Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

SUPPLEMENTARY INFORMATION

Kinetics of metal detection by luminescence-based whole-cell biosensors: connecting biosensor response to metal bioavailability, speciation and cell metabolism.

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This document contains 5 supplementary equations and 2 supplementary figures.

I. Supplementary equations.

The complete expression of $f_{\mathrm{a,M}}$ involved in Eqs. (17) and (19) that define the time constant τ_{o} and the scalar λ_{o}, respectively, reads after algebraic arrangements as

$$f_{\mathrm{a,M}}=\frac{3\varphi}{1-\varphi}\frac{\bar{h}_{\mathrm{a}}^{-2}\dfrac{\bar{K}_{\mathrm{ML}}}{1+\bar{K}_{\mathrm{ML}}}(1-\varepsilon)\left[\bar{h}_{\mathrm{a}}\left(\varphi^{-1/3}\operatorname{sech}(\sigma)-1\right)+\tanh(\sigma)\right]+\dfrac{1}{6}\left(1-\varphi^{-1/3}\right)^{2}\left(1+2\varphi^{1/3}\right)\left(\bar{h}_{\mathrm{a}}-\tanh(\sigma)\right)}{\bar{h}_{\mathrm{a}}\left(1-\varphi^{1/3}\right)-\left(1-\varphi^{1/3}+\varepsilon\bar{K}_{\mathrm{ML}}\right)\tanh(\sigma)} \tag{S1}$$

where σ is given by $\sigma=\bar{h}_{\mathrm{a}}\left(1-\varphi^{-1/3}\right)$ and $\bar{h}_{\mathrm{a}}$ is provided by Eq. (4) in the main text. It is verified that Eq. (S1) in the limit $\varphi<<1$ reduces to Eq. (21) written in terms of the ML lability parameter ξ (Eq. (6)).

Given the expression defining $c_{\mathrm{M}}^{*}(t)$ (Eq. (14) in the main text) obtained after arrangements and Laplace transform of Eqs. (9)-(13), the dependence of the intracellular concentration of free M at *t*, $\phi_{\mathrm{M}}(t)$, can be evaluated, and the result after algebraic manipulations reads as

$$\phi_{\mathrm{M}}(t)=\frac{K_{\mathrm{H}}k_{\mathrm{int}}\tau_{\mathrm{a,i}}c_{\mathrm{M}}^{*,0}}{1+\left(p_{\mathrm{ML}}Bn\right)^{-1}}\left[\frac{\mathrm{e}^{-\frac{1+\bar{K}_{\mathrm{i}}}{\bar{K}_{\mathrm{i}}}\bar{t}}}{\bar{\omega}_{-}-\bar{\omega}_{+}}\sum_{n\equiv+,-}\delta_{n}\left(1-\frac{1}{\bar{\omega}_{n}\bar{K}_{\mathrm{i}}}\right)\left(\mathrm{e}^{\left(\frac{1+\bar{K}_{\mathrm{i}}}{\bar{K}_{\mathrm{i}}}-\bar{\omega}_{n}\right)\bar{t}}-1\right)+\frac{\bar{\tau}_{\mathrm{o}}}{\zeta+\bar{K}_{\mathrm{i}}}\left(1-\mathrm{e}^{-\frac{1+\bar{K}_{\mathrm{i}}}{\bar{K}_{\mathrm{i}}}\bar{t}}\right)\right] \tag{S2}$$

where $\delta_{n}=1$ for $n\equiv+$ and $\delta_{n}=-1$ for $n\equiv-$, and Bn, $\bar{\tau}_{\mathrm{o}}=\tau_{\mathrm{o}}/\tau_{\mathrm{a,i}}$, ζ and $\bar{\omega}_{\pm}$ are given by Eqs. (20), (17), (18) and (16), respectively, and $p_{\mathrm{ML}}\approx p_{\mathrm{o}}=1+\varepsilon\bar{K}_{\mathrm{ML}}\xi$ for $\varphi<<1$ (cf. below Eq. (5)). Combining Eqs. (12) and (S2), the time-dependent concentration of intracellular $\mathrm{MP_{reg}}$ complex, $\phi_{\mathrm{c}}(t)$, can be written in the form

$$\phi_{\mathrm{c}}(t)=\bar{K}_{\mathrm{i}}\frac{K_{\mathrm{H}}k_{\mathrm{int}}\tau_{\mathrm{a,i}}c_{\mathrm{M}}^{*,0}}{1+\left(p_{\mathrm{ML}}Bn\right)^{-1}}\left[\frac{\bar{\tau}_{\mathrm{o}}}{\zeta+\bar{K}_{\mathrm{i}}}-\frac{1}{\bar{K}_{\mathrm{i}}}\frac{1}{\bar{\omega}_{-}-\bar{\omega}_{+}}\sum_{n\equiv+,-}\delta_{n}\left(\bar{\omega}_{n}\right)^{-1}\mathrm{e}^{-\bar{\omega}_{n}\bar{t}}\right] \tag{S3}$$

