# Recovering Diffusivities and Binding Rates via Uncaging

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## int 1. Introduction

(1) Inject a fluorophore (OGB1) and caged $Ca$. Uncage $Ca$ at site $x_0$ and record the ensuing fluorescence, $f(x_j, t)$.

(2) Legislate the concentration of fluorophore bound calcium to be

$$[CaB](x_j, t) = \mathcal{B}\frac{f(x_j, t) - f_{min}}{f_{max} - f_{min}}$$

(3) Note that $b \equiv [CaB]$ and $c \equiv [Ca^{2+}]$ satisfy

$$b_t = D_b b_{xx} - k_- b + c(\mathcal{B} - b)k_-/K_d \quad (1.1)\text{cab}$$
$$c_t = D_c c_{xx} + k_- b - c(\mathcal{B} - b)k_-/K_d - r(c - c_0) + uF(t)\delta(x - x_0) \quad (1.2)\text{ca}$$

subject to the initial conditions

$$b(x, 0) = b^\sharp(x, 0), \quad c(x, 0) = c_0(x) = K_d\frac{b^\sharp(x, 0)}{\mathcal{B} - b^\sharp(x, 0)}$$

and the end conditions

$$b_x(0, t) = b_x(\ell, t) = c_x(0, t) = c_x(\ell, t) = 0.$$

Our task is to recover $p \equiv \{D_b, D_c, k_-, r, u\}$ from knowledge of $b(x_j, \cdot)$ **and** $K_d = k_-/k_+$.

Let us explicitly track the dependence of of $b$ upon $p$ by writing $b = b(x, t; p)$ and write the IBVP above as $\mathcal{R}([b, c], p) = 0$. Now differentiating

$$\mathcal{R}([b(p), c(p)], p) = 0$$

wrt $p$ reveals

$$\partial_{[b,c]}\mathcal{R}\partial_p[b, c] + \partial_p\mathcal{R} = 0$$

or

$$\partial_p[b(p), c(p)] = -\partial_{[b,c]}\mathcal{R}([b(p), c(p)], p)^{-1}\partial_p\mathcal{R}([b(p), c(p)], p) \quad (1.3)\text{g1}$$

We consider

$$\min_p \Phi(p) \quad (1.4)\text{minp}$$

where $\Phi$ is the misfit function

$$\Phi(p) \equiv \phi([b, c](p)) \equiv \frac{1}{2}\int_0^T\int_0^\ell |b^\sharp(x, t) - b(x, t; p)|^2\, dxdt. \quad (1.5)\text{M}$$

Now

$$\begin{aligned}\nabla\Phi(p) &= \partial_p[b(p), c(p)]^*\partial_{[b,c]}\phi([b(p), c(p)]) \\ &= -\partial_p\mathcal{R}([b(p), c(p)], p)^*\partial_{[b,c]}\mathcal{R}([b(p), c(p)], p)^{-*}\partial_{[b,c]}\phi([b(p), c(p)]) \\ &= -(\partial_p\mathcal{R})^*(\partial_{[b,c]}\mathcal{R})^{-*}\phi' a \\ &= (\partial_p\mathcal{R})^*[y, z]\end{aligned} \quad (1.6)\text{g2}$$

Where $[y, z]$ is the solution to the adjoint system

$$(\partial_{[b,c]}\mathcal{R})[y, z] = \phi'$$

This is somewhat easier to follow if we build the Lagrangian

$$L(p,[b,c],[y,z]) = \phi([b,c]) + \langle \mathcal{R}([b,c],p),[y,z]\rangle$$

for now we note that (1.3) is precisely

$$\partial_{[b,c]} L(p,[b,c],[y,z]) = 0.$$

Now

$$\begin{aligned} L(p,&[b,c],[y,z]) = \phi([b,c]) + \langle \mathcal{R}([b,c],p),[y,z]\rangle \\ &= \frac{1}{2}\int_0^T \int_0^\ell |b^\sharp(x,t) - b(x,t)|^2\,dx\,dt \\ &+ \int_0^T \int_0^\ell \{b_t - p_1 b_{xx} + p_2 b - p_2/K_d c(\mathcal{B}-b)\} y(x,t)\,dx\,dt \\ &+ \int_0^T \int_0^\ell \{c_t - p_3 c_{xx} - p_2 b + p_2/K_d c(\mathcal{B}-b) + p_4(c-c_0) - p_5 F(t)\delta(x-x_N)\} z(x,t)\,dxdt. \end{aligned}$$

