Switches Induced by Quorum Sensing in a Model of Enzyme-loaded Microparticles

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Supplementary Information

Neglecting the production of CO_2, for it plays a small role in the dynamics, the full mechanism simplifies into

$$\begin{aligned} \mathrm{S} &\xrightarrow[\mathrm{R([H^+],[S],[E])}]{\text{enzyme}} 2\mathrm{P} \\ \mathrm{P} + \mathrm{H^+} &\underset{\mathrm{k_{2r}}}{\overset{\mathrm{k_2}}{\rightleftharpoons}} \mathrm{PH^+} \\ \mathrm{H^+} + \mathrm{OH^-} &\underset{\mathrm{k_{5r}}}{\overset{\mathrm{k_5}}{\rightleftharpoons}} \mathrm{H_2O} \end{aligned} \tag{S.1}$$

where P, PH^+ and OH^- denote ammonia, ammonium and hydroxide respectively. The corresponding reaction–diffusion equations in one spatial dimension are

$$\partial_t[\mathrm{S}] = D_\mathrm{S}\,\partial_x^2[\mathrm{S}] - \mathrm{R} \tag{S.2a}$$

$$\partial_t[\mathrm{P}] = D_\mathrm{P}\,\partial_x^2[\mathrm{P}] + 2\mathrm{R} - \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}] \tag{S.2b}$$

$$\partial_t[\mathrm{PH^+}] = D_\mathrm{PH}\,\partial_x^2[\mathrm{PH^+}] + \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] - \mathrm{k_{2r}}[\mathrm{PH^+}] \tag{S.2c}$$

$$\partial_t[\mathrm{H^+}] = D_\mathrm{H}\,\partial_x^2[\mathrm{H^+}] + \mathrm{k_{5r}} - \mathrm{k_5}[\mathrm{H^+}][\mathrm{OH^-}] + \mathrm{k_{2r}}[\mathrm{PH^+}] - \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] \tag{S.2d}$$

$$\partial_t[\mathrm{OH^-}] = D_\mathrm{OH}\,\partial_x^2[\mathrm{OH^-}] + \mathrm{k_{5r}} - \mathrm{k_5}[\mathrm{H^+}][\mathrm{OH^-}]. \tag{S.2e}$$

The equilibrium between H_2O, H^+ and OH^- is assumed to be established instantaneously, therefore $[OH^-]$ can be substituted with $K_w/[H^+]$ in eq. (S.2e) converting the LHS into

$$\partial_t[\mathrm{OH^-}] = \frac{\mathrm{d}(\mathrm{K_w}/[\mathrm{H^+}])}{\mathrm{d}[\mathrm{H^+}]}\,\partial_t[\mathrm{H^+}] = -\frac{\mathrm{K_w}}{[\mathrm{H^+}]^2}\,\partial_t[\mathrm{H^+}].$$

Subtracting eq. (S.2e) from eq. (S.2d) and, for convenience, assuming that $D_\mathrm{H} = D_\mathrm{OH}$ as well as using the linearity of differentiation ($D_\mathrm{H}\,\partial_x^2[\mathrm{H^+}] - D_\mathrm{OH}\,\partial_x^2(\mathrm{K_w}/[\mathrm{H^+}]) = D_\mathrm{H}\,\partial_x^2([\mathrm{H^+}] - \mathrm{K_w}/[\mathrm{H^+}])$) yields:

$$\left(1 + \frac{\mathrm{K_w}}{[\mathrm{H^+}]^2}\right)\partial_t[\mathrm{H^+}] = D_\mathrm{H}\,\partial_x^2\left([\mathrm{H^+}] - \frac{\mathrm{K_w}}{[\mathrm{H^+}]}\right) + \mathrm{k_{2r}}[\mathrm{PH^+}] - \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] \tag{S.3}$$

