

Supporting Information

Coupled metal partitioning dynamics and toxicodynamics at biointerfaces: a theory beyond the Biotic Ligand Model framework.

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N.B. Unless otherwise specified, all symbols are defined in the main text (see glossary therein). References are reported at the end of this document.

I. Detailed derivations of eqns (10), (13)-(14).

Starting from the metal concentration profile given by eqns (7)-(8), the spatial integral involved at the left hand side of the mass balance eqn (6) can be written in the form¹

$$\int_{a(t)}^{r_c(t)} \xi^2 c_M(\xi, t) d\xi = -a(t)^2 \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \left[\Omega_1(t) c_M^*(t) + 2\beta_a^{-1} \Omega_2(t) c_M^a(t) \right], \quad (S1)$$

where $\Omega_{1,2}(t)$ are functions that depend here on time t according to²

$$\Omega_1(t) = - \left[G_{r_o(t), r_c(t)} - \left(1 - \varepsilon^{-1} \frac{f_{el}(t)}{f_{el, in}(t)} \right) \frac{H_{r_o(t), r_c(t)}^{r_c(t)}}{F_{r_o(t), r_c(t)}} - H_{a(t), r_o(t)}^{a(t)} a(t) \varepsilon^{-1} f_{el}(t) \right] / \left[a(t)^2 \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \right], \quad (S2)$$

$$\Omega_2(t) = - \left[\Omega_1(t) + G_{a(t), r_c(t)} / \left(a(t)^2 \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \right) \right] / 2. \quad (S3)$$

Using eqns (S1) and (S3), eqn (6) then becomes

$$X(t) \left\{ -\Delta_1(t) \bar{c}_M^*(t) + \beta_a^{-1} \bar{c}_M^a(t) \left[G_{a(t), r_c(t)} + \Delta_1(t) \right] \right\} - \sigma_0 =$$

$$-\frac{a_0^2}{c_M^*} \left\{ \int_0^t [J_u(\xi) - k_e \phi_u(\xi)] \bar{a}(\xi)^2 X(\xi) d\xi + \bar{a}(t)^2 X(t) \Gamma(t) \right\} \quad (S4)$$

where $\sigma_0 = \left[\int_{a_0}^{r_c^0} \xi^2 c_M(\xi, 0) d\xi + a_0^2 \Gamma(0) \right] / c_M^*$ is a scalar independent of t and the function $\Delta_1(t)$ is defined

by $\Delta_1(t) = \left[a(t)^2 \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \right] \Omega_1(t)$, which is eqn (11) in the main text. Equation (S4) identifies with eqn

(10) and after straightforward arrangements, we get

$$-\frac{X(t) \Delta_1(t)}{G_{a_0, r_c^0}} \Delta \bar{c}(t) + \frac{X(t) G_{a(t), r_c(t)}}{G_{a_0, r_c^0}} \bar{c}_M^a(t) - \frac{\beta_a \sigma_0}{G_{a_0, r_c^0}} = -\frac{\beta_a a_0^2}{c_M^* G_{a_0, r_c^0}} \left\{ \int_0^t [J_u(\xi) - k_e \phi_u(\xi)] \bar{a}(\xi)^2 X(\xi) d\xi + \bar{a}(t)^2 X(t) \Gamma(t) \right\}, \quad (S5)$$

where we introduced $\Delta \bar{c}(t) \equiv \beta_a \bar{c}_M^*(t) - \bar{c}_M^a(t)$. For the situations of interest in this work, the potential may be taken constant inside the soft surface layer and zero outside, and the ratio $r_c(t)/r_o(t)$ remains much larger than unity for steady state metal transport conditions to apply. In turn, using eqn (12) and the result $f_{el,in}(t) = \beta_a (1 - \alpha(t))^{-1}$ with $\alpha(t) = a(t)/r_o(t)$, the Taylor expansion of $\Delta_1(t)$ up to the leading order terms $a(t)/r_c(t)$ and $r_o(t)/r_c(t)$ provides

$$\Delta_1(t) \approx \frac{r_c(t)^3}{3} \left[-1 + \frac{r_o(t)}{2r_c(t)} \left(1 + \frac{\alpha(t) - 1}{1 + \alpha(t)(\varepsilon \beta_a - 1)} \right) \right]. \quad (S6)$$

To further proceed, it is useful to realize that $X(t) = N(t)/N_0$ is equivalently defined by

$$X(t) = (r_c^0)^3 / r_c(t)^3, \quad (S7)$$

which simply originates from the definition of the Kuwabara unit cell radius $r_c(t) = [4\pi N(t)/3V_T]^{-1/3}$. In

addition, the ratio $r_o(t)/r_c(t) = (r_o(t)/r_o^0)(r_o^0/r_c^0)(r_c^0/r_c(t))$ may be rewritten in the form

$$r_o(t)/r_c(t) = \frac{\varphi_0^{1/3}}{1 + d/a_0} (\bar{a}(t) + d/a_0) X(t)^{1/3}, \quad (S8)$$

where we used eqn (S7) and the definition of the initial cell volume fraction

$\varphi_0 = 4\pi (r_o^0)^3 N_0 / 3V_T = (r_o^0/r_c^0)^3$. Using eqns (S6)-(S8) and the result $G_{a_0, r_c^0} = (4\pi)^{-1} \beta_a V_{soft}^0 + (r_c^0)^3 / 3$

with $V_{\text{soft}}^0 = 4\pi[(a_0 + d)^3 - a_0^3]/3$ the initial volume of the soft surface layer, the quantity $X(t)\Delta_1(t)/G_{a_0, r_c^0}$ involved in eqn (S5) becomes for $r_0(t)/r_c(t) \ll 1$

