Supplementary material for "Do we really understand how drug eluted from stents modulates arterial healing?"

Alistair McQueen[1], Javier Escuer[2], Ankush Aggarwal[3], Simon Kennedy[4], Christopher McCormick[5], Keith Oldroyd[4], Sean McGinty[1,*]

[*]Corresponding author: Email address: sean.mcginty@glasgow.ac.uk.

[1]Division of Biomedical Engineering, University of Glasgow, Glasgow, UK.

[2]Aragón Institute for Engineering Research (I3A), University of Zaragoza, Spain

[3]Glasgow Computational Engineering Centre, Division of Infrastructure and Environment, University of Glasgow, Glasgow, UK.

[4]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[5]Department of Biomedical Engineering, University of Strathclyde, Glasgow, UK

1. Non-dimensional analysis of the drug models

1.1. Non-dimensionalisation of Model D1

The dimensional model equations are given by (Eqn. 3.2-3.3) in the main text. These equations are non-dimensionalised using the scalings:

$$t^* = gt, \qquad c^* = \frac{c}{K}, \qquad b^* = \frac{b}{Bc}. \tag{A.1}$$

Applying (A.1) to (Eqn. 3.2-3.3) results in the following equations, where asterisks have been omitted from variables for convenience:

$$\frac{db(t)}{dt} = \beta_1^{D1}\left(1 - b(t)\right) - \beta_2^{D1} b(t), \quad t > 0, \quad b(0) = 0, \tag{A.2}$$

$$\frac{dc(t)}{dt} = c(t)\left(1 - c(t)\right)\left(1 - b(t)\right), \quad t > 0, \quad c(0) = C^0. \tag{A.3}$$

The three non-dimensional constants appearing in (A.2-A.3) are given by

$$\beta_1^{D1} = \frac{k_f c_d}{g}, \quad \beta_2^{D1} = \frac{k_r}{g}, \quad C^0 = \frac{c_0}{K}. \tag{A.4}$$

1.2. Non-dimensionalisation of Model D2

The dimensional equations are given by (Eqn. 3.4-3.5) in the main text.These equations are non-dimensionalised using the scalings:

$$t^* = gt, \qquad c^* = \frac{c}{K}, \qquad b^{I*} = \frac{b^I}{k_{50}}. \tag{A.5}$$

Applying (A.5) to (Eqn. 3.4-3.5) results in the following equations, where asterisks have been omitted from variables for convenience:

$$\frac{db^I(t)}{dt} = \beta_1^{D2} - \beta_2^{D2} b^I(t), \quad t > 0, \quad b^I(0) = 0, \tag{A.6}$$

$$\frac{dc(t)}{dt} = c(t)\left(1 - c(t)\right)\left(1 - \frac{k_{max} b^I(t)}{b^I(t) + 1}\right), \quad t > 0, \quad c(0) = C^0, \tag{A.7}$$

The three new non-dimensional constants appearing in (A.6-A.7) are given by

$$\beta_1^{D2} = \frac{\alpha c_d}{g k_{50}}, \quad \beta_2^{D2} = \frac{\alpha}{g K_p}, \quad C^0 = \frac{c_0}{K}. \tag{A.8}$$

1.3. Non-dimensionalisation of Model D3

The dimensional model equations are given by (Eqn. 3.6a-3.6b) in the main text. These equations are non-dimensionalised using the scalings:

$$t^* = gt, \qquad \tau^* = g\tau, \qquad c^* = \frac{c}{K}, \qquad c_d^* = \frac{c_d}{k_{50}} \tag{A.9}$$

Applying (A.9) to (Eqn. 3.6a-3.6b) results in the following equations, where asterisks have been omitted from variables for convenience:

$$\frac{dc(t)}{dt} = \begin{cases} c(t)\left(1-c(t)\right)\left(1-\dfrac{k_{max}c_d^*}{c_d^*+1}\right), \quad 0 < t \leq \tau, \quad c(0) = C^0, & \text{(A.10a)} \\ c(t)\left(1-c(t)\right)\left(1-\dfrac{k_{max}c_d^* \exp(-\beta_1^{D3}\left(t-\tau\right))}{c_d^* \exp -\beta_1^{D3}\left(t-\tau\right))+1}\right), \quad t > \tau, & \text{(A.10b)} \end{cases}$$

