Supplemental Text S2: Derivation of an analytical solution for the bulk activation model

Here we derive an exact solution for the bulk activation model described in the main text. In this model, Ras-GDP particles are converted at random to Ras-GTP at a constant frequency (# of molecules/s), taken as f_{GEF}. The steady-state equation conserving the density of free Ras-GTP in the membrane (n_S^*) and the corresponding boundary condition at the receptor ($r = S$) are given by

$$\begin{aligned} \frac{\partial n_S^*}{\partial t} &= D\nabla^2 n_S^* + \frac{f_{GEF}}{A} - k_{GAP} n_S^* - k_{on,SP} n_S^* + k_{off,SP} n_{PS} = 0; \\ -2\pi SD \left.\frac{\partial n_S^*}{\partial r}\right|_{r=S} &= 2\left(-K_{RP+S} P_P \left. n_S^*\right|_{r=S} + k_{off,SP} P_{PS}\right). \end{aligned} \tag{S2-1}$$

Here, n_{PS} is the density of Ras/PI3K complexes in the membrane, and P_P and P_{PS} are defined as the probabilities that each PI3K binding site on the receptor is occupied by PI3K alone and PI3K in complex with Ras-GTP, respectively. The factor of 2 in the boundary condition accounts for the two PI3K binding sites on the receptor (note that, for the full model, the boundary condition would have also included the time-averaged frequency of Ras-GTP generation by receptor-bound GEF activity). The steady-state conservation equation and boundary condition for n_{PS} are

$$\begin{aligned} \frac{\partial n_{PS}}{\partial t} &= D\nabla^2 n_{PS} + k_{on,SP} n_S^* - k_{off,SP} n_{PS} = 0; \\ -2\pi SD \left.\frac{\partial n_{PS}}{\partial r}\right|_{r=S} &= 2\left[k_{off,RP} P_{PS} - K_{R+PS}\left(1 - P_P - P_{PS}\right) \left. n_{PS}\right|_{r=S}\right]. \end{aligned} \tag{S2-2}$$

In this model, P_P and P_{PS} are conserved by

$$\begin{aligned} \frac{dP_P}{dt} &= k_{on,RP}\left(1 - P_P - P_{PS}\right) - k_{off,RP} P_P + k_{off,SP} P_{PS} - K_{RP+S} P_P \left. n_S^*\right|_{r=S} = 0; \\ \frac{dP_{PS}}{dt} &= K_{RP+S} P_P \left. n_S^*\right|_{r=S} + K_{R+PS}\left(1 - P_P - P_{PS}\right) \left. n_{PS}\right|_{r=S} - \left(k_{off,RP} + k_{off,SP}\right) P_{PS} = 0. \end{aligned} \tag{S2-3}$$

From Eqs. S2-1-3, it follows that

$$\begin{aligned} -2\pi SD \left.\frac{\partial\left(n_S^* + n_{PS}\right)}{\partial r}\right|_{r=S} &= -2\frac{dP_{PS}}{dt} = 0; \\ \therefore \quad n_S^* + n_{PS} &= \text{constant}. \end{aligned} \tag{S2-4}$$

Adding Eqs. S2-1 and -2, it is subsequently found that

$$\begin{aligned} \frac{\partial\left(n_S^* + n_{PS}\right)}{\partial t} &= \frac{f_{GEF}}{A} - k_{GAP} n_S^* = 0; \\ n_S^* = \frac{f_{GEF}}{k_{GAP} A}; \quad n_{PS} &= \frac{k_{on,SP}}{k_{off,SP}} n_S^* = \frac{k_{on,SP}}{k_{off,SP}} \frac{f_{GEF}}{k_{GAP} A}. \end{aligned} \tag{S2-5}$$

Finally, incorporating these results into Eq. S2-3,

$$T_P = P_P + P_{PS} = \frac{k_{on,RP} + K_{R+PS} \dfrac{k_{on,SP}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}}{k_{off,RP} + k_{on,RP} + K_{R+PS} \dfrac{k_{on,SP}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}}. \tag{S2-6}$$

The fraction of Ras-mediated receptor binding events, M_P, is found from T_P as explained in the main text.

$$M_P = \frac{K_{R+PS} \dfrac{k_{on,SP}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}}{k_{on,RP} + K_{R+PS} \dfrac{k_{on,SP}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}} = \frac{\dfrac{K_{RP+S}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}}{1 + \dfrac{K_{RP+S}}{k_{off,SP}} \dfrac{f_{GEF}}{k_{GAP} A}}. \tag{S2-7}$$