The gradient of $L$ with respect to $[b,c]$ in the direction $[\tilde{b},\tilde{c}]$ is

$$\begin{aligned} \langle \partial_{[b,c]} L(p,[b,c],[y,z]),[\tilde{b},\tilde{c}]\rangle &= \lim_{\varepsilon\to 0} \frac{L(p,[b+\varepsilon\tilde{b},c+\varepsilon\tilde{c}],[y,z]) - L(p,[b,c],[y,z])}{\varepsilon} \\ = \int_0^T \int_0^\ell & (b(x,t) - b^\sharp(x,t))\tilde{b}(x,t)\,dx\,dt \\ + \int_0^T \int_0^\ell & \{\tilde{b}_t - p_1\tilde{b}_{xx} + p_2\tilde{b} - p_2/K_d(\tilde{c}(\mathcal{B}-b) - c\tilde{b})\} y(x,t)\,dx\,dt \\ + \int_0^T \int_0^\ell & \{\tilde{c}_t - p_3\tilde{c}_{xx} - p_2\tilde{b} + p_2/K_d(\tilde{c}(\mathcal{B}-b) - c\tilde{b}) + p_4\tilde{c}\} z(x,t)\,dx\,dt. \end{aligned}$$

where, in order that $[b+\varepsilon\tilde{b}, c+\varepsilon\tilde{c}]$ satisfy the same initial and boundary conditions as $[b,c]$, we require

$$\tilde{b}_x(0,t) = \tilde{b}_x(\ell,t) = \tilde{b}(x,0) = \tilde{c}(x,0) = 0.$$

With this we now integrate the double integral by parts and find

$$\begin{aligned} \langle \partial_{[b,c]} L(p,[b,c],[y,z]),[\tilde{b},\tilde{c}]\rangle &= \int_0^T \int_0^\ell (b(x,t) - b^\sharp(x,t))\tilde{b}(x,t)\,dx\,dt \\ + \int_0^\ell y(x,T)\tilde{b}(x,T)\,dx &+ \int_0^\ell z(x,T)\tilde{c}(x,T)\,dx \\ + \int_0^T y_x(0,t)\tilde{b}(0,t) - y_x(\ell,t)\tilde{b}(\ell,t)\,dt &+ \int_0^T z_x(0,t)\tilde{c}(0,t) - z_x(\ell,t)\tilde{c}(\ell,t)\,dt \\ + \int_0^T \int_0^\ell \{-y_t - p_1 y_{xx} &+ p_2(y-z) + p_2/K_d c(y-z)\}\tilde{b}(x,t)\,dx\,dt \\ + \int_0^T \int_0^\ell \{-z_t - p_3 z_{xx} &- p_2/K_d(y-z)(\mathcal{B}-b) + p_4 z\}\tilde{c}(x,t)\,dx\,dt \end{aligned}$$

and arrive at the adjoint system

$$\begin{aligned} -y_t - p_1 y_{xx} + p_2(c/K_d + 1)(y-z) &= -b(x,t) + b^\sharp(x,t) \\ -z_t - p_3 z_{xx} - (p_2/K_d)(y-z)(\mathcal{B}-b) + p_4 z &= 0 \end{aligned} \qquad (1.7)_{\text{yz}}$$

subject to the boundary conditions

$$y_x(0,t) = y_x(\ell,t) = z_x(0,t) = z_x(\ell,t) = 0 \tag{1.8}$$ yzbc

and the final time conditions

$$y(x,T) = z(x,T) = 0. \tag{1.9}$$ yzT

With $[y,z]$ in hand we next pursue

$$\nabla_p L(p,[b,c],[y,z]) = \begin{pmatrix} \int_0^T \int_0^\ell b_x y_x \, dx \, dt \\ \int_0^T \int_0^\ell (b - c(\mathcal{B}-b)/K_d)(y-z) \, dx \, dt \\ \int_0^T \int_0^\ell c_x z_x \, dx \, dt \\ \int_0^T \int_0^\ell (c-c_0) z \, dx \, dt \\ -\int_0^T F(t) z(x_N,t) \, dt \end{pmatrix}$$

Finally, the action of the Hessian onto a given vector $s$ is

$$\nabla^2 \Phi(p) s = (\nabla_p \mathcal{R}(u(p),p))^* \psi - (\nabla_{up} L)\eta \tag{1.10}$$ hmult

where $\eta$ is the solution to

$$\nabla_u \mathcal{R}(u(p),p)\eta = \nabla_p \mathcal{R} s \tag{1.11}$$ eta

and $\psi$ is the solution of

$$(\nabla_u \mathcal{R}(u(p),p))^* \psi = (\nabla_{uu} L)\eta - (\nabla_{up} L) s \tag{1.12}$$ psi

In terms of $\eta = [m,\ n]$, (1.11) takes the form

$$\begin{aligned} m_t - p_1 m_{xx} + p_2 m + (p_2/K_d)(cm + n(b-\mathcal{B})) &= -s_1 b_{xx} - (s_2/K_d)c(\mathcal{B}-b) + s_2 b \\ n_t - p_3 n_{xx} - p_2 m - (p_2/K_d)(cm + n(b-\mathcal{B})) + p_4 n &= -s_3 c_{xx} + (s_2/K_d)c(\mathcal{B}-b) - s_2 b + s_4(c-c_0) - s_5 F\delta \end{aligned}$$

and moving on to (1.12) we note that

$$\nabla_{uu} L = \begin{pmatrix} I & p_2(y-z)/K_d \\ p_2(y-z)/K_d & 0 \end{pmatrix}$$

and

$$\nabla_{up} L = \begin{pmatrix} -y_{xx} & (c/K_d+1)(y-z) & 0 & 0 & 0 \\ 0 & (z-y)(\mathcal{B}-b)/K_d & -z_{xx} & z & 0 \end{pmatrix}$$

and so in terms of $\psi = [q,\ r]$, (1.12) takes the form

$$\begin{aligned} -q_t - p_1 q_{xx} + p_2(c/K_d+1)(q-r) &= m + p_2/K_d n(y-z) + s_1 y_{xx} - s_2(c/K_d+1)(y-z) \\ -r_t - p_3 r_{xx} - p_2/K_d(q-r)(\mathcal{B}-b) + p_4 r &= p_2/K_d m(y-z) + s_3 z_{xx} - s_2/K_d(z-y)(\mathcal{B}-b) - s_4 z \end{aligned}$$

