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Corrigendum

Corrigendum to "Does anisotropy promote spatial uniformity of stent-delivered drug distribution in arterial tissue?" [Int. J. Heat Mass Transfer 90 (2015) 266-279]

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The authors would like to draw attention to the fact that we have identified a numerical implementation error which affects some of the results and conclusions of the paper "Does anisotropy promote spatial uniformity of stent-delivered drug distribution in arterial tissue?". Most significantly, the conclusion that the convection dominated case results in the highest levels of uniformity is replaced with the conclusion that the diffusion dominated case in fact results in the highest levels of uniformity, followed by the reaction dominated case and lastly by the convection dominated case. The updated plots for the convection dominated case are presented below (Fig. 1) whilst the plots for the diffusion and reaction dominated cases are not provided, since they are visibly very similar to those of the original paper. However, we provide updated numerical values (which quantify the uniformity and agreement between the one-dimensional and three-dimensional models) in Tables 1 and 2 for all three cases (convection dominated, diffusion dominated, reaction dominated). While the newly tabulated results for the diffusion and reaction dominated cases show some change, these data represent differences between concentration profiles that have visibly not changed greatly. These data are thus only provided for the sake of completeness. Values referred to in the text of the original paper should be regarded as updated by the values of the tables presented here. The text of Sections 4.1.1 and 4.2.1 is replaced by the updated text below. The plots associated with Section 4.5 (varying strut thickness and separation) are also affected and we provide below in Fig. 2 the updated plots for the convection dominated case (diffusion dominated and reaction dominated figures are visibly very similar to the original paper). Finally, for the benefit of the reader, we provide a completely revised Section 5.

4.1. Uniformity of the drug concentrations

4.1.1. Convection dominated system (updated)

From Fig. 1 (top) we observe that in the convection dominated regime the P_1 and P_2 concentration profiles differ substantially close to the lumen. These differences reduce with time, but even after 24 h, there is still a noticeable difference between the two profiles. This is backed up by Table 1, where $\|P_1 - P_2\|$ is 7.4% after one hour, and reduces only slightly to 6.3% by 3 h where it stays for the remainder of the 28 days studied. Looking more closely at Fig. 1 (top), we see that the region over which P_1 and P_2 noticeably differ extends one fifth of the way into the arterial wall. Beyond this thickness, uniform profiles are observed within one hour. In Fig. 1 (bottom) we also display tissue concentration profiles within abluminal-facing (y–z plane) slices taken at three different thicknesses and at two different times. The particular (narrow) scale has been chosen to emphasize the differences, and this highlights the non-uniformity of the profiles, especially closest to the lumen. The conclusion is that in this convection dominated system, non-uniform profiles are observed close to the wall, but highly uniform concentration profiles may still be achieved throughout the majority of the arterial wall, because of the anisotropic nature of the diffusivity.

4.2. Comparison between three-dimensional and one-dimensional models

4.2.1. Convection dominated system (updated)

In the convection dominated case we see poor agreement between the one-dimensional and the three-dimensional models (Fig. 1 (top)). This is evidenced by the $\|P_{1_{1D}} - P_{1_{3D}}\|$ values in Table 2. After one hour, $\|P_{1_{1D}} - P_{1_{3D}}\|$ is 22.0% and drops only slightly to 19.9% by hour 3. Thus in this convection dominated case, the one-dimensional model poorly predicts the arterial wall drug distribution.

