Supplementary material for "Combining mathematical modelling with *in vitro* experiments to predict *in vivo* drug-eluting stent performance"

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Here we provide details of the numerical schemes used to solve the models in the main text.

Coupled two-layer model

We start by nondimensionalising the coupled two-layer model given by equations (1-2) and 4 (with $a = r_l - L_p$ and $b = r_l$) and equations (7-13) from the main text. Letting

$$\bar{r} = \frac{r}{L_w}, \quad \bar{t} = \frac{D_w}{L_w^2}t, \quad \bar{c_p^{(i)}} = \frac{c_p^{(i)}}{C^{(1)}}, \quad \bar{c_w^{(i)}} = \frac{c_w^{(i)}}{C^{(1)}},$$

$$\bar{b_s^{(i)}} = \frac{b_s^{(i)}}{C^{(1)}}, \quad \bar{b_{ns}^{(i)}} = \frac{b_{ns}^{(i)}}{C^{(1)}}, \quad \bar{B_s} = \frac{B_s}{C^{(1)}}, \quad \bar{B_{ns}} = \frac{B_{ns}}{C^{(1)}},$$

then the model becomes (after dropping over bars)

$$\frac{\partial c_p^{(i)}}{\partial t} = \delta^{(i)}\left(\frac{\partial^2 c_p^{(i)}}{\partial r^2} + \frac{1}{r}\frac{\partial c_p^{(i)}}{\partial r}\right), \quad i = 1, 2, \quad L^- < r < L, \quad t > 0, \tag{S1}$$

$$\begin{aligned}\frac{\partial c_w^{(i)}}{\partial t} &= \frac{\partial^2 c_w^{(i)}}{\partial r^2} + \frac{1}{r}\frac{\partial c_w^{(i)}}{\partial r} - Pe\frac{\partial c_w^{(i)}}{\partial r}\\ &\quad -Da_s^f c_w^{(i)}\left(1 - \frac{b_s^{(1)} - b_s^{(2)}}{B_s}\right) + Da_s^r b_s^{(i)}\\ &\quad -Da_{ns}^f c_w^{(i)}\left(1 - \frac{b_{ns}^{(1)} - b_{ns}^{(2)}}{B_{ns}}\right) + Da_{ns}^r b_{ns}^{(i)}, \quad i = 1, 2, \quad L < r < L^+, \quad t > 0,\end{aligned} \tag{S2}$$

$$\frac{\partial b_s^{(i)}}{\partial t} = Da_s^f c_w^{(i)}\left(1 - \frac{b_s^{(1)} - b_s^{(2)}}{B_s}\right) - Da_s^r b_s^{(i)}, \quad i = 1, 2, \quad L < r < L^+, \quad t > 0, \tag{S3}$$

$$\frac{\partial b_{ns}^{(i)}}{\partial t} = Da_{ns}^f c_w^{(i)}\left(1 - \frac{b_{ns}^{(1)} - b_{ns}^{(2)}}{B_{ns}}\right) - Da_{ns}^r b_{ns}^{(i)}, \quad i = 1, 2, \quad L < r < L^+, \quad t > 0, \tag{S4}$$

subject to the following boundary conditions:

$$\frac{\partial c_p^{(i)}}{\partial r} = 0, \quad i = 1, 2, \quad r = L^-, \tag{S5}$$

$$c_w^{(i)} = 0, \quad i = 1, 2, \quad r = L^+, \tag{S6}$$

interface conditions:

$$-\alpha\delta^{(i)}\frac{\partial c_p^{(i)}}{\partial r} = -\frac{\partial c_w^{(i)}}{\partial r} + Pec_w^{(i)}, \quad i = 1, 2, \quad r = L, \quad t > 0, \tag{S7}$$

$$c_p^{(i)} = c_w^{(i)}, \quad i = 1, 2, \quad r = L, \quad t > 0, \tag{S8}$$

and initial conditions:

$$c_p^{(1)} = 1, \quad L^- \le r \le L, \quad t = 0, \tag{S9}$$

$$c_p^{(2)} = C, \quad L^- \le r \le L, \quad t = 0, \tag{S10}$$

$$c_w^{(i)} = = b_s^{(i)} = b_{ns}^{(i)} = 0, \quad i = 1, 2, \quad L < r \le L^+, \quad t = 0, \tag{S11}$$

where

$$\delta^{(i)} = \frac{D_p^{(i)}}{D_w}, \quad L^- = \frac{r_l - L_p}{L_w}, \quad L = \frac{r_l}{L_w}, \quad L^+ = \frac{r_l + L_w}{L_w} = 1 + L,$$

$$Pe = \frac{L_w v_w}{D_w}, \quad Da_s^f = \frac{k_s^f B_s L_w^2}{D_w}, \quad Da_{ns}^f = \frac{k_{ns}^f B_{ns} L_w^2}{D_w},$$

$$Da_s^r = \frac{k_s^r L_w^2}{D_w}, \quad Da_{ns}^r = \frac{k_{ns}^r L_w^2}{D_w}, \quad C = \frac{C^{(2)}}{C^{(1)}}.$$

We adopt the approach of discretizing equations (S1-S11) spatially and then solving the resulting system of ordinary differential equations (ODEs). Let us firstly subdivide the interval (L^-, L) into $N_p + 1$ equally spaced grid nodes $r_p^j = L^- + (j-1)\,\Delta r_p$, $j = 1, 2, 3, ..., N_P + 1$, and the interval (L, L^+) into $N_w + 1$ equally spaced points $r_w^j = L + (j-1)\,\Delta r_w, \quad j = 1, 2, 3, ..., N_w + 1$. Here, Δr_p and Δr_w represent the mesh spacing in the polymer coating and wall layers, respectively. In each layer, we approximate the diffusive terms by considering a standard second order central difference in space at internal nodes $r_\star^j$ ($j = 2, ..., N_\star$, $\star = p, w$). The reaction terms in (S2)-(S4) do not contain any derivatives and therefore are discretized pointwise. Equations (S1-S4) then become

$$\frac{dc_p^{(i)}}{dt}\Big|_{r_p^j} \approx \delta^{(i)} \frac{c_p^{(i),j-1} - 2c_p^{(i),j} + c_p^{(i),j+1}}{\Delta r_p^2} \qquad j = 2, ..., N_p, \quad i = 1, 2, \tag{S12}$$

$$\begin{aligned} \frac{dc_w^{(i)}}{dt}\Big|_{r_w^j} \approx\ & \frac{c_w^{(i),j-1} - 2c_w^{(i),j} + c_w^{(i),j+1}}{\Delta r_w^2} + \left(\frac{1}{r_w^j} - Pe\right) \frac{c_w^{(i),j+1} - c_w^{(i),j-1}}{2\Delta r_w} \\ & - Da_s^f c_w^{(i),j} \left(1 - \frac{b_s^{(1),j} - b_s^{(2),j}}{B_s}\right) + Da_s^r b_s^{(i),j} \\ & - Da_{ns}^f c_w^{(i),j} \left(1 - \frac{b_{ns}^{(1),j} - b_{ns}^{(2),j}}{B_{ns}}\right) + Da_s^r b_{ns}^{(i),j} \qquad j = 2, ..., N_w, \quad i = 1, 2. \end{aligned} \tag{S13}$$

$$\frac{db_s^{(i)}}{dt}\Big|_{r_w^j} \approx Da_s^f c_w^{(i),j} \left(1 - \frac{b_s^{(1),j} - b_s^{(2),j}}{B_s}\right) - Da_s^r b_s^{(i),j}, \qquad j = 1, ..., N_w + 1, \quad i = 1, 2, \tag{S14}$$

$$\frac{db_{ns}^{(i)}}{dt}|_{r_w^j} \approx Da_{ns}^f c_w^{(i),j}\left(1-\frac{b_{ns}^{(1),j}-b_{ns}^{(2),j}}{B_{ns}}\right)-Da_s^r b_{ns}^{(i),j}, \qquad j=1,...,N_w+1, \quad i=1,2. \tag{S15}$$