## num 2. Numerics

We solve for $[b,c]$ via CN in time and fem in space. In particular we partition space and time according to

$$[0, h, 2h, \ldots, (N_x-1)h = \ell] \quad \text{and} \quad [0, \tau, 2\tau, \ldots, (N_t-1)\tau = T]$$

and

$$b(x,t) = \sum_{i=1}^{N_x} \mathsf{b}_i(t) H_i(x) \quad \text{and} \quad c(x,t) = \sum_{i=1}^{N_x} \mathsf{c}_i(t) H_i(x)$$

where

$$H_i(x) = \begin{cases} 1 - |x-(i-1)h|/h & \text{if } (i-2)h < x < ih \\ 0 & \text{if otherwise} \end{cases}$$

FEM on the $b$ equation produces

$$\mathtt{Mb}' = p_1\mathtt{Kb} - p_2\mathtt{Mb} + (p_2/K_d)\mathcal{B}\mathtt{Mc} - (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{c})$$

and next

$$\begin{aligned}
\mathtt{Mb}_{:,j+1} - \mathtt{Mb}_{:,j} &= \int_{t_j}^{t_{j+1}} \mathtt{Mb}'(t)\,dt \\
&= \int_{t_j}^{t_{j+1}} (p_1\mathtt{K} - p_2\mathtt{M})\mathtt{b}(t) + (p_2/K_d)\mathcal{B}\mathtt{Mc}(t) - (p_2/K_d)\mathtt{P}(\mathtt{b}(t),\mathtt{c}(t))\,dt \\
&\approx \{(p_1\mathtt{K} - p_2\mathtt{M})\mathtt{b}_{:,j} + (p_2/K_d)\mathcal{B}\mathtt{Mc}_{:,j} - (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j},\mathtt{c}_{:,j}) \\
&\quad + (p_1\mathtt{K} - p_2\mathtt{M})\mathtt{b}_{:,j+1} + (p_2/K_d)\mathcal{B}\mathtt{Mc}_{:,j+1} - (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1},\mathtt{c}_{:,j+1})\}\tau/2
\end{aligned}$$

which yields, under the additional assumption $\mathtt{P}(\mathtt{b}_{:,j},\mathtt{c}_{:,j}) \approx \mathtt{P}(\mathtt{b}_{:,j+1},\mathtt{c}_{:,j+1})$,

$$((2/\tau + p_2)\mathtt{M} - p_1\mathtt{K})\mathtt{b}_{:,j+1} - (p_2/K_d)\mathcal{B}\mathtt{Mc}_{:,j+1} = (p_1\mathtt{K} - (p_2 - 2/\tau)\mathtt{M})\mathtt{b}_{:,j} + (p_2/K_d)\mathcal{B}\mathtt{Mc}_{:,j} - 2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j},\mathtt{c}_{:,j})$$

where $\mathtt{M}$ and $\mathtt{K}$ are the symmetric tridiagonal matrices

$$\begin{aligned}
\mathtt{M}(i,i+1) &= \frac{h}{6} \qquad \mathtt{M}(i,i) = \frac{h}{6}\begin{cases} 2 & \text{if } i=1 \quad \text{or} \quad i=N_x \\ 4 & \text{otherwise} \end{cases} \\
\mathtt{K}(i,i+1) &= -\frac{1}{h} \qquad \mathtt{K}(i,i) = \frac{1}{h}\begin{cases} 1 & \text{if } i=1 \quad \text{or} \quad i=N_x \\ 2 & \text{otherwise} \end{cases}
\end{aligned}$$

and $\mathtt{P}$ is the product term

$$\begin{aligned}
\mathtt{P}_i &= \int_0^{\ell} c(x)b(x)H_i(x)\,dx \\
&= \frac{h}{12}\begin{cases} 3c_1b_1 + c_1b_2 + c_2b_1 + c_2b_2 & \text{if } i=1 \\ \mathtt{c}_{i-1}\mathtt{b}_{i-1} + (\mathtt{c}_{i-1} + 6\mathtt{c}_i + \mathtt{c}_{i+1})\mathtt{b}_i + \mathtt{c}_i(\mathtt{b}_{i-1} + \mathtt{b}_{i+1}) + \mathtt{c}_{i+1}\mathtt{b}_{i+1} & \text{if } 1 < i < N_x \\ 3c_{N_x}b_{N_x} + c_{N_x}b_{N_x-1} + c_{N_x-1}b_{N_x} + c_{N_x-1}b_{N_x-1} & \text{if } i = N_x \end{cases}
\end{aligned}$$