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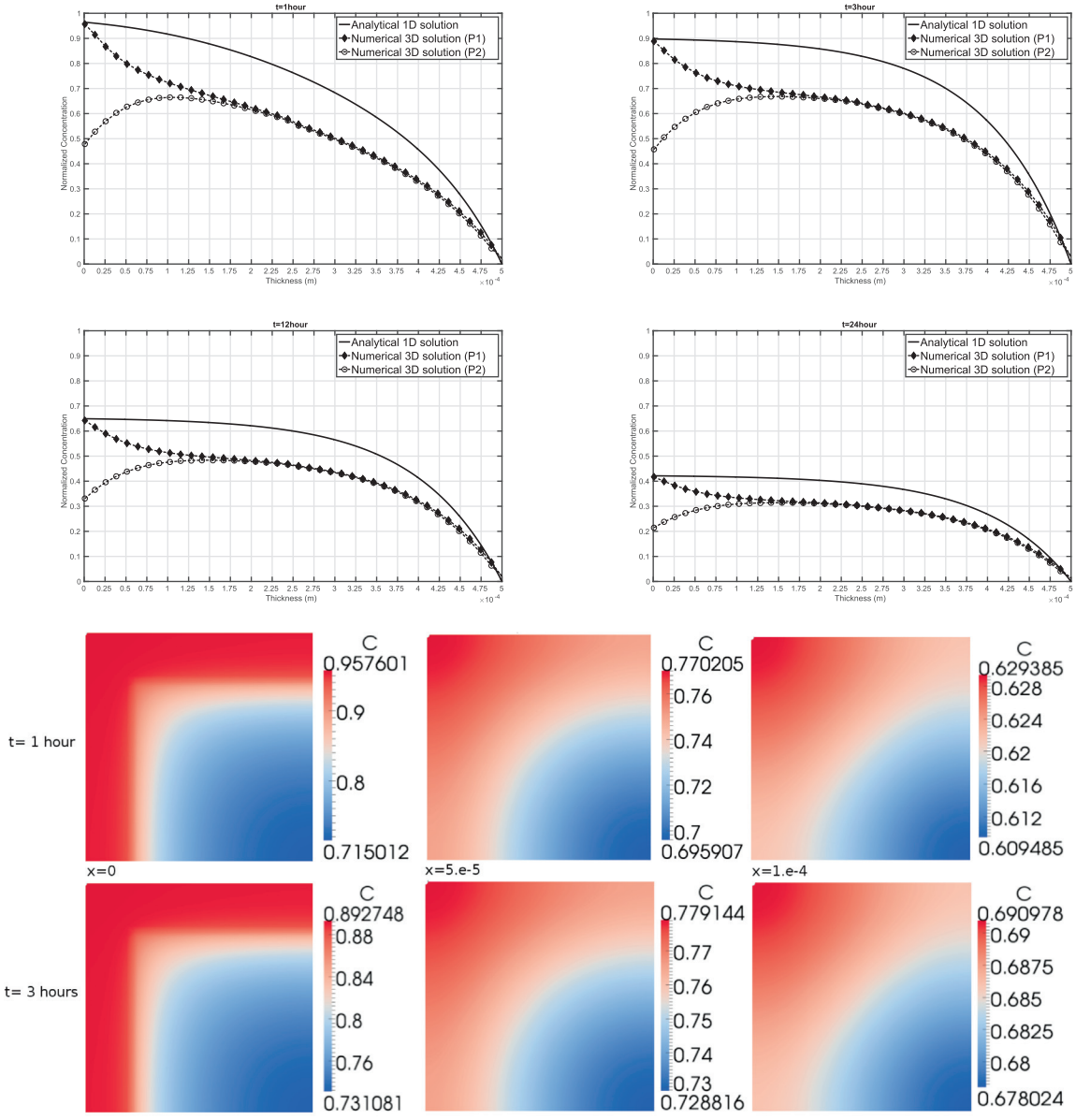

Fig. 1. Updated results for convection dominated regime. This replaces Fig. 3. of the original paper.

5. Discussion (*updated*)

In this paper we have addressed the validity of two common assumptions that are made in modeling the distribution of drug in the arterial wall following stent-based delivery. Firstly, we have derived two conditions which must be satisfied to allow us to reasonably approximate the curved arterial wall geometry as a rectangular geometry. These conditions depend on the ratio of the arterial wall thickness to the arterial radius, the ratio of arterial wall thickness to strut separation and the ratio of the radial diffusion coefficient to the axial/circumferential diffusion coefficient. This analysis validates the extensive use of this assumption in the literature, at least for the range of parameter values considered here. Secondly, by comparing drug transport and distribution predicted by an idealized three-dimensional model with that of a one-dimensional model, we have been able to show that a one-dimensional model is adequate in certain circumstances. Furthermore, we have verified that the anisotropic nature of diffusivity in the arterial wall enhances the agreement between the one-dimensional and three-dimensional models.

We have analyzed three distinct regimes within the range of typical parameter values considered. For the diffusion dominated system, near-uniform profiles are achieved, although the influence of the strut geometry is transmitted a small distance into the arterial wall. When drug absorption is the significant feature, as in the reaction dominated case, the influence of the strut geometry is even more evident. The reason for this lies in the fact that high drug absorption rates reduce the transport of drug through the arterial wall. In both the diffusion and reaction dominated cases, the majority of the arterial wall sees near uniform profiles for most of the period studied. In each of these cases, the one-dimensional model provides a good approximation to the three-dimensional model, especially at later times within the first 24 h. For the convection dominated regime, there is a region close to the lumen where the concentration profile is non-uniform. In this case the strut geometry has a large influence on the concentration profiles observed, with high concentrations observed directly behind the struts and a trough observed between struts. Consequently, the one-dimensional model provides a less than ideal approximation to the three-dimensional model. Generally speaking, the better the levels