$$\frac{X(t)\Delta_1(t)}{G_{a_0, r_c^0}} \approx \bar{V} \left(-1 + \frac{\varphi_0^{1/3}}{2(1+d/a_0)} (\bar{a}(t) + d/a_0) \rho(t) X(t)^{1/3} \right), \quad (\text{S9})$$

where we introduced $\rho(t) = 1 + \frac{\alpha(t) - 1}{1 + \alpha(t)(\varepsilon\beta_a - 1)}$ and $\bar{V} = V_f^0 / (\beta_a V_{\text{soft}}^0 + V_f^0)$ with $V_f^0 = 4\pi(r_c^0)^3/3$ the volume of the Kuwabara unit cell at $t=0$. The ratio $G_{a(t), r_c(t)} / G_{a_0, r_c^0}$ involved in eqn (S5) may be further arranged in the form³

$$\frac{G_{a(t), r_c(t)}}{G_{a_0, r_c^0}} = 1 + \bar{V} \left(\frac{1}{X(t)} - 1 \right) + \frac{V_{\text{soft}}(t) - V_{\text{soft}}^0}{V_{\text{soft}}^0 + V_f^0 / \beta_a} \approx 1 + \bar{V} \left(\frac{1}{X(t)} - 1 \right), \quad (\text{S10})$$

where $V_{\text{soft}}(t)$ is the volume of the surrounding soft surface layer at t . The second equality in eqn (S10) is easily verified for dilute dispersions of microorganisms for which the thickness of the soft surface layer d (~ 0 -100 nm) is generally much lower than the cell radius $a(t)$ (μm scale or above), so that, in turn, changes in soft surface layer volume over time can be reasonably discarded, *i.e.* $\frac{V_{\text{soft}}(t) - V_{\text{soft}}^0}{V_{\text{soft}}^0 + V_f^0 / \beta_a} \rightarrow 0$. Finally,

considering the metal membrane transfer time scale defined by $\tau_L^0 = R_s G_{a_0, r_c^0} / a_0^2$ with

$R_s = 1 / \left(\sum_{j=1}^{N_{s,u}} K_{H,u}^{(j)} k_{\text{int}}^{(j)} \beta_a \right)$ the resistance associated with this membrane transfer process, we obtain

$$\frac{a_0^2}{c_M^* G_{a_0, r_c^0}} = \frac{1}{\tau_L^0 \sum_{j=1}^{N_{s,u}} J_u^{(j)} / A_{s,u}^{(j)}}, \quad (\text{S11})$$

where we used the dimensionless metal affinity $A_{s,u}^{(j)} = K_{s,u}^{(j)} / (\beta_a c_M^*)$ for the j -th type of internalization sites S_u and the relationship $J_u^{*(j)} = k_{\text{int}}^{(j)} K_{H,u}^{(j)} K_{s,u}^{(j)}$. After substitution of eqns (S9)-(S11) into eqn (S5), we finally get

$$\bar{V} \left\{ 1 - \frac{\varphi_0^{1/3}}{2(1+d/a_0)} (\bar{a}(t) + d/a_0) \rho(t) X(t)^{1/3} \right\} \Delta \bar{c}(t) + \{ X(t)(1 - \bar{V}) + \bar{V} \} \bar{c}_M^a(t) - \frac{\beta_a \sigma_0}{G_{a_0, r_c^0}} =$$

$$-\frac{\beta_a}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^*(j)}{A_{s,u}^{(j)}}} \left\{ \int_0^t [J_u(\xi) - k_e \phi_u(\xi)] \bar{a}(\xi)^2 X(\xi) d\xi + \bar{a}(t)^2 X(t) \Gamma(t) \right\}, \quad (S12)$$

which is eqn (13) in the main text. The uptake flux $J_u(t)$ defined by eqn (2), and the metal surface concentration $\Gamma(t) = \sum_{k=i,u,p} \Gamma_{s,k}(t)$ expressed by eqn (1), can be further rearranged according to

$$J_u(t) = \sum_{j=1}^{N_{s,u}} \frac{\bar{c}_M^a(t) J_u^*(j)}{\beta_a A_{s,u}^{(j)} + \bar{c}_M^a(t)}, \quad (S13)$$

and

$$\Gamma(t) = \sum_{k=i,u,p} \Gamma_{s,k}(t) = \sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \frac{\bar{c}_M^a(t) \Gamma_{s,k}^{\max,(j)}}{\beta_a A_{s,k}^{(j)} + \bar{c}_M^a(t)}, \quad (S14)$$

respectively. The time derivative $d\Gamma(t)/dt$ is further provided by

$$\frac{d\Gamma(t)}{dt} = \frac{d\bar{c}_M^a(t)}{dt} \sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \frac{\beta_a A_{s,k}^{(j)} \Gamma_{s,k}^{\max,(j)}}{(\beta_a A_{s,k}^{(j)} + \bar{c}_M^a(t))^2}. \quad (S15)$$