Next, FEM on the $c$ equation produces

$$\mathtt{Mc}' = p_3\mathtt{Kc} + p_2\mathtt{Mb} - (p_2/K_d)\mathcal{B}\mathtt{Mc} + (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{c}) - p_4\mathtt{M}(\mathtt{c} - \mathtt{c}_0) + p_5F(t)\mathtt{e}_N$$

where $\mathtt{e}_N$ is the vector of zeros save a 1 in the $N$th slot and hence

$$\begin{aligned}
\mathtt{Mc}_{:,j+1} - \mathtt{Mc}_{:,j} &= \int_{t_j}^{t_{j+1}} (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{c} + p_2\mathtt{Mb} + (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{c}) + p_4\mathtt{Mc}_0 + p_5F(t)\mathtt{e}_N\,dt \\
&= \tau p_4\mathtt{Mc}_0 + \{(p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{c}_{:,j} + p_2\mathtt{Mb}_{:,j} + (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j},\mathtt{c}_{:,j}) + p_5F_j \\
&\quad + (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{c}_{:,j+1} + p_2\mathtt{Mb}_{:,j+1} + (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1},\mathtt{c}_{:,j+1}) + p_5F_{j+1})\}\tau/2
\end{aligned}$$

or

$$\begin{aligned}
((2/\tau + (p_2/K_d)\mathcal{B} + p_4)\mathtt{M} - p_3\mathtt{K})\mathtt{c}_{:,j+1} - p_2\mathtt{Mb}_{:,j+1} &= (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4 - 2/\tau)\mathtt{M})\mathtt{c}_{:,j} + p_2\mathtt{Mb}_{:,j} + \\
&\quad 2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j},\mathtt{c}_{:,j}) + 2p_4\mathtt{Mc}_0 + p_5(F_{j+1} + F_j)\mathtt{e}_N
\end{aligned}$$

and so the $[b, c]$ system takes the form

$$\begin{aligned}
&\begin{pmatrix} (p_2 + 2/\tau)\mathtt{M} - p_1\mathtt{K} & -(p_2/K_d)\mathcal{B}\mathtt{M} \\ -p_2\mathtt{M} & ((p_2/K_d)\mathcal{B} + p_4 + 2/\tau)\mathtt{M} - p_3\mathtt{K} \end{pmatrix} \begin{pmatrix} \mathtt{b}_{:,j+1} \\ \mathtt{c}_{:,j+1} \end{pmatrix} \\
&\quad = \begin{pmatrix} p_1\mathtt{K} - (p_2 - 2/\tau)\mathtt{M} & (p_2/K_d)\mathcal{B}\mathtt{M} \\ p_2\mathtt{M} & p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4 - 2/\tau)\mathtt{M} \end{pmatrix} \begin{pmatrix} \mathtt{b}_{:,j} \\ \mathtt{c}_{:,j} \end{pmatrix} \\
&\qquad + \begin{pmatrix} -2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j}, \mathtt{c}_{:,j}) \\ 2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j}, \mathtt{c}_{:,j}) + 2p_4\mathtt{M}\mathtt{c}_0 + p_5(F_{j+1} + F_j)\mathtt{e}_N \end{pmatrix}
\end{aligned}$$

Next, FEM on the $y$ equation produces

$$-\mathtt{M}\mathtt{y}' = p_1\mathtt{K}\mathtt{y} - p_2\mathtt{M}\mathtt{y} + p_2\mathtt{M}\mathtt{z} - (p_2/K_d)\mathtt{P}(\mathtt{c}, \mathtt{y} - \mathtt{z}) + \mathtt{M}(\mathtt{b}^\sharp - \mathtt{b})$$

and so

$$\begin{aligned}
\mathtt{M}\mathtt{y}_{:,j} - \mathtt{M}\mathtt{y}_{:,j+1} &= -\int_{t_j}^{t_{j+1}} \mathtt{M}\mathtt{y}'\,dt \\
&= \int_{t_j}^{t_{j+1}} (p_1\mathtt{K} - p_2\mathtt{M})\mathtt{y} + p_2\mathtt{M}\mathtt{z} - (p_2/K_d)\mathtt{P}(\mathtt{c}, \mathtt{y} - \mathtt{z}) + \mathtt{M}(\mathtt{b}^\sharp - \mathtt{b})\,dt \\
&\approx \{(p_1\mathtt{K} - p_2\mathtt{M})(\mathtt{y}_{:,j} + \mathtt{y}_{:,j+1}) + p_2\mathtt{M}(\mathtt{z}_{:,j} + \mathtt{z}_{:,j+1}) \\
&\quad + \mathtt{M}(\mathtt{b}^\sharp_{:,j} - \mathtt{b}_{:,j} + \mathtt{b}^\sharp_{:,j+1} - \mathtt{b}_{:,j+1})\}\tau/2 - \tau(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1})
\end{aligned}$$

and so

$$\begin{aligned}
((2/\tau + p_2)\mathtt{M} - p_1\mathtt{K})\mathtt{y}_{:,j} - p_2\mathtt{M}\mathtt{z}_{:,j} &= (p_1\mathtt{K} - (p_2 - 2/\tau)\mathtt{M})\mathtt{y}_{:,j+1} + p_2\mathtt{M}\mathtt{z}_{:,j+1} \\
&\quad + \mathtt{M}(\mathtt{b}^\sharp_{:,j} - \mathtt{b}_{:,j} + \mathtt{b}^\sharp_{:,j+1} - \mathtt{b}_{:,j+1}) - 2(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1})
\end{aligned}$$