The two new non-dimensional constants appearing in (A.10a-A.10b) are given by

$$\beta_1^{D3} = \frac{k_d}{g}, \quad C^0 = \frac{c_0}{K}. \tag{A.11}$$

2. Tables

	Parameter						
	Model D1		***Model D2***			***Model D3***	
data set	k_f	k_r	k_{max}^{D2}	$\frac{\alpha}{k_{50}}$	$\frac{\alpha}{K_P}$	k_{max}^{D3}	k_{50}
H_{12}^m	547.94	0.021	1.127	1.31e3	0.922	14.416	0.0706
M_{12}^m	157.998	0.188	17.077	9.407	0.344	10.4171	0.0347
L_{12}^m	1.36e-6	0.002	0.4	6.16e-2	0.542	5.266	0.1906

Table S1: Inversely estimated parameters of models D1, D2 and D3 when fitting is performed against each individual data set of Marra *et al.* [1] The best fitting parameters vary not only across the various doses for a given model, but also between the models.

		Quality of Predictions - ε		
		Model D1		
F	**P**	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$
H_{12}^m	L_{12}^m & M_{12}^m	0.0229	0.2822	0.0929
M_{12}^m	L_{12}^m & H_{12}^m	0.2367	0.0163	0.0265
L_{12}^m	M_{12}^m & H_{12}^m	10.6067	0.1230	0.0455
		Model D2		
F	**P**	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$
H_{12}^m	L_{12}^m & M_{12}^m	0.0235	0.8243	0.4637
M_{12}^m	L_{12}^m & H_{12}^m	1.3106	0.0163	0.0521
L_{12}^m	M_{12}^m & H_{12}^m	26.5717	0.4287	0.0455
		Model D3		
F	**P**	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$
H_{12}^m	L_{12}^m & M_{12}^m	0.0273	0.0652	0.05
M_{12}^m	L_{12}^m & H_{12}^m	0.9015	0.0294	0.0529
L_{12}^m	M_{12}^m & H_{12}^m	18.3403	0.3537	0.046

Table S2: Quality of predictions when best-fitting model parameters based on a single Marra *et al.* [1] data set are used in the prediction of the other Marra *et al.* [1] data sets. Coloured cells correspond to the error value (ε) of the data set on which the fit was performed. **F** and **P** refer to the fitted and predicted data set(s), respectively.

	Parameter			Error - ε			
Model	k_f	k_r	-	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$	$\varepsilon_{H_4^m}$
D1	4.96e2	0.313	-	0.148	0.188	0.078	0.068
	k_{max}^{D2}	$\frac{\alpha}{k_{50}}$	$\frac{\alpha}{K_P}$	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$	$\varepsilon_{H_4^m}$
D2	1.79	2.088e2	0.828	0.051	0.021	0.055	0.078
	k_{max}^{D3}	k_{50}	k_d	$\varepsilon_{H_{12}^m}$	$\varepsilon_{M_{12}^m}$	$\varepsilon_{L_{12}^m}$	$\varepsilon_{H_4^m}$
D3	2.65	8.54e-3	0.253	0.035	0.03	0.053	0.038

Table S3: Best-fitting parameters and associated error for each of three models D1, D2 and D3, when a multi-fit is used to inversely estimate the model parameters before the effect of the low dose drug L_{12}^m is predicted to the Marra *et al.* [1] dataset. For Models D1 and D2, the M_{12}^m, H_{12}^m and H_4^m data sets were used in the multi-fit. For Model D3, the M_{12}^m and H_{12}^m data sets were used in the multi-fit with a subsequent fitting step using the H_4^m data set required to estimate the parameter associated with drug retention (k_d).