Making use of eqns (S13)-(S15), the derivation of both members of eqn (S12) with respect to time t leads to

$$\begin{aligned} \frac{d\bar{c}_M^a(t)}{dt} = & - \left\{ X(t) \left[1 - \bar{V} + \bar{a}(t)^2 \frac{\sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \frac{\beta_a^2 A_{s,k}^{(j)} \Gamma_{s,k}^{\max,(j)}}{(\beta_a A_{s,k}^{(j)} + \bar{c}_M^a(t))^2}}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^*(j)}{A_{s,u}^{(j)}}} \right] + \bar{V} \right\}^{-1} \times \left\{ (1 - \bar{V}) \frac{dX(t)}{dt} \bar{c}_M^a(t) + \right. \\ & \left. \frac{\beta_a \bar{a}(t)^2 X(t)}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^*(j)}{A_{s,u}^{(j)}}} \sum_{j=1}^{N_{s,u}} J_u^*(j) \left(\frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)} + \bar{c}_M^a(t)} - \bar{\phi}_u(t) \right) + \bar{V} \left\{ \frac{d\Delta\bar{c}(t)}{dt} - \frac{\varphi_0^{1/3}}{2(1+d/a_0)} \frac{d[(\bar{a}(t)+d/a_0)\rho(t)\Delta\bar{c}(t)X(t)^{1/3}]}{dt} \right\} \right. \\ & \left. + \frac{d[\bar{a}(t)^2 X(t)]}{dt} \frac{\sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \frac{\beta_a \bar{c}_M^a(t) \Gamma_{s,k}^{\max,(j)}}{\beta_a A_{s,k}^{(j)} + \bar{c}_M^a(t)}}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^*(j)}{A_{s,u}^{(j)}}} \right\}, \quad (S16) \end{aligned}$$

which is eqn (14) in the main text.

II. Detailed derivations of eqns (20)-(23), (25)-(26).

Combination of eqns (15)-(16) leads to

$$X(t)[J_M(t) - J_u(t)]e^{k_e t + 2\ln[\bar{a}(t)]} = -k_e \left\{ \phi_u^0 + \int_0^t J_u(\xi) X(\xi) e^{k_e \xi + 2\ln[\bar{a}(\xi)]} d\xi \right\}. \quad (S17)$$

After derivation of eqn (S17) with respect to time, use of eqn (17) and algebraic arrangements, we obtain

$$-\frac{d\Delta\bar{c}(t)}{dt} - \Delta\bar{c}(t) \left[k_e + \frac{d\ln[\bar{a}(t)^2 X(t) J_M^*(t)]}{dt} \right] + \frac{J_u(t)}{J_M^*(t)} \frac{d\ln[\bar{a}(t)^2]}{dt} + \frac{1}{J_M^*(t)} \frac{dJ_u(t)}{dt} \frac{d\bar{c}_M^a(t)}{dt} + \frac{J_u(t)}{J_M^*(t)} \frac{d\ln[X(t)]}{dt} = 0, \quad (S18)$$

where the limiting M transport flux $J_M^*(t)$ is defined by eqn (18). For dilute suspensions of microorganisms with $d \ll a(t)$, $f_{el}(t)$ may be approximated by eqn (19) so that

$$\frac{d\ln[J_M^*(t)]}{dt} \approx -\frac{d\ln[\bar{a}(t)]}{dt} - \frac{\gamma d}{a_0} \frac{d(\bar{a}(t)^{-1})}{dt}, \quad (S19)$$

where we introduced $\gamma = (\varepsilon\beta_a)^{-1} - 1$. In addition the ratio $J_u(t)/J_M^*(t)$ involved in eqn (S18) may be written in the form

$$\frac{J_u(t)}{J_M^*(t)} = \sum_{j=1}^{N_{s,u}} \frac{\bar{c}_M^a(t) / Bn_t^{(j)}}{1 + \bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)}}, \quad (S20)$$

where we used eqn (S13), eqn (18) and the definition of the here time-dependent Bosma number

$Bn_t^{(j)} = \frac{f_{el}(t) D_{M,out} a(t)^{-1}}{\beta_a k_{int}^{(j)} K_{H,u}^{(j)}}$ pertaining to the internalization of M by the j -th type of S_u sites. Finally, the

evaluation of the quantity $\frac{1}{J_M^*(t)} \frac{dJ_u(t)}{dt}$ in eqn (S18) is straightforward

$$\frac{1}{J_M^*(t)} \frac{dJ_u(t)}{dt} = \sum_{j=1}^{N_{s,u}} \frac{1 / Bn_t^{(j)}}{\left(1 + \bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)}\right)^2}. \quad (S21)$$

Substitution of eqns (S19)-(S21) into eqn (S18) provides

$$\frac{d\Delta\bar{c}(t)}{dt} = \frac{d\bar{c}_M^a(t)}{dt} \sum_{j=1}^{N_{s,u}} \frac{1 / Bn_t^{(j)}}{\left(1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}\right)^2} - \Delta\bar{c}(t) \left\{ k_e + \frac{d}{dt} \left[\ln[\bar{a}(t) X(t)] - \frac{\gamma d / a_0}{\bar{a}(t)} \right] \right\}$$

$$+\bar{c}_M^a(t) \frac{d \ln [\bar{a}(t)^2 X(t)]}{dt} \sum_{j=1}^{N_{s,u}} \frac{1/Bn_t^{(j)}}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}}, \quad (\text{S22})$$

which corresponds to eqn (20) given in the main text. The general solution $\Delta \bar{c}(t)$ of the differential equation (S22) is given by

$$\Delta \bar{c}(t) = \omega_0 \frac{e^{-k_e t + \chi(t)}}{\bar{a}(t) X(t)} + \omega(t) \frac{e^{-k_e t + \chi(t)}}{\bar{a}(t) X(t)}. \quad (\text{S23})$$

where $\chi(t) = \gamma d / a(t)$, ω_0 is a constant (independent of time) and $\omega(t)$ is a time-dependent function defined by

$$\omega(t) = \int_0^t \bar{a}(\xi) X(\xi) e^{k_e \xi - \chi(\xi)} \left\{ \frac{d\bar{c}_M^a(\xi)}{d\xi} \sum_{j=1}^{N_{s,u}} \frac{1/Bn_\xi^{(j)}}{\left(1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}\right)^2} + \bar{c}_M^a(\xi) \frac{d \ln [\bar{a}(\xi)^2 X(\xi)]}{d\xi} \sum_{j=1}^{N_{s,u}} \frac{1/Bn_\xi^{(j)}}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \right\} d\xi \quad (\text{S24})$$