Next, FEM on the $z$ equation produces

$$-\mathtt{M}\mathtt{z}' = (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{z} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{y} - (p_2/K_d)\mathtt{P}(\mathtt{b}, \mathtt{y} - \mathtt{z})$$

and so

$$\begin{aligned}
\mathtt{M}\mathtt{z}_{:,j} - \mathtt{M}\mathtt{z}_{:,j+1} &= \int_{t_j}^{t_{j+1}} (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{z} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{y} - (p_2/K_d)\mathtt{P}(\mathtt{b}, \mathtt{y} - \mathtt{z})\,dt \\
&\approx \{(p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})(\mathtt{z}_{:,j} + \mathtt{z}_{:,j+1}) + (p_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{y}_{:,j} + \mathtt{y}_{:,j+1})\}\tau/2 \\
&\quad - \tau(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1})
\end{aligned}$$

and so

$$\begin{aligned}
((2/\tau + (p_2/K_d)\mathcal{B} + p_4)\mathtt{M} - p_3\mathtt{K})\mathtt{z}_{:,j} - (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{y}_{:,j} &= (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4 - 2/\tau)\mathtt{M})\mathtt{z}_{:,j+1} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{y}_{:,j+1} \\
&\quad - 2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1})
\end{aligned}$$

and so the $[y, z]$ system takes the form

$$\begin{aligned}
&\begin{pmatrix} (p_2 + 2/\tau)\mathtt{M} - p_1\mathtt{K} & -p_2\mathtt{M} \\ -(p_2/K_d)\mathcal{B}\mathtt{M} & ((p_2/K_d)\mathcal{B} + p_4 + 2/\tau)\mathtt{M} - p_3\mathtt{K} \end{pmatrix} \begin{pmatrix} \mathtt{y}_{:,j} \\ \mathtt{z}_{:,j} \end{pmatrix} \\
&\quad = \begin{pmatrix} p_1\mathtt{K} - (p_2 - 2/\tau)\mathtt{M} & p_2\mathtt{M} \\ (p_2/K_d)\mathcal{B}\mathtt{M} & p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4 - 2/\tau)\mathtt{M} \end{pmatrix} \begin{pmatrix} \mathtt{y}_{:,j+1} \\ \mathtt{z}_{:,j+1} \end{pmatrix} \\
&\qquad + \begin{pmatrix} \mathtt{M}(\mathtt{b}^\sharp_{:,j} - \mathtt{b}_{:,j} + \mathtt{b}^\sharp_{:,j+1} - \mathtt{b}_{:,j+1}) - 2(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1}) \\ -2(p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1}, \mathtt{y}_{:,j+1} - \mathtt{z}_{:,j+1}) \end{pmatrix}
\end{aligned}$$

Finally, the gradient requires computation of

$$\int_0^T \int_0^\ell b_x(x,t) y_x(x,t)\,dx\,dt = (\tau/h) \sum_{j=1}^{N_j} \langle \mathtt{diff}(\mathtt{b}_{:,j}), \mathtt{diff}(\mathtt{y}_{:,j}) \rangle$$

Next, FEM on the $m$ equation produces

$$\mathtt{M}\mathtt{m}' = p_1\mathtt{K}\mathtt{m} - p_2\mathtt{M}\mathtt{m} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{n} - (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{m}) - (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{n}) - s_1\mathtt{K}\mathtt{b} - (s_2/K_d)\mathcal{B}\mathtt{M}\mathtt{c} + (s_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{b}) + s_2\mathtt{M}\mathtt{b}$$

and so

$$\begin{aligned}
\mathtt{M}\mathtt{m}_{:,j+1} - \mathtt{M}\mathtt{m}_{:,j} &= \int_{t_j}^{t_{j+1}} \{(p_1\mathtt{K} - p_2\mathtt{M})\mathtt{m} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{n} - (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{m}) - (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{n}) \\
&\qquad - (s_2/K_d)\mathcal{B}\mathtt{M}\mathtt{c} + (s_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{b}) + (s_2\mathtt{M} - s_1\mathtt{K})\mathtt{b}\}\,dt \\
&\approx \{(p_1\mathtt{K} - p_2\mathtt{M})(\mathtt{m}_{:,j} + \mathtt{m}_{:,j+1}) + (p_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{n}_{:,j} + \mathtt{n}_{:,j+1}) \\
&\quad - (p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}, \mathtt{m}_{:,j}) - (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1} + \mathtt{b}_{:,j}, \mathtt{n}_{:,j}) \\
&\quad - (s_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}) + (s_2/K_d)(\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{b}_{:,j+1}) + \mathtt{P}(\mathtt{c}_{:,j}, \mathtt{b}_{:,j})) \\
&\quad + (s_2\mathtt{M} - s_1\mathtt{K})(\mathtt{b}_{:,j} + \mathtt{b}_{:,j+1})\}\tau/2
\end{aligned}$$