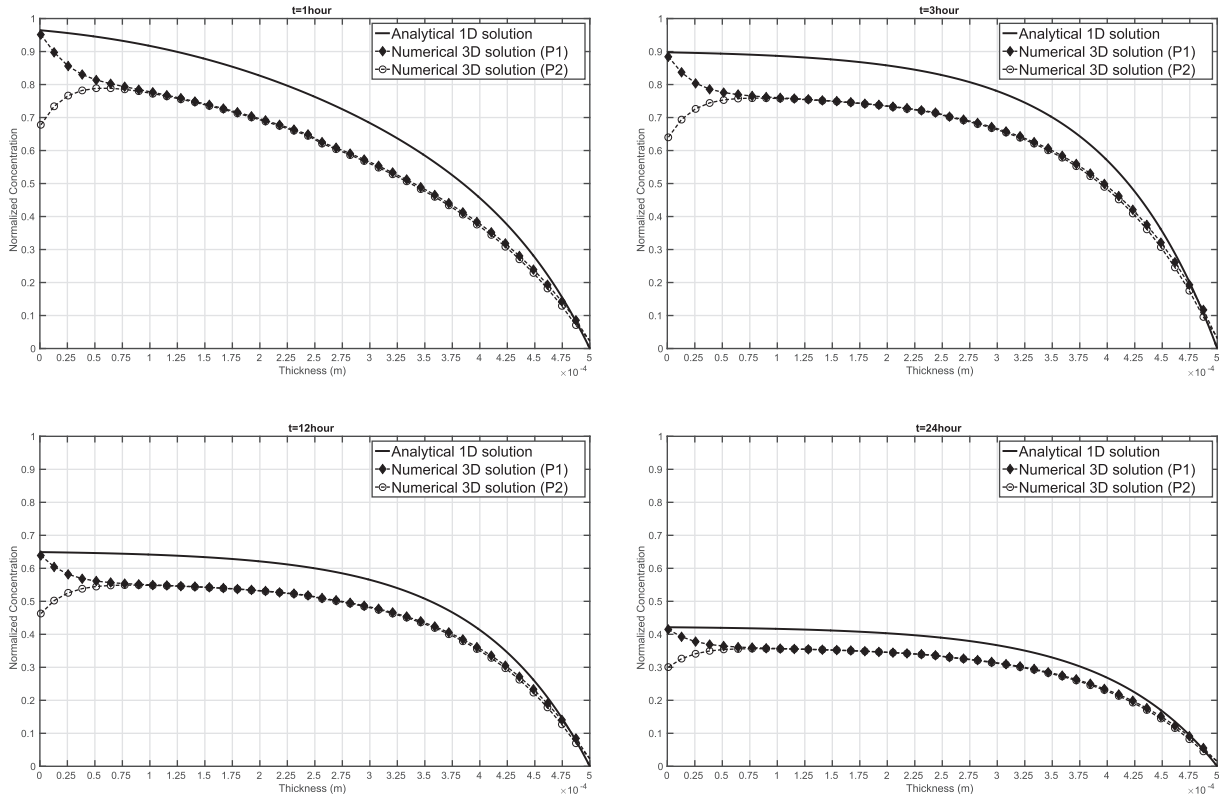

Fig. 2. Updated results for the case of halved strut thickness and separation. Convection dominated regime. This replaces Fig. 7 of the original paper.

Table 1
Updated results $\|P_1 - P_2\|$ and $\|P_{1_{1D}} - P_{1_{3D}}\|$. This replaces Tables 4 and 5 of the original paper.

Regime	1 h (%)	3 h (%)	12 h (%)	24 h (%)	28 days (%)
$P_1 - P_2$					
Convection dominated	7.4	6.3	6.3	6.3	6.3
Diffusion dominated	5.8	3.7	3.5	3.5	3.5
Reaction dominated	7.2	5.5	5.4	5.4	5.4
$P_{1_{1D}} - P_{1_{3D}}$					
Convection dominated	22.0	19.9	19.9	19.9	19.9
Diffusion dominated	12.8	7.4	6.6	6.6	6.6
Reaction dominated	13.4	9.6	9.3	9.3	9.3

Table 2
Updated results for the case of halved strut thickness and separation. This replaces Table 6 of the original paper.