From Eqs. (S2) and (S3), we infer that the concentrations of intracellular M and $\mathrm{MP_{reg}}$ complexes at $t\rightarrow\infty$, denoted as $\phi_{\mathrm{M}}^{\infty}$ and $\phi_{\mathrm{c}}^{\infty}$, respectively, are interrelated by the equilibrium expression

$$\phi_{\mathrm{M}}^{\infty}=\phi_{\mathrm{c}}^{\infty}/\bar{K}_{\mathrm{i}}=\frac{K_{\mathrm{H}}k_{\mathrm{int}}\tau_{\mathrm{o}}c_{\mathrm{M}}^{*,0}}{\left[1+\left(p_{\mathrm{ML}}Bn\right)^{-1}\right]\left(\zeta+\bar{K}_{\mathrm{i}}\right)} \tag{S4}$$

Finally, solution of Eqs. (9)-(13) leads to the following expression of the M surface concentration at equilibrium, $c_{\mathrm{M}}^{\mathrm{a}}\left(t\rightarrow\infty\right)=c_{\mathrm{M}}^{a,\infty}$,

$$c_{\mathrm{M}}^{a,\infty}/c_{\mathrm{M}}^{*,0}=\frac{1}{1+\left(p_{\mathrm{ML}}Bn\right)^{-1}}\left(c_{\mathrm{M}}^{*,\infty}/c_{\mathrm{M}}^{*,0}+\frac{k_{\mathrm{e}}\tau_{\mathrm{o}}\left(p_{\mathrm{ML}}Bn\right)^{-1}}{\left[1+\left(p_{\mathrm{ML}}Bn\right)^{-1}\right]\left(\zeta+\bar{K}_{\mathrm{i}}\right)}\right) \tag{S5}$$

where $c_{\mathrm{M}}^{*,\infty}/c_{\mathrm{M}}^{*,0}$ is defined by Eq. (22).