and so

$$((2/\tau + p_2)\mathtt{M} - p_1\mathtt{K})\mathtt{m}_{:,j+1} - (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{n}_{:,j+1} = (p_1\mathtt{K} - (p_2 - 2/\tau)\mathtt{M})\mathtt{m}_{:,j} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{n}_{:,j} + \mathtt{G}_j$$

where

$$\begin{aligned}
\mathtt{G}_j \equiv &-(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}, \mathtt{m}_{:,j}) - (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1} + \mathtt{b}_{:,j}, \mathtt{n}_{:,j}) \\
&- (s_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}) + (s_2/K_d)(\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{b}_{:,j+1}) + \mathtt{P}(\mathtt{c}_{:,j}, \mathtt{b}_{:,j})) \\
&+ (s_2\mathtt{M} - s_1\mathtt{K})(\mathtt{b}_{:,j} + \mathtt{b}_{:,j+1})
\end{aligned}$$

Next, FEM on the $n$ equation produces

$$\begin{aligned}
\mathtt{M}\mathtt{n}' = &\, p_3\mathtt{K}\mathtt{n} + p_2\mathtt{M}\mathtt{m} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M}\mathtt{n} + (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{m}) + (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{n}) \\
&+ (((s_2/K_d)\mathcal{B} + s_4)\mathtt{M} - s_3\mathtt{K})\mathtt{c} - (s_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{b}) - s_2\mathtt{M}\mathtt{b} - s_4\mathtt{M}\mathtt{c}_0 - s_5\mathtt{F}\mathtt{e}_N
\end{aligned}$$

and so

$$\begin{aligned}
\mathtt{M}\mathtt{n}_{:,j+1} - \mathtt{M}\mathtt{n}_{:,j} &= \int_{t_j}^{t_{j+1}} \{(p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})\mathtt{n} + p_2\mathtt{M}\mathtt{m} + (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{m}) + (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{n}) \\
&\qquad + (((s_2/K_d)\mathcal{B} + s_4)\mathtt{M} - s_3\mathtt{K})\mathtt{c} - (s_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{b}) - s_2\mathtt{M}\mathtt{b} - s_5\mathtt{F}\mathtt{e}_N\}\,dt - \tau s_4\mathtt{M}\mathtt{c}_0 \\
&\approx \{(p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4)\mathtt{M})(\mathtt{n}_{:,j} + \mathtt{n}_{:,j+1}) + p_2\mathtt{M}(\mathtt{m}_{:,j} + \mathtt{m}_{:,j+1}) \\
&\quad + (p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}, \mathtt{m}_{:,j}) + (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1} + \mathtt{b}_{:,j}, \mathtt{n}_{:,j}) \\
&\quad + (((s_2/K_d)\mathcal{B} + p_4)\mathtt{M} - s_3\mathtt{K})(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}) - (s_2/K_d)(\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{b}_{:,j+1}) + \mathtt{P}(\mathtt{c}_{:,j}, \mathtt{b}_{:,j})) \\
&\quad - s_2\mathtt{M}(\mathtt{b}_{:,j} + \mathtt{b}_{:,j+1}) - s_5(\mathtt{F}_{j+1} + \mathtt{F}_j)\mathtt{e}_N\}\tau/2 - \tau s_4\mathtt{M}\mathtt{c}_0
\end{aligned}$$

and so

$$((2/\tau + (p_2/K_d)\mathcal{B} + p_4)\mathtt{M} - p_3\mathtt{K})\mathtt{n}_{:,j+1} - p_2\mathtt{M}\mathtt{m}_{:,j+1} = (p_3\mathtt{K} - ((p_2/K_d)\mathcal{B} + p_4 - 2/\tau)\mathtt{M})\mathtt{n}_{:,j} + p_2\mathtt{M}\mathtt{m}_{:,j} + \mathtt{J}_j$$

where

$$\begin{aligned}
\mathtt{J}_j \equiv &\,(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j+1} + \mathtt{c}_{:,j}, \mathtt{m}_{:,j}) + (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j+1} + \mathtt{b}_{:,j}, \mathtt{n}_{:,j}) \\
&- s_2\mathcal{B}\mathtt{M}(\mathtt{b}_{:,j+1} + \mathtt{b}_{:,j}) - (s_2/K_d)(\mathtt{P}(\mathtt{c}_{:,j+1}, \mathtt{b}_{:,j+1}) + \mathtt{P}(\mathtt{c}_{:,j}, \mathtt{b}_{:,j})) \\
&+ (((s_2/K_d)\mathcal{B} + p_4)\mathtt{M} - s_3\mathtt{K})(\mathtt{c}_{:,j} + \mathtt{c}_{:,j+1}) - s_5(\mathtt{F}_{j+1} + \mathtt{F}_j)\mathtt{e}_N - 2s_4\mathtt{M}\mathtt{c}_0
\end{aligned}$$

