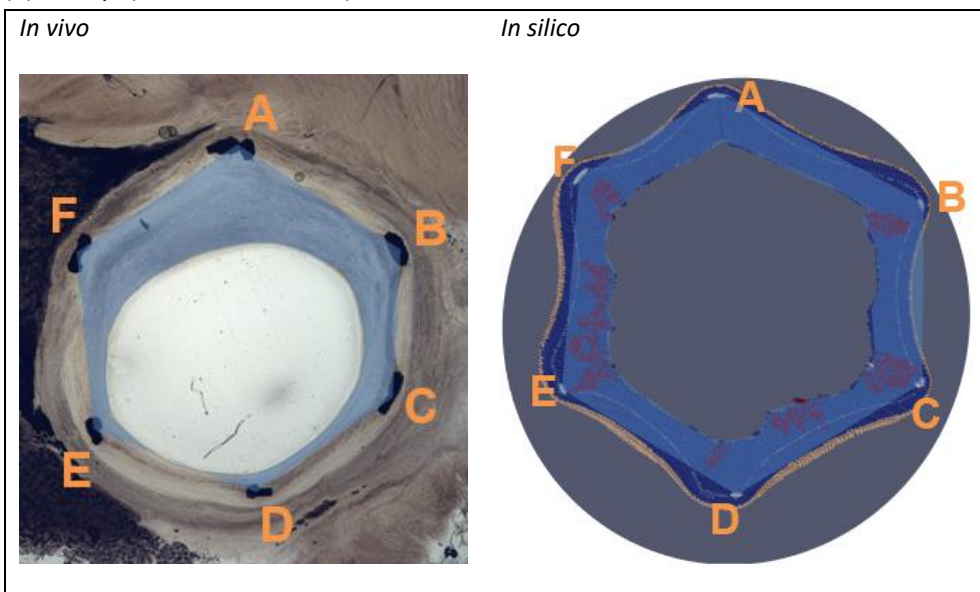
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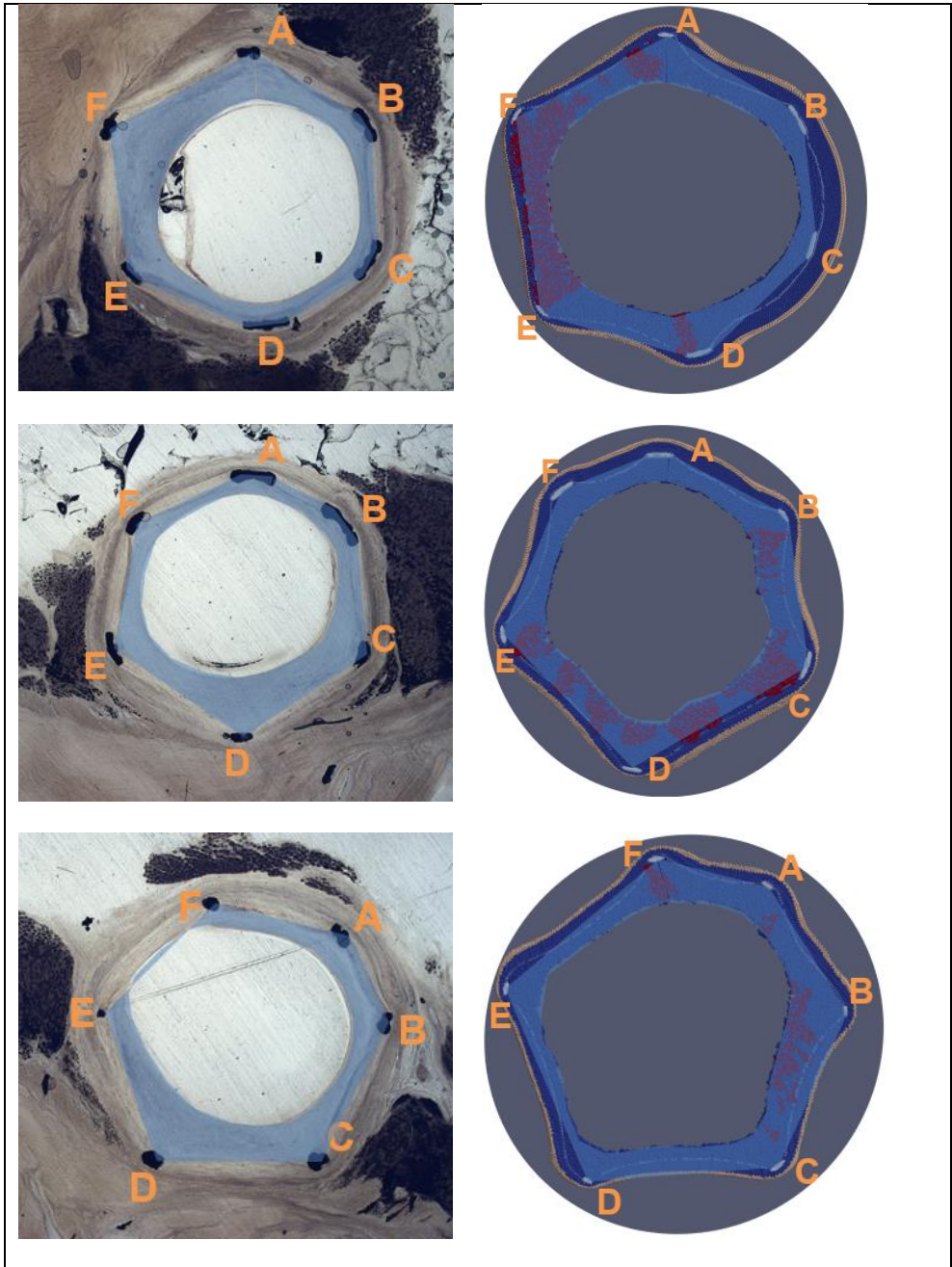[4]   Stephenson NL. Reference conditions for giant sequoia forest restoration: structure, process, and precision. vol. 9. 1999.

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