	Parameter							
	Model D1		***Model D2***			***Model D3***		
data set	k_f	k_r	k_{max}^{D2}	$\frac{\alpha}{k_{50}}$	$\frac{\alpha}{K_P}$	k_{max}^{D3}	k_{50}	k_d
H_{60}^s	3.15e6	1.31e-4	0.977	1.027e7	7.38e-4	2.65	3.01e-5	1.25e-4
H_{10}^s	2.23e7	6.73e-3	1.979	8.135e6	1.24e-2	2.72	2.98e-5	1.27e-4
H_3^s	9.39e7	5.48e-3	1.823	3.27e7	6.37e-4	1.58	1.01e-5	2.54e-8
L_{60}^s	1.01e7	1.11e-2	2.569	3.32e6	2.3e-3	3.61	1.08e-5	1.52e-4

Table S4: Inversely estimated parameters of models D1, D2 and D3 when fitting is performed against each individual data set of Scheller *et al.* [2] The best fitting parameters vary not only across the various doses for a given model, but also between the models.

		Quality of Predictions - ε			
		Model D1			
F	**P**	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
H^s_{60}	H^s_{10}, H^s_3 & L^s_{60}	0.0632	19.0104	36.8325	0.3546
H^s_{10}	H^s_{60}, H^s_3 & L^s_{60}	0.3928	0.0286	15.5023	0.675
H^s_3	H^s_{60}, H^s_{10} & L^s_{60}	0.4249	0.3811	0.0536	1.9741
L^s_{60}	H^s_{60}, H^s_{10} & H^s_3	0.2863	3.9501	28.9952	0.0069
		Model D2			
F	**P**	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
H^s_{60}	H^s_{10}, H^s_3 & L^s_{60}	0.0786	8.3835	30.1301	0.0248
H^s_{10}	H^s_{60}, H^s_3 & L^s_{60}	3.1154	0.0284	21.88	0.322
H^s_3	H^s_{60}, H^s_{10} & L^s_{60}	3.2635	2.5687	0.0356	2.8331
L^s_{60}	H^s_{60}, H^s_{10} & H^s_3	3.2313	2.9855	30.065	0.0052
		Model D3			
F	**P**	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
H^s_{60}	H^s_{10}, H^s_3 & L^s_{60}	0.0549	0.0304	0.1378	0.4848
H^s_{10}	H^s_{60}, H^s_3 & L^s_{60}	0.0863	0.0593	0.0463	0.4729
H^s_3	H^s_{60}, H^s_{10} & L^s_{60}	0.1259	0.0967	0.0346	0.3062
L^s_{60}	H^s_{60}, H^s_{10} & H^s_3	3.5872	3.6166	3.6055	0.0048

Table S5: Quality of predictions when best-fitting model parameters based on a single Scheller *et al.* [2] data set are used in the prediction of the other Scheller *et al.* [2] data sets. Coloured cells correspond to the error value (ε) of the data set on which the fit was performed. **F** and **P** refer to the fitted and predicted data set(s), respectively.

	Parameter			Error - ε			
Model	k_f	k_r	-	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
D1	8.85e6	3.56e-2	-	0.22	8.02	31.52	0.033
	k^{D2}_{max}	$\frac{\alpha}{k_{50}}$	$\frac{\alpha}{K_P}$	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
D2	0.95	1.13e7	2.3e-3	0.13	8.2	29.75	0.02
	k^{D3}_{max}	k_{50}	k_d	$\varepsilon_{H^s_{60}}$	$\varepsilon_{H^s_{10}}$	$\varepsilon_{H^s_3}$	$\varepsilon_{L^s_{60}}$
D3	0.95	2.14e-5	2.14e-4	0.13	0.10	0.45	0.019

Table S6: Best-fitting parameters and associated error for each of three models D1, D2 and D3, when a multi-fit is used to inversely estimate the model parameters to the Scheller *et al.* [2] dataset. The 60 min exposure of low and high drug dose data sets were used simultaneously to find the best fitting parameters, with the effect of the shorter exposure times of the high drug dose predicted.

References

[1] Diego E. Marra, Tommaso Simoncini, and James K. Liao. Inhibition of vascular smooth muscle cell proliferation by sodium salicylate mediated by upregulation of $p21_{Waf1}$ and $p27_{Kip1}$. *Circulation*, 102(17):2124–2130, 2000.

[2] Bruno Scheller, Ulrich Speck, Alexander Schmitt, Michael Böhm, and Georg Nickenig. Addition of paclitaxel to contrast media prevents restenosis after coronary stent implantation. *Journal of the American College of Cardiology*, 42(8):1415 – 1420, 2003.