It is straightforward to verify that $1/Bn_t^{(j)} = \bar{a}(t)h(t)/Bn_0^{(j)}$ with $Bn_0^{(j)} = Bn_{t=0}^{(j)}$ and $h(t)$ is the function given by $h(t) = \frac{1 - \gamma d / a_0}{1 - \gamma d / a(t)} \approx (1 - \gamma d / a_0)(1 + \gamma d / a(t)) + O([d/a(t)]^2)$ where the notation $O(\)$ indicates that high-order terms in $d/a(t)$ are neglected. Using the above expression that connects $1/Bn_t^{(j)}$ to $1/Bn_0^{(j)}$, one can show after integration by parts

$$\int_0^t \bar{a}(\xi) X(\xi) e^{k_e \xi - \chi(\xi)} \frac{d\bar{c}_M^a(\xi)}{d\xi} \sum_{j=1}^{N_{s,u}} \frac{1/Bn_\xi^{(j)}}{\left(1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}\right)^2} d\xi = -\bar{a}(t)^2 h(t) X(t) e^{k_e t - \chi(t)} \sum_{j=1}^{N_{s,u}} \frac{\beta_a A_{s,u}^{(j)} / Bn_0^{(j)}}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} + \int_0^t \sum_{j=1}^{N_{s,u}} \frac{\beta_a A_{s,u}^{(j)} / Bn_0^{(j)}}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \frac{d \left[\bar{a}(\xi)^2 h(\xi) X(\xi) e^{k_e \xi - \chi(\xi)} \right]}{d\xi} d\xi, \quad (\text{S25})$$

where we did not report the term that is independent of time because the latter can be subsumed into ω_0 .

Using eqn (S25), the expression (S24) for $\omega(t)$ becomes after arrangements

$$\omega(t) = -e^{k_e t - \chi(t)} \sum_{j=1}^{N_{s,u}} \left(\beta_a A_{s,u}^{(j)} / Bn_0^{(j)} \right) \left\{ \frac{\bar{a}(t)^2 h(t) X(t)}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} - e^{-k_e t + \chi(t)} \times \int_0^t e^{k_e \xi - \chi(\xi)} \left[\frac{\bar{a}(\xi)^2 X(\xi)}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \left[h(\xi) \left(k_e - \frac{d\chi(\xi)}{d\xi} \right) + \frac{dh(\xi)}{d\xi} \right] + h(\xi) \frac{d(\bar{a}(\xi)^2 X(\xi))}{d\xi} \right] d\xi \right\}. \quad (S26)$$

Substitution of eqn (S26) into eqn (S23) then leads to

$$\Delta \bar{c}(t) = \omega_0 \frac{e^{-k_e t + \chi(t)}}{\bar{a}(t) X(t)} - \sum_{j=1}^{N_{s,u}} \left(\beta_a A_{s,u}^{(j)} / Bn_t^{(j)} \right) \left\{ \frac{1}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} - \frac{e^{-k_e t + \chi(t)}}{\bar{a}(t)^2 h(t) X(t)} \times \int_0^t e^{k_e \xi - \chi(\xi)} \left[\frac{\bar{a}(\xi)^2 X(\xi)}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \left[h(\xi) \left(k_e - \frac{d\chi(\xi)}{d\xi} \right) + \frac{dh(\xi)}{d\xi} \right] + h(\xi) \frac{d(\bar{a}(\xi)^2 X(\xi))}{d\xi} \right] d\xi \right\}. \quad (S27)$$

At $t = 0$, eqn (S27) reduces to

$$1 - \beta_a^{-1} \bar{c}_M^a(0) = \beta_a^{-1} \omega_0 e^{\chi_0} - \sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)} / Bn_0^{(j)}}{1 + \frac{\bar{c}_M^a(0)}{\beta_a A_{s,u}^{(j)}}}, \quad (S28)$$

where we used $\bar{c}_M^*(t=0) = 1$, $\Delta \bar{c}(0) = \beta_a - \bar{c}_M^a(0)$, $\bar{a}(t=0) = 1$, $X(t=0) = 1$ and $Bn_{t=0}^{(j)} = Bn_0^{(j)}$. In order to evaluate the constant ω_0 , a boundary condition at $t = 0$ is further required. The latter is provided by the steady-transport condition expressed by eqn (15) and applied at $t = 0$, which, after developments, provides the following relationship

$$1 - \beta_a^{-1} \bar{c}_M^a(0) = \sum_{j=1}^{N_{s,u}} \frac{\beta_a^{-1} \bar{c}_M^a(0) / Bn_0^{(j)}}{1 + \frac{\bar{c}_M^a(0)}{\beta_a A_{s,u}^{(j)}}} - \frac{k_e \phi_u^0 R_T^0}{c_M^{*0}}. \quad (S29)$$