Figure 1 shows the rate terms ($2\mathrm{R} - \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}]$) and ($-\mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}]$) during a cycle. It can be seen that $2\mathrm{R} - \mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}] \approx 0$ for the acidic part of a cycle where autocatalysis occurs (Figure 1a, solid line), and that $-\mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}] \approx 0$ for the remainder (Figure 1a, dashed line). Using the latter assumption to reduce the model removes the feedback mechanism and results in the loss of oscillations. Hence, we substitute ($-\mathrm{k_2}[\mathrm{P}][\mathrm{H^+}] + \mathrm{k_{2r}}[\mathrm{PH^+}]$) with $-2\mathrm{R}$ in eq. (S.3) on the basis that this simplification alters the dynamics only moderately. As a result eq. (S.2) reduces into the 2–variable model:

$$\begin{aligned} \partial_t[\mathrm{S}] &= D_\mathrm{S}\,\partial_x^2[\mathrm{S}] - \mathrm{R} \\ \partial_t[\mathrm{H^+}] &= \left[D_\mathrm{H}\,\partial_x^2\left([\mathrm{H^+}] - \frac{\mathrm{K_w}}{[\mathrm{H^+}]}\right) - 2\mathrm{R}\right]\left(1 + \frac{\mathrm{K_w}}{[\mathrm{H^+}]^2}\right)^{-1}. \end{aligned} \tag{S.4}$$

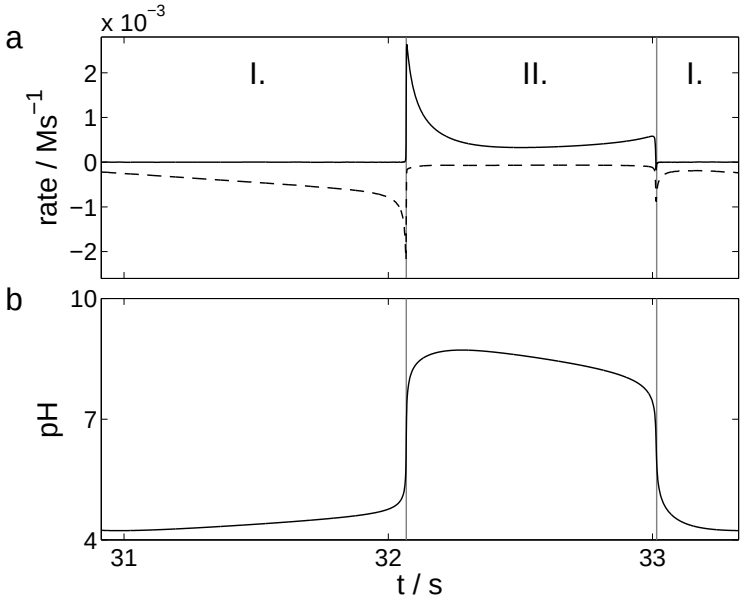

Figure 1: Comparison of rates during a single oscillation in the five–variable model: (a) solid line: $2\mathrm{R} - \mathrm{k_2[P][H^+]} + \mathrm{k_{2r}[PH^+]}$; dashed line: $-\mathrm{k_2[P][H^+]} + \mathrm{k_{2r}[PH^+]}$. (b) pH. Gray lines mark the boundary between the acidic (I.) and basic (II.) parts of a cycle. Parameters as in fig. 2.

pH traces for the five– and two–variable models are shown in Figure 2. The reduced model captures the main characteristics of the oscillatory cycle reasonably well, *i.e.* the period and amplitude.

Introducing $s = [\mathrm{S}]/\mathrm{K_m}$, $h = [\mathrm{H^+}]/\mathrm{K_{ES1}}$, $d = D_\mathrm{H}/D_\mathrm{S}$, $\kappa = \mathrm{K_m}/\mathrm{K_{ES1}}$, $\kappa_\mathrm{es} = \mathrm{K_{ES2}}/\mathrm{K_{ES1}}$, $\kappa_\mathrm{w} = \mathrm{K_w}/\mathrm{K_{ES1}^2}$, $\tau = t\mathrm{k_E[E]}/\mathrm{K_m}$, $x' = x(\mathrm{k_E[E]})^{1/2}(\mathrm{D_S K_m})^{-1/2}$, where τ and x' are dimensionless time and space, respectively; the one–dimensional spatial model corresponding to eq. (S.4) becomes:

$$\begin{aligned} \partial_\tau s &= \partial^2_{x'} s - r \\ \partial_\tau h &= \left[d\,\partial^2_{x'} \left(h - \frac{\kappa_\mathrm{w}}{h} \right) - 2\kappa r \right] \left(1 + \frac{\kappa_\mathrm{w}}{h^2} \right)^{-1} \end{aligned} \tag{S.5}$$