And so the $[m,n]$ system takes the form

$$\begin{pmatrix} (p_2+2/\tau)\mathtt{M}-p_1\mathtt{K} & -(p_2/K_d)\mathcal{B}\mathtt{M} \\ -p_2\mathtt{M} & ((p_2/K_d)\mathcal{B}+p_4+2/\tau)\mathtt{M}-p_3\mathtt{K} \end{pmatrix} \begin{pmatrix} \mathtt{m}_{:,j+1} \\ \mathtt{n}_{:,j+1} \end{pmatrix}$$
$$= \begin{pmatrix} p_1\mathtt{K}-(p_2-2/\tau)\mathtt{M} & (p_2/K_d)\mathcal{B}\mathtt{M} \\ p_2\mathtt{M} & p_3\mathtt{K}-((p_2/K_d)\mathcal{B}+p_4-2/\tau)\mathtt{M} \end{pmatrix} \begin{pmatrix} \mathtt{m}_{:,j} \\ \mathtt{n}_{:,j} \end{pmatrix} + \begin{pmatrix} \mathtt{G}_j \\ \mathtt{J}_j \end{pmatrix}$$

And so finally, FEM on the $q$ equation brings

$$\begin{aligned} -\mathtt{M}\mathtt{q}' &= p_1\mathtt{K}\mathtt{q} - (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{q}-\mathtt{r}) - p_2\mathtt{M}(\mathtt{q}-\mathtt{r}) \\ &\quad + \mathtt{M}\mathtt{m} + \mathtt{P}((p_2/K_d)\mathtt{n}-(s_2/K_d)\mathtt{c},\mathtt{y}-\mathtt{z}) - (s_2\mathtt{M}-s_1\mathtt{K})\mathtt{y} + s_2\mathtt{M}\mathtt{z} \end{aligned}$$

and so

$$\begin{aligned} \mathtt{M}(\mathtt{q}_{:,j}-\mathtt{q}_{:,j+1}) &= \int_{t_j}^{t_{j+1}} \{(p_1\mathtt{K}-p_2\mathtt{M})\mathtt{q} + p_2\mathtt{M}\mathtt{r} - (p_2/K_d)\mathtt{P}(\mathtt{c},\mathtt{q}-\mathtt{r}) \\ &\qquad + \mathtt{M}\mathtt{m} + \mathtt{P}((p_2/K_d)\mathtt{n}-(s_2/K_d)\mathtt{c},\mathtt{y}-\mathtt{z}) - (s_2\mathtt{M}-s_1\mathtt{K})\mathtt{y} + s_2\mathtt{M}\mathtt{z}\}\,dt \\ &\approx \{(p_1\mathtt{K}-p_2\mathtt{M})(\mathtt{q}_{:,j}+\mathtt{q}_{:,j+1}) + p_2\mathtt{M}(\mathtt{r}_{:,j}+\mathtt{r}_{:,j+1}) + \mathtt{Q}_j\}(\tau/2) \end{aligned}$$

where

$$\begin{aligned} \mathtt{Q}_j \equiv &-(p_2/K_d)\mathtt{P}(\mathtt{c}_{:,j}+\mathtt{c}_{:,j+1},\mathtt{q}_{:,j}-\mathtt{r}_{:,j}) + \mathtt{M}(\mathtt{m}_{:,j}+\mathtt{m}_{:,j+1}) \\ &+ \mathtt{P}((p_2/K_d)\mathtt{n}_{:,j}-(s_2/K_d)\mathtt{c}_{:,j},\mathtt{y}_{:,j}-\mathtt{z}_{:,j}) + \mathtt{P}((p_2/K_d)\mathtt{n}_{:,j+1}-(s_2/K_d)\mathtt{c}_{:,j+1},\mathtt{y}_{:,j+1}-\mathtt{z}_{:,j+1}) \\ &- (s_2\mathtt{M}-s_1\mathtt{K})(\mathtt{y}_{:,j}+\mathtt{y}_{:,j+1}) + s_2\mathtt{M}(\mathtt{z}_{:,j}+\mathtt{z}_{:,j+1}) \end{aligned}$$

and so

$$((2/\tau+p_2)\mathtt{M}-p_1\mathtt{K}))\mathtt{q}_{:,j} - p_2\mathtt{M}\mathtt{r}_{:,j} = (p_1\mathtt{K}-(p_2-2/\tau)\mathtt{M})\mathtt{q}_{:,j+1} + p_2\mathtt{M}\mathtt{r}_{:,j+1} + \mathtt{Q}_j.$$

FEM on the $r$ equation brings

$$\begin{aligned} -\mathtt{M}\mathtt{r}' &= p_3\mathtt{K}\mathtt{r} - (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{q}-\mathtt{r}) + (p_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{q}-\mathtt{r}) \\ &\quad - p_4\mathtt{M}\mathtt{r} + \mathtt{P}((p_2/K_d)\mathtt{m}-(s_2/K_d)\mathtt{b},\mathtt{y}-\mathtt{z}) + s_3\mathtt{K}\mathtt{z} + (s_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{y}-\mathtt{z}) - s_4\mathtt{M}\mathtt{z} \end{aligned}$$