Combining eqns (S28) and (S29), it follows

$$\omega_0 = \beta_a e^{-\lambda_0} \left\{ \sum_{j=1}^{N_{s,u}} A_{s,u}^{(j)} / Bn_0^{(j)} - \frac{k_e \phi_u^0 R_T^0}{c_M^{*0}} \right\}. \quad (S30)$$

Realizing that $\bar{c}_M^*(t) = \beta_a^{-1} \Delta \bar{c}(t) + \beta_a^{-1} \bar{c}_M^a(t)$, we then obtain after substitution of eqn (S30) into eqn (S27)

$$\bar{c}_M^*(t) = \beta_a^{-1} \bar{c}_M^a(t) + \left(\sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_0^{(j)}} - \frac{k_e \phi_u^0 R_T^0}{c_M^{*0}} \right) \frac{e^{-k_e t + \chi(t) - \lambda_0}}{\bar{a}(t) X(t)} - \sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_t^{(j)}} \times \left\{ \frac{1}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} - \frac{e^{-k_e t + \chi(t)}}{\bar{a}(t)^2 h(t) X(t)} \int_0^t e^{k_e \xi - \chi(\xi)} \left[\frac{\bar{a}(\xi)^2 X(\xi)}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \left[h(\xi) \left(k_e - \frac{d\chi(\xi)}{d\xi} \right) + \frac{dh(\xi)}{d\xi} \right] + h(\xi) \frac{d(\bar{a}(\xi)^2 X(\xi))}{d\xi} \right] d\xi \right\} \quad (S31)$$

which is eqn (21) in the main text.

In the extremes where $k_e \rightarrow 0$, $\bar{a}(t) = 1$, $X(t) = 1$ and $N_{s,u} = 1$, eqn (S31) simplifies into

$$c_M^* = K_{s,u}^{(1)} \beta_a^{-1} / Bn^{(1)} + \beta_a^{-1} \left[c_M^a - \frac{K_{s,u}^{(1)} / Bn^{(1)}}{1 + c_M^a / K_{s,u}^{(1)}} \right], \quad (S32)$$

where we have dropped the variable t for simplicity and used $Bn_0^{(j)} = Bn_t^{(j)} \equiv Bn^{(j)}$ valid for $\bar{a}(t) = 1$.

Equation (S32) may be rewritten in the form of a second order polynomial equation in $x = c_M^a / (\beta_a c_M^*)$ according to

$$A + x[1 - A - B] - x^2 = 0, \quad (S33)$$

with $A = K_{s,u}^{(1)} / (\beta_a c_M^*)$ and $B = J_u^{(1)*} a_0 / [f_{el}(0) D_{M,out} c_M^*] \equiv A / Bn^{(1)}$. The physically-consistent solution of eqn (S33) reads as

$$x = \left\{ [1 - A - B] + \left\{ [A + B - 1]^2 + 4A \right\}^{1/2} \right\} / 2, \quad (S34)$$

which is eqn (25) in the main text.

Starting from eqn (S31) and following the procedure that leads to eqn (S34), one may show that the initial metal concentrations at the biosurface and in bulk solution are interrelated for $N_{s,u} = 1$ via the expression

$$x_0 = \left\{ \left[1 - A_{s,u}^{(1)} - B_0 (1 - \omega^0) \right] + \left\{ \left[A_{s,u}^{(1)} + B_0 (1 - \omega^0) - 1 \right]^2 + 4A_{s,u}^{(1)} \left[1 + B_0 \omega^0 \right] \right\}^{1/2} \right\} / 2, \quad (S35)$$

with $x_0 = c_M^a(0) / (\beta_a c_M^{*0})$, $B_0 = J_u^{(1)*} a_0 / [f_{el}(0) D_{M,out} c_M^{*0}]$ and $\omega^0 = k_e \phi_u^0 / J_u^{*(1)}$. This equation correctly compares with that we previously obtained for situations where $N_{s,u} = 1$ and cell density is independent of time.¹

Let us now analyze the limit of eqn (S31) for $k_e \rightarrow 0$ with no *a priori* assumption on the time derivative of $\bar{a}(t)$ and $X(t)$. Under such conditions, eqn (S31) reduces to

$$\begin{aligned} \bar{c}_M^*(t) = \beta_a^{-1} \bar{c}_M^a(t) + \left(\sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_0^{(j)}} \right) \frac{e^{\chi(t) - \chi^0}}{\bar{a}(t) X(t)} - \sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_t^{(j)}} \times \left\{ \frac{1}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} - \right. \\ \left. \frac{e^{\chi(t)}}{\bar{a}(t)^2 h(t) X(t)} \int_0^t e^{-\chi(\xi)} \left[\frac{\bar{a}(\xi)^2 X(\xi)}{1 + \frac{\bar{c}_M^a(\xi)}{\beta_a A_{s,u}^{(j)}}} \left[-h(\xi) \frac{d\chi(\xi)}{d\xi} + \frac{dh(\xi)}{d\xi} \right] + h(\xi) \frac{d(\bar{a}(\xi)^2 X(\xi))}{d\xi} \right] d\xi \right\}. \end{aligned} \quad (S36)$$

For practical cases where $d/a(t) \ll 1$, we have $e^{-\chi(t)} = e^{-\gamma d/a(t)} \approx 1 - \gamma d/a(t) + O(d/a(t))$, or equivalently, $e^{-\chi(t)} \approx (1 - \gamma d/a_0) / h(t)$ where we used the definition of the function $h(t) = \frac{1 - \gamma d/a_0}{1 - \gamma d/a(t)}$.