where

$$r = \frac{s}{(1+s)\,(1+\kappa_\mathrm{es}/h + h)}.$$

In three–dimensions, diffusive transport is considered through applying the $\nabla^2 = (\partial_x^2 + \partial_y^2 + \partial_z^2)$ Laplace operator to the concentration field of chemical components. The finite difference form of the Laplacian is chosen depending on the spatial geometry of the studied system. Having enzyme-loaded beads in a 2D hexagonal lattice within a 3D volume lends itself to resolving the entire space as a hexagonal–close–packed (*hcp*) array of cells (Figure 3a). To approximate the diffusion-induced concentration change with time inside each cell, we define vectors $\vec{u_i} = (u_{i,x}, u_{i,y}, u_{i,z})$ pointing from the center of a cell to the center of the adjacent cells, with $|\vec{u_i}| = 1$ being the grid spacing (Figure 3b). The $D_{\vec{u}}\, f|_{f_0}$ and $D^2_{\vec{u}}\, f|_{f_0}$ directional first and second derivatives of f at f_0 along $\overline{f_0 f_i}$ are computed (after dropping i) according to

$$D_{\vec{u}}\, f = (u_x, u_y, u_z) \cdot (\partial_x f, \partial_y f, \partial_z f) = u_x\, \partial_x f + u_y\, \partial_y f + u_z\, \partial_z f,$$

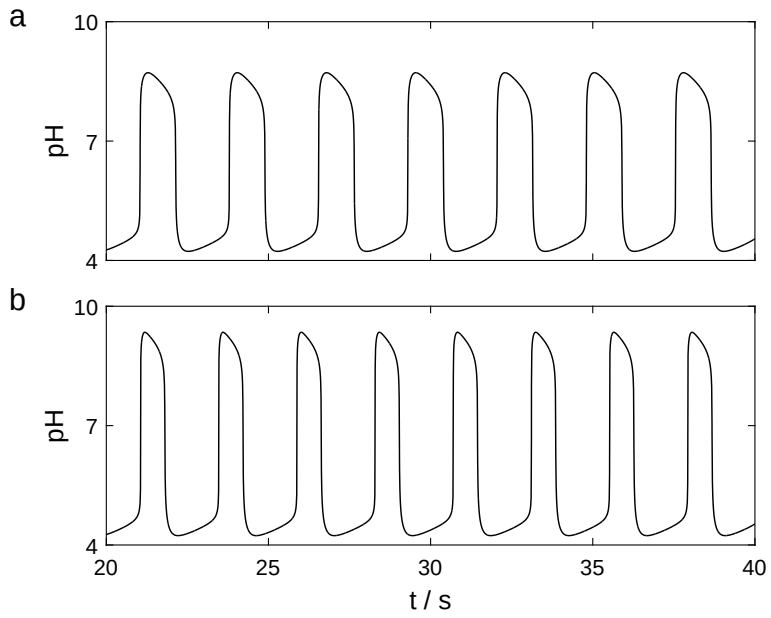

Figure 2: pH oscillations in the middle of a 100 μm wide, urease-loaded (E = 12000 u/ml) 1D compartment in contact with acidic urea solution ($[\mathrm{S}]_0 = 0.35$ mM; $[\mathrm{H}^+]_0 = 0.1$ mM) in the (a) five–variable model: eq. (S.2); and (b) two–variable model: eq. (S.4). In the five–variable model $D_\mathrm{S} = D_\mathrm{P} = D_\mathrm{PH} = 1.4 \times 10^{-5}$ cm^2 s^{-1}; $D_\mathrm{H} = 9 \times 10^{-5}$ cm^2 s^{-1}; $D_\mathrm{OH} = 6 \times 10^{-5}$ cm^2 s^{-1}.

$$D^2_{\vec{u}}\, f = D_{\vec{u}}\,(D_{\vec{u}}\, f) = u_x^2\, \partial_x^2 f + u_y^2\, \partial_y^2 f + u_z^2\, \partial_z^2 f + 2u_x u_y\, \partial^2_{xy} f + 2u_x u_z\, \partial^2_{xz} f + 2u_y u_z\, \partial^2_{yz} f$$

which, in turn, can be used in estimating f_i via Taylor–expansion as

$$f_i \approx f_0 + l\, D_{\vec{u_i}}\, f\big|_{f_0} + \frac{l^2}{2}\, D^2_{\vec{u_i}}\, f\big|_{f_0}\,.$$

By realizing that the first and mixed second partial derivatives cancel out (coefficients for