II. Supplementary Figures.

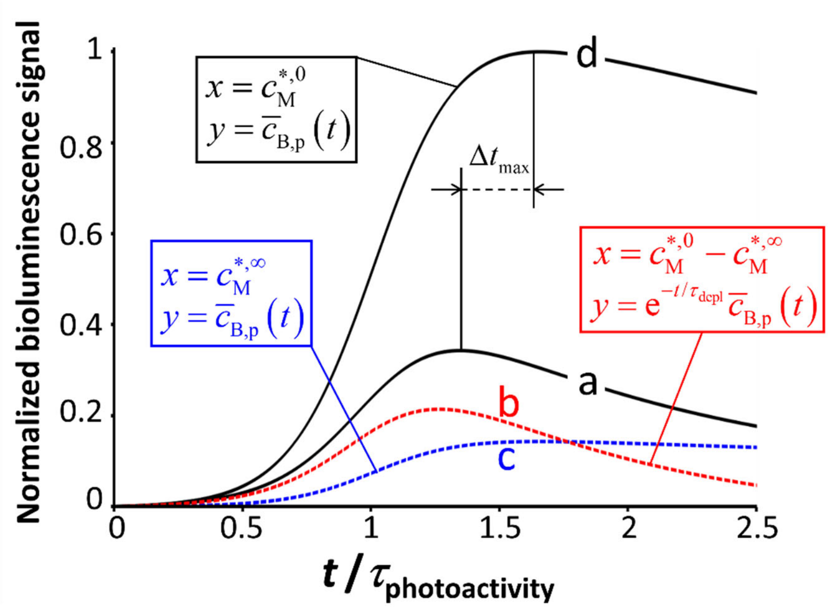

Figure S1. Illustration of the decomposition of the bioluminescence signal with account of metal depletion in bulk solution (curve (a)) on the basis of the two terms defined by Eq. (40) in the main text (curves (b) and (c)). Accordingly, the signal corresponding to curve (a) is the sum of the signals pictured by curves (b) and (c). Curve (d) represents the signal obtained without considering the effects of bulk metal depletion. All signals are here normalized by the maximum of bioluminescence reached in the absence of bulk M depletion. The time axis is scaled by $\tau_{\mathrm{photoactivity}}$ which is the time at which the (dimensionless) concentration of photoactive cells, $\bar{c}_{\mathrm{B,p}}(t)$, features an inflexion point (cf. main text for details and Figure 5A, red curve therein). The (dummy) variables *x* and *y* are those defined below Eq. (40), and they specify which bulk M concentration is applicable for computing the signals (b), (c) and (d) (variable *x*) and which expression of the concentration of photoactive cells is relevant to each signal (variable *y*). $\Delta t_{\max}$ represents the shift in position of the bioluminescence maximum as a result of bulk M depletion. Using the notations detailed in the main text (cf. Eq. (40)), curves (a), (c), (b) and (d) correspond to $\overline{Lum}(t)/\overline{Lum}_{\max}\big|_{\varphi<<\varphi^*}$, $\overline{Lum}^{(0)}\left(t,c_{\mathrm{M}}^{*,\infty},\bar{c}_{\mathrm{B,p}}(t)\right)/\overline{Lum}_{\max}\big|_{\varphi<<\varphi^*}$, $\overline{Lum}^{(0)}\left(t,c_{\mathrm{M}}^{*,0}-c_{\mathrm{M}}^{*,\infty},\mathrm{e}^{-t/\tau_{\mathrm{depl}}}\bar{c}_{\mathrm{B,p}}(t)\right)/\overline{Lum}_{\max}\big|_{\varphi<<\varphi^*}$ and $\overline{Lum}(t)\big|_{\varphi<<\varphi^*}/\overline{Lum}_{\max}\big|_{\varphi<<\varphi^*}$, respectively, where

$\overline{Lum}(t)=Lum(t)/\left[c_{\mathrm{B}}\left(1-\tilde{K}_{\mathrm{H}}S_{\mathrm{a}}c_{\mathrm{B}}\right)\right]$ and $\overline{Lum}^{(0)}(t,x,y)=Lum^{(0)}(t,x,y)/\left[c_{\mathrm{B}}\left(1-\tilde{K}_{\mathrm{H}}S_{\mathrm{a}}c_{\mathrm{B}}\right)\right]$. Figure S1 holds for $\varphi/\varphi^{*}=6$ with the model parameters adopted in Figure 5B of the main text.