In turn, it comes that the product $e^{-\chi(t)} \times h(t) = 1 - \gamma d/a_0$ does not depend on time. Subsequently, we can write $d[e^{-\chi(t)} \times h(t)] / dt = 0$, which provides

$$-h(t) d\chi(t) / dt + dh(t) / dt = 0. \quad (S37)$$

Substituting eqn (S37) into eqn (S36) and using the equality $e^{-\chi(t)} \times h(t) = 1 - \gamma d/a_0 = 1 - \chi^0$, we obtain

$$\bar{c}_M^*(t) = \beta_a^{-1} \bar{c}_M^a(t) + \left(\sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_0^{(j)}} \right) \frac{e^{\chi(t) - \chi^0}}{\bar{a}(t) X(t)} - \sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_t^{(j)}} \times \left\{ \frac{1}{1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}}} - \frac{(1 - \chi^0) e^{\chi(t)}}{h(t)} \left(1 - \frac{1}{\bar{a}(t)^2 X(t)} \right) \right\} \quad (S38)$$

Further realizing that $(1 - \chi^0) e^{\chi(t)} / h(t) \approx e^{\chi(t) - \chi^0} / h(t)$ for $d/a_0 \ll 1$, $(1 - \chi^0) e^{\chi(t)} / h(t) \approx 1$ and

$1/Bn_0^{(j)} = (1/Bn_t^{(j)}) / (\bar{a}(t) h(t))$, eqn (S38) finally simplifies into

$$\bar{c}_M^*(t) = \beta_a^{-1} \bar{c}_M^a(t) + \sum_{j=1}^{N_{s,u}} \frac{A_{s,u}^{(j)}}{Bn_t^{(j)}} \times \frac{\bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)}}{1 + \bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)}}, \quad (\text{S39})$$

which is eqn (26) in the main text.

III. Derivations of analytical expressions for $\bar{c}_M^*(t)$ and $c_M^a(t)$ in the limits $\bar{a}(t)=1$, $\mu \rightarrow 0$ and/or $\Psi(t) \rightarrow 1$.

As argued in the main text, eqn (20) (or, equivalently, eqn (21)) reduces to $\bar{c}_M^a(t) = \beta_a \bar{c}_M^*(t)$ for cases where the rate of metal biouptake is limited by the sole internalisation step (*i.e.* $1/Bn_t^{(j)} \rightarrow 0$ or $R_T \rightarrow 0$). Under such conditions that warrant applicability of the BLM framework, eqn (14) satisfactorily reproduces the mass balance equation that we previously derived assuming equilibrium partitioning of M at the biointerface.³ The analytical expression for $\bar{c}_M^*(t)$, as obtained from the solution of eqn (14) under such BLM conditions, is derived elsewhere³ in the limits $\bar{a}(t)=1$, $\mu \rightarrow 0$ and/or $\Psi(t) \rightarrow 1$ in the extremes where the affinity of M for the various cell-surface adsorption sites $S_{i,u,p}$ is low (*i.e.* $K_{s,k=i,u,p}^{(j)} \gg \beta_a \bar{c}_M^*(t)$) or high (*i.e.* $K_{s,k=i,u,p}^{(j)} \ll \beta_a \bar{c}_M^*(t)$). The reader is referred to the Supporting Information of Ref. [3] for details. In this section, we are therefore concerned with the derivation of the solution of eqns (3), (5), (14) and (20) for dynamic cases where $1/Bn_t^{(j)}$ does not necessarily tend to zero and the affinity of M for the adsorption $S_{i,u,p}$ sites is either high or low in the limits $\bar{a}(t)=1$, $\mu \rightarrow 0$ and/or $\Psi(t) \rightarrow 1$. For these situations where cell size and cell density are constant over time, eqns (14) and (20) simplify into

$$\frac{d\bar{c}_M^a(t)}{dt} = - \left\{ 1 + \frac{\sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \frac{\beta_a^2 A_{s,k}^{(j)} \Gamma_{s,k}^{\max,(j)}}{(\beta_a A_{s,k}^{(j)} + \bar{c}_M^a(t))^2}}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^{*(j)}}{A_{s,u}^{(j)}}} \right\}^{-1} \times \left\{ \frac{\beta_a}{\tau_L^0 \sum_{j=1}^{N_{s,u}} \frac{J_u^{*(j)}}{A_{s,u}^{(j)}}} \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \left(\frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)} + \bar{c}_M^a(t)} - \bar{\phi}_u(t) \right) + \frac{d\Delta\bar{c}(t)}{dt} \bar{V} \left(1 - \frac{\rho\phi_0^{1/3}}{2} \right) \right\} \quad (\text{S40})$$

and

$$\frac{d\Delta\bar{c}(t)}{dt} = \frac{d\bar{c}_M^a(t)}{dt} \sum_{j=1}^{N_{s,u}} \frac{1/Bn_0^{(j)}}{\left(1 + \frac{\bar{c}_M^a(t)}{\beta_a A_{s,u}^{(j)}} \right)^2} - k_e \Delta\bar{c}(t), \quad (\text{S41})$$

respectively, where the function ρ is now independent of time.

In the high M affinity regime defined here by the inequality $K_{s,k=i,u,p}^{(j)} \ll c_M^a(t)$ or, equivalently, $\bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)} \gg 1$, eqn (S41) may be approximated by $d\Delta\bar{c}(t)/dt \approx -k_e \Delta\bar{c}(t)$, for which the only physical solution reads as $\bar{c}_M^a(t) = \beta_a \bar{c}_M^*(t)$. The latter implies that equilibrium M partitioning systematically applies in the high M affinity regime, a case that we have already treated in a previous report.³ The solution of eqn (S40) then identifies with the expression provided for the ‘high affinity case’ in Table S1 of the Supporting Information in Ref. [3]. For the sake of completeness, we report in **Table SII** below these expressions.