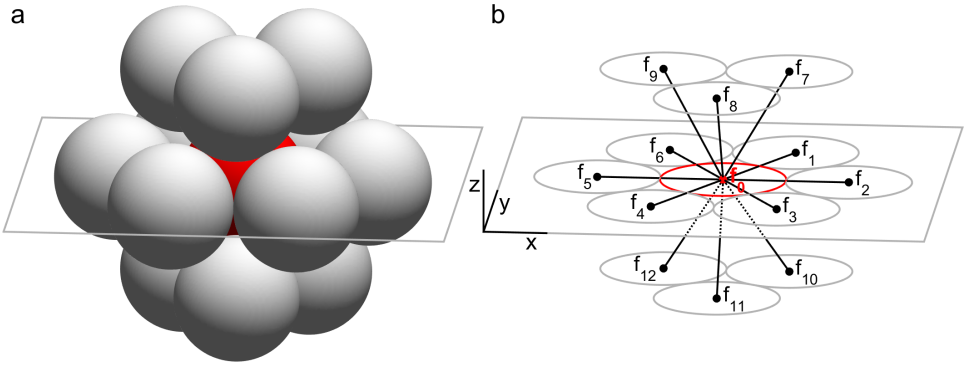

Figure 3: Unit cell configuration of hexagonal close-packed grid. f denotes $f(x, y, z)$, whereas f_0 and f_i stand for $f(x_0, y_0, z_0)$ and $f(x_i, y_i, z_i)$, respectively at the same instant in time.

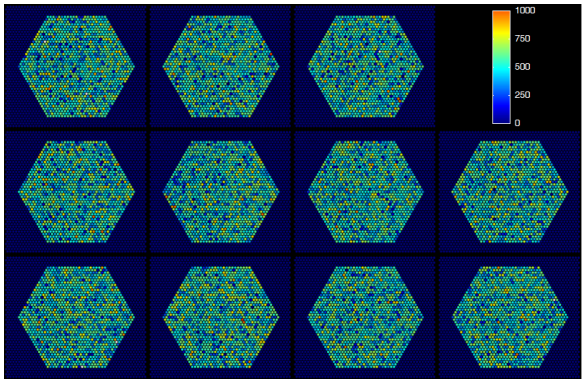

Figure 4: Spatial distributions of enzyme with mean 500 and standard deviation 150 ($\mu = 1,\ \sigma = 0.3$) within arrays of beads.

the partial derivatives are listed in Table 1), we find that

$$\sum f_i \approx 12 f_0 + 2l^2(\partial_x^2 f|_{f_0} + \partial_y^2 f|_{f_0} + \partial_z^2 f|_{f_0}),$$

thus for a grid node representing a cell in an *hcp* lattice the Laplacian can be approximated as

$$\nabla^2_{hcp} f_0 \approx \frac{\sum f_i - 12\, f_0}{2l^2}. \tag{S.6}$$

Spatial inhomogeneity in enzyme was implemented though multiplying the rate term for each microbead with a coefficient. Coefficient values were generated using the Marsaglia–Bray method [S1] and followed the normal distribution with mean (μ) equal to one and standard deviations (σ): 0.1, 0.2 and 0.3.

i	u_x	u_y	u_z
1	$1/2$	$\sqrt{3}/2$	0
2	1	0	0
3	$1/2$	$-\sqrt{3}/2$	0
4	$-1/2$	$-\sqrt{3}/2$	0
5	-1	0	0
6	$-1/2$	$\sqrt{3}/2$	0
7	$1/2$	$\sqrt{3}/6$	$\sqrt{6}/3$
8	0	$-\sqrt{3}/3$	$\sqrt{6}/3$
9	$-1/2$	$\sqrt{3}/6$	$\sqrt{6}/3$
10	$1/2$	$\sqrt{3}/6$	$-\sqrt{6}/3$
11	0	$-\sqrt{3}/3$	$-\sqrt{6}/3$
12	$-1/2$	$\sqrt{3}/6$	$-\sqrt{6}/3$

Table 1: Coefficients for partial derivatives in $D_{\vec{u}}\, f\big|_{f_0}$ and $D^2_{\vec{u}}\, f\big|_{f_0}$.

References

[S1] G. Marsaglia and T.A. Bray, *A convenient method for generating normal variables*, SIAM Review, 6, 260, 1964