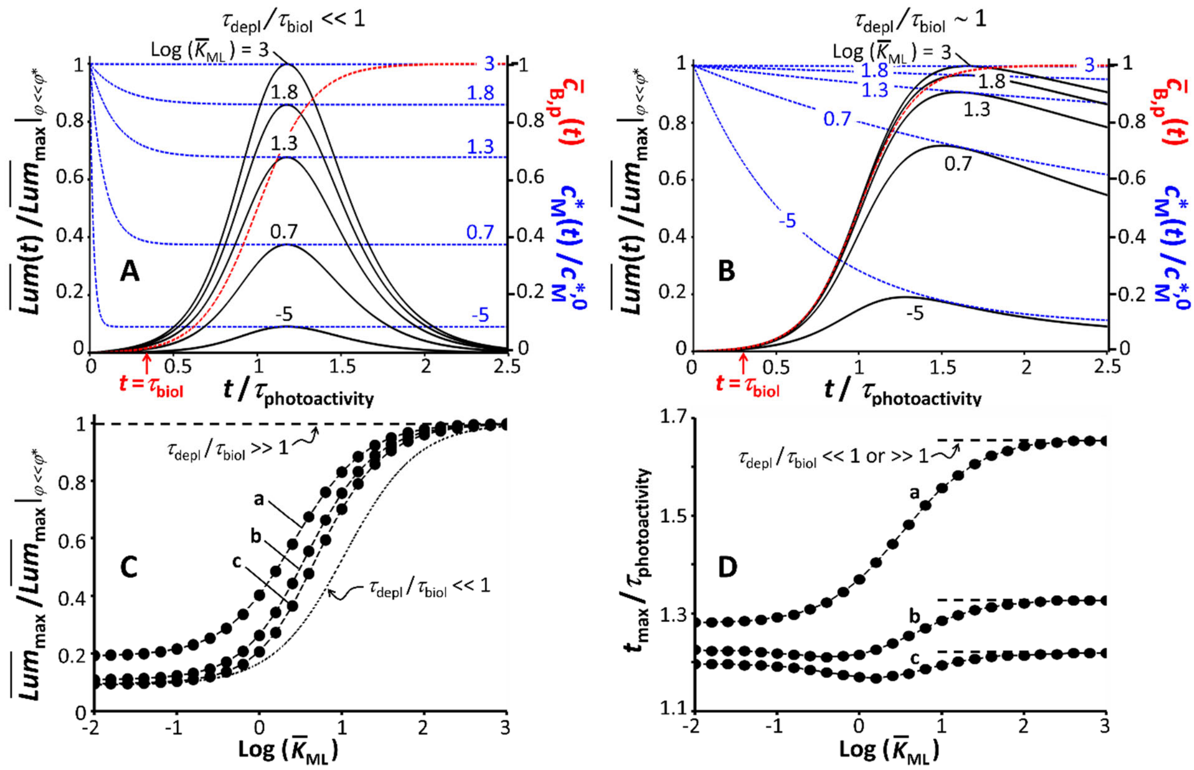

Figure S2. Illustrations of the dependence of the dimensionless bioluminescence signal $\overline{Lum}(t)/\overline{Lum}_{\max}\big|_{\varphi<<\varphi^{*}}$ (evaluated from Eq. (39)) on time for different dimensionless ML stability constants $\bar{K}_{\mathrm{ML}}$ (indicated) for the situations $\tau_{\mathrm{depl}}/\tau_{\mathrm{biol}}<<1$ **(A)** and $\tau_{\mathrm{depl}}/\tau_{\mathrm{biol}}\sim 1$ **(B).** τ_{depl} is the timescale for depletion of bulk M concentration and τ_{biol} marks the onset of the increase in the concentration of photoactive cells $\bar{c}_{\mathrm{B,p}}(t)$ with time (red dotted curves). The time axis is scaled by $\tau_{\mathrm{photoactivity}}$ which is the time at which $\bar{c}_{\mathrm{B,p}}(t)$ features an inflexion point. Blue dotted curves represent the time-dependent (dimensionless) bulk M concentration, $c_{\mathrm{M}}^{*}(t)/c_{\mathrm{M}}^{*,0}$, for each selected value of $\bar{K}_{\mathrm{ML}}$ (Eqs. (14)-(22) or, equivalently, Eq. (25) under the conditions adopted in this figure). The (dimensionless) maxima of the bioluminescence signals and their time-positions $t_{\max}/\tau_{\mathrm{photoactivity}}$ under the conditions in **(B)** (where $\tau_{\mathrm{depl}}/\tau_{\mathrm{biol}}\sim 1$) are reported in **(C)** and **(D)**, respectively. We further provide in **(C)** and **(D)** the signal maxima and associated $t_{\max}/\tau_{\mathrm{photoactivity}}$, respectively, as a function of $\bar{K}_{\mathrm{ML}}$ in the extremes $\tau_{\mathrm{depl}}/\tau_{\mathrm{biol}}<<1$ and $\tau_{\mathrm{depl}}/\tau_{\mathrm{biol}}>>1$ for the conditions that hold in **(B)** (indicated). Unless otherwise specified in the figure, adopted model parameters are: $\varphi/\tilde{\varphi}=10$ with $\tilde{\varphi}=\varphi^{*}/\left(1+\bar{K}_{\mathrm{ML}}\right)$ ($\tilde{\varphi}$ is independent of $\bar{K}_{\mathrm{ML}}$), $\varepsilon=1$, $a=1$ µm, $D_{\mathrm{M}}=10^{-9}$ m² s⁻¹, $Bn^{-1}=0.1$, $\xi\rightarrow 0$, $\bar{K}_{\mathrm{i}}=10$, $\tau_{\mathrm{a,i}}=0.1$ s, $k_{\mathrm{r}}\tau_{\mathrm{a,i}}=10^{-4}$, $k_{\mathrm{e}}=10^{-3}$ s^{-1} **(A)**, $k_{\mathrm{e}}=10^{-4.5}$ s^{-1} **(B,C,D)**, $\tau_{\mathrm{photoactivity}}$ = 15 h in **(A)**, **(B)**, **(C)** (curve (a)) and **(D)** (curve (a)), $\tau_{\mathrm{photoactivity}}$ = 30 h for curves (b) in **(C)** and **(D)**, $\tau_{\mathrm{photoactivity}}$ = 45 h for curves (c) in **(C)** and **(D)**. The expression adopted for $F(t)$ in Eq. (39) correspond to Eq. (16) in Ref. [22]. In **(C)** and **(D)**, dotted lines connecting symbols are guides to the eye.