In order to derive the analytical solution of eqns (3), (5), (14) and (20) in the low affinity regime (or Henry regime) defined by $K_{s,k=i,u,p}^{(j)} \gg c_M^a(t)$ (or, equivalently, $\bar{c}_M^a(t) / \beta_a A_{s,u}^{(j)} \ll 1$) with time-independent cell size and cell density, we follow step-by-step the procedure extensively detailed in Ref. [1] where M partitioning dynamics at biointerfaces was examined for $\bar{a}(t)=1$ and $X(t)=1$ with explicit account of M conductive-diffusion transport *albeit* in the restrictive case $N_{s,u} = 1$. After lengthy and tedious algebraic developments, we then obtain the expressions of the time-dependent surface and bulk metal concentrations detailed in **Table SI2** below. It is straightforward to verify that these expressions correctly compare with those obtained in Ref. [1] in the limit $N_{s,u} = 1$, after realizing that the definition of c_M^{*0} in Ref. [1] is slightly different from that adopted here. Indeed, the initial bulk metal concentration c_M^{*0} in Ref. [1] was corrected for the initial adsorbed amount $\Gamma(0)$ of M at the biosurface, so that $\Gamma(0)$ was not explicitly involved in the equation reflecting the mass balance condition. Here, on the contrary, $\Gamma(0)$ is explicitly considered in eqn (6). The reader is referred to the Supporting Information in Ref. [3] for further comments on this issue. Finally, we further verify that the expressions reported in **Table SI2** considered in the BLM limit ($1/Bn^{(j)} \rightarrow 0$ or $R_T \rightarrow 0$) appropriately reproduce those derived in Ref. [3] in the low affinity case under equilibrium conditions. The reader is referred to our previous reports¹⁻³ for further comments on the physical meaning of the time constants τ_o , $\tilde{\tau}_o$, $\tau_{E,L}^0$ and $\tilde{\tau}_{E,L}^0$ involved in the expressions defining $c_M^a(t)$ and $c_M^*(t)$ in the high and low M affinity regimes.

High affinity case

$$K_{s,k=i,u,p}^{(j)} \ll c_M^a(t) :$$

$$c_M^a(t) = \beta_a c_M^*(t)$$

$$c_M^*(t) =$$

$$\left\{ c_M^{*0} + \frac{1+k_e\tau_o}{k_e\tau_L^0} \left[\sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\beta_a \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) \right] \right\} e^{-k_e t} - \frac{1+k_e\tau_o}{k_e\tau_L^0} \left[\sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\beta_a \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) \right]$$

$$\text{with } \tau_o = - \left(\phi_u^0 + c_M^{*0} \tau_L^0 \sum_{j=1}^{N_{s,u}} 1/R_s^{(j)} \right) / \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \quad \text{and} \quad \tau_L^0 = G_{a_0, r_c^0} / \left\{ a_0^2 \sum_{j=1}^{N_{s,u}} (1/R_s^{(j)}) \right\}$$

Table SI1. Expressions for the time-dependent surface and bulk metal concentrations ($c_M^a(t)$ and $c_M^*(t)$, respectively) in the limits $K_{s,k=i,u,p}^{(j)} \ll c_M^a(t)$ (corresponding to high affinity of M for the various cell-surface adsorption sites $S_{i,u,p}$), $\bar{a}(t)=1$ (or $a(t)=a_0$) and $X(t)=1$. These expressions are the solutions of eqns (3), (5), (14) and (20) considered in these limits. See text for details.

Low affinity case (Henry regime)

$$K_{s,k=i,u,p}^{(j)} \gg c_M^a(t) :$$

$$\left\{ \begin{aligned} c_M^a(t) &= \left\{ \frac{k_e \tilde{\tau}_o}{1+k_e \tilde{\tau}_L^0} \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) \right\} \left(e^{-t/\tilde{\tau}_d^0} - 1 \right) + c_M^a(0) e^{-t/\tilde{\tau}_d^0} \\ c_M^*(t) &= \alpha_1 e^{-k_e t} - \frac{k_e \tilde{\tau}_o}{1+k_e \tilde{\tau}_L^0} \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\beta_a \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) + \\ & e^{-t/\tilde{\tau}_d^0} \left\{ \frac{k_e \tilde{\tau}_o}{1+k_e \tilde{\tau}_L^0} \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\beta_a \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) + \beta_a^{-1} c_M^a(0) \right\} \left\{ 1 + \frac{1+k_e \tilde{\tau}_L^0}{1+k_e (\tilde{\tau}_L^0 - \tilde{\tau}_E^0)} \sum_{j=1}^{N_{s,u}} \frac{1}{Bn_0^{(j)}} \right\} \end{aligned} \right.$$