The derivative boundary conditions (S5) are approximated by a central difference as follows:

$$\frac{c_p^{(i),2}-c_p^{(i),0}}{2\Delta r_p}=0, \quad i=1,2, \tag{S16}$$

where $c_p^{(i),0}$ are fictitious points. This gives rise to the following at r_p^1:

$$\frac{dc_p^{(i)}}{dt}|_{r_p^1} \approx 2\delta^{(i)}\frac{c_p^{(i),2}-c_p^{(i),1}}{\Delta r_p^2}, \quad i=1,2. \tag{S17}$$

At the periadventitial surface, the boundary condition (S6) straightforwardly becomes

$$c_w^{(i),N_w+1}=0, \quad i=1,2. \tag{S18}$$

Deriving the appropriate approximation for the interface conditions (S7-S8) involves considerably more work. Briefly, we employ scheme (S12) at $r_p^{N_p+1}$ and scheme (S13) at r_w^1, which introduces two additional fictitious points for each phase of drug. These fictitious points are eliminated by application of the central difference approximation to (S7) and the condition (S8). After some algebraic manipulation, we arrive at:

$$\frac{dc_p^{(i)}}{dt}|_{r_p^{N_p+1}}=\frac{dc_w^{(i)}}{dt}|_{r_w^1} \quad \approx \quad \Gamma_1 c_p^{(i),N_p}-\Gamma_2 c_p^{(i),N_p+1}+\Gamma_3 c_w^{(i),2}+\Gamma_4\left(Da_s^r b_s^{(i),1}+Da_{ns}^r b_{ns}^{(i),1}\right), \tag{S19}$$

where

$$\begin{aligned}
\Gamma_1 &= \frac{2\delta^{(i)}}{\Delta r_p \Delta r_w}\left[1-\Gamma_4\right],\\
\Gamma_2 &= \frac{2}{\Delta r_w}\left(\frac{\delta^{(i)}}{\Delta r_p}+\frac{Pe}{\alpha}\right)\\
&\quad +\Gamma_4\left(\frac{2}{\Delta r_w}\left(\frac{1-\delta^{(i)}}{\Delta r_p}-\frac{Pe}{\alpha}\right)+Da_s^f\left(1-\frac{b_s^{(1),1}-b_s^{(2),1}}{B_s}\right)+Da_{ns}^f\left(1-\frac{b_{ns}^{(1),1}-b_{ns}^{(2),1}}{B_{ns}}\right)\right),\\
\Gamma_3 &= \frac{2}{\alpha\Delta r_w}-\Gamma_4\left(\frac{2}{\Delta r_w}\left(\frac{1}{\alpha}-1\right)+Pe-\frac{1}{r_w^1}\right),\\
\Gamma_4 &= \frac{2}{\alpha\Delta r_w\left(\frac{2}{\Delta r_p}+Pe+\frac{2}{\alpha\Delta r_w}-\frac{1}{r_w^1}\right)}.
\end{aligned}$$

After spatial discretization, the system of PDEs reduces to a system of nonlinear ordinary differential equations (ODEs) of the form:

$$\frac{d\mathbf{Y}}{dt}=\gamma(\mathbf{Y}), \tag{S20}$$

where $\mathbf{Y}$ is the vector containing all the free and bound concentrations $(c_p^{(i),j},\ c_w^{(i),j},\ b_s^{(i),j},\ b_{ns}^{(i),j})$ and $\gamma(\mathbf{Y})$ contains the discretized equations. The system (S20) is solved by the routine ode15s of Matlab based on a Runge-Kutta type method with backward differentiation formulas, and an adaptive time step [1]. In the final simulations, we chose $N_p = N_W = 150$. A mesh twice as fine resulted in results that were indistinguishable.