Regime	1 h (%)	3 h (%)	12 h (%)	24 h (%)	28 days (%)
$P_1 - P_2$					
Convection dominated	2.5	2.1	2.1	2.1	2.1
Diffusion dominated	2.5	1.7	1.7	1.7	1.7
Reaction dominated	3.0	2.3	.3	.3	.3
$P_{1_{1D}} - P_{1_{3D}}$					
Convection dominated	15.2	13.5	13.5	13.5	13.5
Diffusion dominated	8.0	4.5	4.0	4.0	4.0
Reaction dominated	8.7	6.2	6.0	6.0	6.0

of uniformity observed, the better is the one-dimensional model at replicating the results of the three-dimensional model. It is worth emphasizing that the degree of variability of the estimates of the parameters is substantially greater than the difference between the one-dimensional and the three-dimensional model, lending support to the hypothesis that, for the most part, a one-dimensional model provides an adequate description of the diffusion process.

It is interesting to assess our findings in the context of clinical and manufacturing considerations. Clinicians suggest that uniform drug concentration profiles are desirable. If it were the case that drug distribution followed the pattern of the struts then large areas of tissue would be exposed to levels of drug that would be ineffective while those areas directly behind the struts may receive toxic levels of drug. From our analysis, we have shown that if uniform

profiles were to be required in the early hours of implantation then diffusion dominated transport would be desired. We have also demonstrated that designing struts that are thinner and closer together results in greater uniformity of drug concentrations more quickly, resulting in better agreement between the one-dimensional and three-dimensional models. Of course there are physiological and mechanical constraints on how close together the struts can be placed and on how thin they can be. Thus there is a balance to be struck between reducing strut thickness and separation to ensure a uniform drug distribution and maintaining mechanical integrity and sufficient tissue exposure to the lumen.

As we have already mentioned, many of the parameters in our model are in fact drug-dependent. Bozsak et al. [15] studied the transport properties of two commercial drugs, paclitaxel and sirolimus, used to coat current drug-eluting stents. They found that due to differences in the diffusion coefficients and binding parameters of these drugs, the main mechanism of transport was different. They found that for paclitaxel the timescale for convection is faster than that for drug binding while for sirolimus the timescale for binding was faster than that for convection. Whilst it should be stressed that [15] considered a more sophisticated model of binding, it is still, nonetheless, interesting to interpret their findings in the context of this present work. If paclitaxel transport through the arterial wall is indeed within the convection dominated regime, then our results suggest that non-uniform drug concentrations may be achieved close to the lumen for this drug, with the stent strut geometry having a large influence on drug distribution. However, if sirolimus transport through the arterial wall is within the reaction dominated regime then our results suggest more uniform profiles, with the stent strut geometry having a smaller influence on drug distribution close to the lumen. However, in both cases, the majority of the arterial wall would see near-uniform concentration profiles. This would suggest a one-dimensional model may more closely replicate the three-dimensional results of sirolimus transport through the arterial wall.

Our results have demonstrated that the higher the value of the axial and circumferential diffusion coefficient, D_1, with $D_1/D \geqslant 10$, the quicker the time taken for uniform drug concentrations to be achieved in the abluminal-facing plane, and the better the comparison between the one-dimensional and three-dimensional models. Also, we have demonstrated that the greater the level of anisotropy, i.e. the greater the value of D_1/D, the more uniform the drug concentrations are and the better the comparison between the one-dimensional and three-dimensional models.

In summary, the least ideal situation from a clinical point of view would appear to be the manufacturing of a device with thick struts that are far apart and contain a drug that possesses slow circumferential and axial diffusion coefficients of the same order as the radial diffusion coefficient and satisfying $Pe > 1$. Under these conditions, uniform drug concentrations would not be achieved throughout the wall and this could result in regions of toxicity and/or regions of under-exposure to therapeutic levels of drug. A non-negligible area of highly non-uniform drug concentrations would persist close to the lumen even after 24 h. For these reasons, in this case the one-dimensional model would be a poor representation of the three-dimensional model. In contrast, the ideal situation from a drug delivery point of view would appear to be the manufacturing of a device with thin struts that are close together, containing a drug that possesses fast circumferential and axial diffusion coefficients which are much larger than the radial diffusion coefficient ($D_1/D \gg 1$), and satisfy $Pe < 1$ and $Da_1 < 1$. Under these conditions, near-uniform drug concentrations would be achieved quickly and would be transmitted through the arterial wall. In this case the one-dimensional model would best replicate the three-dimensional model.