with

$$\left\{ \begin{aligned} \alpha_1 &= -k_e \phi_u^0 R_T^0 - \beta_a^{-1} \sum_{j=1}^{N_{s,u}} (1/Bn_0^{(j)}) \frac{k_e}{1+k_e (\tilde{\tau}_L^0 - \tilde{\tau}_E^0)} \left[c_M^a(0) \tilde{\tau}_E^0 + \tilde{\tau}_o \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / \left(\sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) \right] \\ \tilde{\tau}_E^0 &= \tau_L^0 - \Omega_1 R_T^0 \sum_{j=1}^{N_{s,u}} J_u^{*(j)}, \quad \tau_L^0 = G_{a_0, r_c^0} / \left\{ a_0^2 \sum_{j=1}^{N_{s,u}} (1/R_s^{(j)}) \right\}, \quad c_M^a(0) = \frac{\beta_a (c_M^*(0) + k_e \phi_u^0 R_T^0)}{1 + \sum_{j=1}^{N_{s,u}} (1/Bn_0^{(j)})} \\ \tilde{\tau}_{E,L}^0 &= \tau_{E,L}^0 + \left(\sum_{k=i,u,p} \sum_{j=1}^{N_{s,k}} \Gamma_{s,k}^{\max.(j)} / K_{s,k}^{(j)} \right) / \left(\sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right), \quad \tilde{\tau}_d^0 = \tilde{\tau}_E^0 / (1+k_e \tilde{\tau}_L^0) \\ \tilde{\tau}_o &= -k_e \Omega_1 \phi_u^0 R_T^0 - \left(1 / \sum_{j=1}^{N_{s,u}} J_u^{*(j)} \right) \left(\phi_u^0 + c_M^a(0) \tilde{\tau}_E^0 \sum_{j=1}^{N_{s,u}} J_u^{*(j)} / K_{s,u}^{(j)} \right) \end{aligned} \right.$$

Table SI2. Expressions for the time-dependent surface and bulk metal concentrations ($c_M^a(t)$ and $c_M^*(t)$,

respectively) in the limits $K_{s,k=i,u,p}^{(j)} \gg c_M^a(t)$ (corresponding to low affinity of M for the various cell-surface adsorption sites $S_{i,u,p}$), $\bar{a}(t)=1$ (or $a(t)=a_0$) and $X(t)=1$. These expressions are the solutions of eqns (3), (5), (14) and (20) considered in these limits. See text for details.

IV. Supporting Figures.

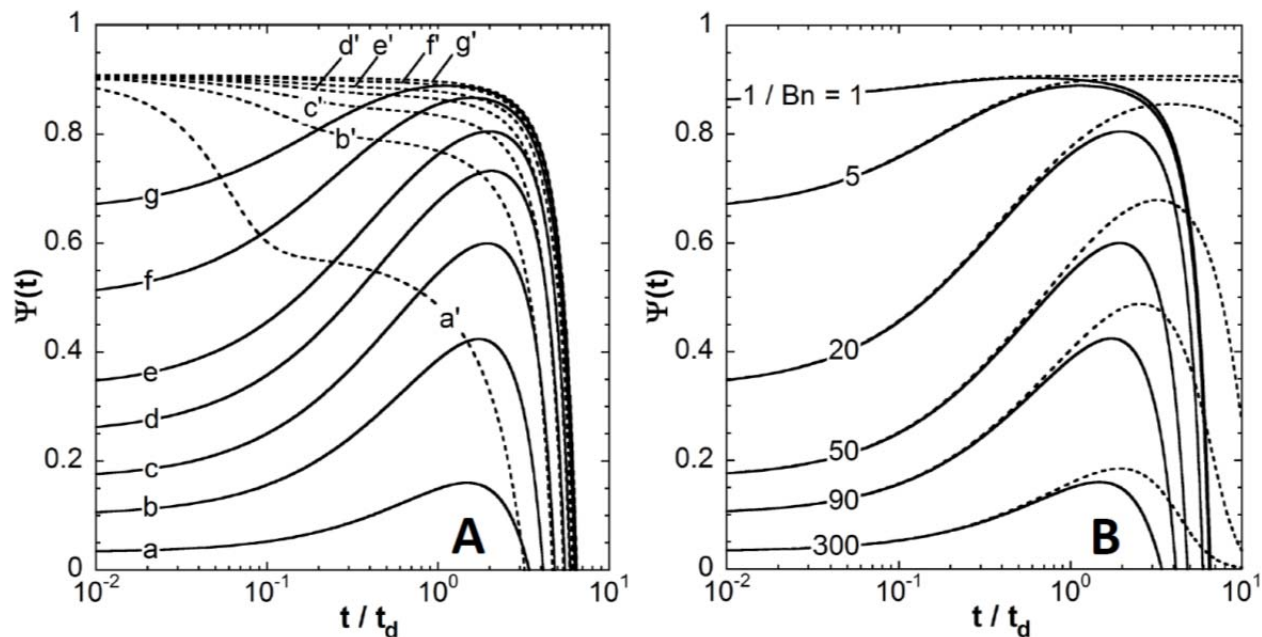


Figure S1. (A) Time evolution of the growth inhibition function $\Psi(t)$ at different values of $1/Bn$. Meaning of the letters (a,a') to (g,g'): as in Figure 2B. Solid lines: rigorous solution of eqns (3), (5), (14) and (20). Dotted lines: evaluation with discarding M diffusion. (B) Time evolution of the growth inhibition function $\Psi(t)$ at different values of $1/Bn$ (indicated) with $X_c = 15$ (solid lines) and $X_c \rightarrow \infty$ (dotted lines) and account of M diffusion transport. Other model parameters in (A) and (B): as in Figure 1. Figure S1B illustrates the different behavior of $\Psi(t)$ at long exposure time t with or without account of a growth stationary regime. These differences directly follow from the definition of $\Psi(t)$, *i.e.* from inspection of the slopes $d \ln(X(t))/dt$ in the presence and absence of M within the limits $X_c \rightarrow \infty$ (no stationary growth phase) or for finite values of X_c .

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