One-layer model

We proceed to nondimensionalise the one-layer model equations (15-20) from the main text using the same non-dimensionalisation as with the two-layer model:

$$\bar{r} = \frac{r}{L_w}, \quad \bar{t} = \frac{D_w}{L_w^2}t, \quad \bar{c_w} = \frac{c_w}{C^{(1)}},$$

$$\bar{b_s} = \frac{b_s}{C^{(1)}}, \quad \bar{b_{ns}} = \frac{b_{ns}}{C^{(1)}}, \quad \bar{B_s} = \frac{B_s}{C^{(1)}}, \quad \bar{B_{ns}} = \frac{B_{ns}}{C^{(1)}}.$$

The model becomes (after dropping primes)

$$\begin{aligned}\frac{\partial c_w}{\partial t} &= \frac{\partial^2 c_w}{\partial r^2} + \frac{1}{r}\frac{\partial c_w}{\partial r} - Pe\frac{\partial c_w}{\partial r} \\ &\quad -Da_s^f c_w\left(1 - \frac{b_s}{B_s}\right) + Da_s^r b_s \\ &\quad -Da_{ns}^f c_w\left(1 - \frac{b_{ns}}{B_{ns}}\right) + Da_{ns}^r b_{ns}, \quad L < r < L^+, \quad t > 0,\end{aligned} \tag{S21}$$

$$\frac{\partial b_s}{\partial t} = Da_s^f c_w\left(1 - \frac{b_s}{B_s}\right) - Da_s^r b_s, \quad L < r < L^+, \quad t > 0, \tag{S22}$$

$$\frac{\partial b_{ns}}{\partial t} = Da_{ns}^f c_w\left(1 - \frac{b_{ns}}{B_{ns}}\right) - Da_{ns}^r b_{ns}, \quad L < r < L^+, \quad t > 0, \tag{S23}$$

subject to the following boundary conditions:

$$-\frac{\partial c_w}{\partial r} + Pec_w = K(t), \quad r = L, \quad t > 0, \tag{S24}$$

$$c_w = 0, \quad r = L^+, \quad t > 0, \tag{S25}$$

and initial conditions:

$$c_w = b_s = b_{ns} = 0, \quad L \le r \le L^+, \quad t = 0, \tag{S26}$$

where

$$K(t) = -\frac{\alpha M_0}{AL_w C^{(1)}}\frac{dM(t)}{dt} \tag{S27}$$

is the nondimensional flux of drug entering the arterial wall and $M(t)$ is the nondimensional mass of drug on the stent.

We employ the same numerical approach as with the two-layer model. Equations (S21-S23) and (S25) are discretized in a similar way to the corresponding equations of the two-layer model. To discretize (S24), we employ the scheme associated with (S21) at r_w^1, which introduces a fictitious point. This fictitious point is eliminated by application of a central difference approximation to (S24). We obtain:

$$\begin{aligned}\frac{dc_w}{dt}|_{r_w^1} \approx\ & \frac{2}{\Delta r_w^2}\left(c_w^{j+1} - c_w^j\right) + \left(K(t) - Pec_w^j\right)\left(Pe + \frac{2}{\Delta r_w} - \frac{1}{r_w}\right) \\ & - Da_s^f c_w^j \left(1 - \frac{b_s^j}{B_s}\right) + Da_s^r b_s^j - Da_{ns}^f c_w^j \left(1 - \frac{b_{ns}^j}{B_{ns}}\right) + Da_{ns}^r b_{ns}^j. \quad \text{(S28)}\end{aligned}$$

The solution is obtained by solving the resulting system of ODE's as with the two-layer model. In the final simulations, we chose $N_w = 150$. A mesh twice as fine resulted in results that were indistinguishable.

References

[1] L.F. Shampine and M.W. Reichelt. The matlab ode suite. *SIAM J. Sci. Comput.*, 18:1–22, 1997.