and so

$$\begin{aligned} \mathtt{M}(\mathtt{r}_{:,j}-\mathtt{r}_{:,j+1}) &= \int_{t_j}^{t_{j+1}} \{(p_3\mathtt{K}-((p_2/K_d)\mathcal{B}+p_4)\mathtt{M})\mathtt{r} + (p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{q} + \mathtt{P}((p_2/K_d)\mathtt{m}-(s_2/K_d)\mathtt{b},\mathtt{y}-\mathtt{z}) \\ &\qquad - (p_2/K_d)\mathtt{P}(\mathtt{b},\mathtt{q}-\mathtt{r}) + s_3\mathtt{K}\mathtt{z} + (s_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{y}-\mathtt{z}) - s_4\mathtt{M}\mathtt{z}\}\,dt \\ &\approx \{(p_3\mathtt{K}-((p_2/K_d)\mathcal{B}+p_4)\mathtt{M})(\mathtt{r}_{:,j}+\mathtt{r}_{:,j+1}) + (p_2/K_d)\mathcal{B}\mathtt{M}(\mathtt{q}_{:,j}+\mathtt{q}_{:,j+1}) + \mathtt{R}_j\}\tau/2 \end{aligned}$$

where

$$\begin{aligned} \mathtt{R}_j \equiv\ &\mathtt{P}((p_2/K_d)\mathtt{m}_{:,j}-(s_2/K_d)\mathtt{b}_{:,j},\mathtt{y}_{:,j}-\mathtt{z}_{:,j}) + \mathtt{P}((p_2/K_d)\mathtt{m}_{:,j+1}-(s_2/K_d)\mathtt{b}_{:,j+1},\mathtt{y}_{:,j+1}-\mathtt{z}_{:,j+1}) \\ &- (p_2/K_d)\mathtt{P}(\mathtt{b}_{:,j}+\mathtt{b}_{:,j+1},\mathtt{q}_{:,j}-\mathtt{r}_{:,j}) \\ &- (s_4\mathtt{M}-s_3\mathtt{K})(\mathtt{z}_{:,j}+\mathtt{z}_{:,j+1}) + (s_2/K_d)\mathcal{B}\mathtt{M}((\mathtt{y}_{:,j}+\mathtt{y}_{:,j+1}-\mathtt{z}_{:,j}-\mathtt{z}_{:,j+1}) \end{aligned}$$

and so

$$((2/\tau+(p_2/K_d)\mathcal{B}+p_4)\mathtt{M}-p_3\mathtt{K}))\mathtt{r}_{:,j}-(p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{q}_{:,j} = (p_3\mathtt{K}-((p_2/K_d)\mathcal{B}+p_4-2/\tau)\mathtt{M})\mathtt{r}_{:,j+1}+(p_2/K_d)\mathcal{B}\mathtt{M}\mathtt{q}_{:,j+1}+\mathtt{R}_j.$$

and so the $[q,r]$ system takes the form

$$\begin{pmatrix} (p_2+2/\tau)\mathtt{M}-p_1\mathtt{K} & -p_2\mathtt{M} \\ -(p_2/K_d)\mathcal{B}\mathtt{M} & ((p_2/K_d)\mathcal{B}+p_4+2/\tau)\mathtt{M}-p_3\mathtt{K} \end{pmatrix} \begin{pmatrix} \mathtt{q}_{:,j} \\ \mathtt{r}_{:,j} \end{pmatrix}$$
$$= \begin{pmatrix} p_1\mathtt{K}-(p_2-2/\tau)\mathtt{M} & p_2\mathtt{M} \\ (p_2/K_d)\mathcal{B}\mathtt{M} & p_3\mathtt{K}-((p_2/K_d)\mathcal{B}+p_4-2/\tau)\mathtt{M} \end{pmatrix} \begin{pmatrix} \mathtt{q}_{:,j+1} \\ \mathtt{r}_{:,j+1} \end{pmatrix} + \begin{pmatrix} \mathtt{Q}_j \\ \mathtt{R}_j \end{pmatrix}$$

We now assemble

$$(\nabla_{pu}L)\eta = \begin{pmatrix} \int_0^T \int_0^\ell y_x m_x \, dx \, dt \\ \int_0^T \int_0^\ell (y-z)((c/K_d+1)m - n(\mathcal{B}-b)/K_d) \, dx \, dt \\ \int_0^T \int_0^\ell z_x n_x \, dx \, dt \\ \int_0^T \int_0^\ell zn \, dx \, dt \\ 0 \end{pmatrix}$$

and

$$\begin{aligned}(\nabla_p \mathcal{R})^* \psi &= \begin{pmatrix} -b_{xx} & b - c(\mathcal{B}-b)/K_d & 0 & 0 & 0 \\ 0 & c(\mathcal{B}-b)/K_d - b & -c_{xx} & c - c_0 & -F\delta \end{pmatrix}^* \begin{pmatrix} q \\ r \end{pmatrix} \\ &= \begin{pmatrix} \int_0^T \int_0^\ell b_x q_x \, dx \, dt \\ \int_0^T \int_0^\ell (r-q)(c(\mathcal{B}-b)/K_d - b) \, dx \, dt \\ \int_0^T \int_0^\ell c_x r_x \, dx \, dt \\ \int_0^T \int_0^\ell (c-c_0) r \, dx \, dt \\ -\int_0^T F(t) r(x_N, t) \, dt \end{pmatrix}\end{aligned}$$