Supplemental Text S1: Detailed description of the Brownian dynamics algorithm

The Brownian dynamics (BD) approach developed here is quite general and can be used to simulate enzymatic reactions at cell membranes including arbitrary arrays of receptors and membrane-associated membrane particles. The basic idea and numerical aspects of the model have already been described in our preceding paper (1). The existing algorithm was extended to account for more realistic interactions and is composed of the following modules:

(I) A system of spatially independent processes, which includes binding and dissociation reactions of cytosolic enzymes on receptors and substrate particles, as well as the enzyme-catalyzed substrate transitions;

(II) Substrate diffusion, which combines the first-passage time algorithm to model two-dimensional diffusion of Ras particles and the acceptance-rejection rules to describe lateral interactions between substrate-bound enzymes and receptors.

The two modules of the algorithm are repeated in a loop. Discretization in time is organized so that these modules share numerical data at certain matching time points, at which the data is also redirected to output files. The accuracy of the BD algorithm has been checked against the theory (1) and nice agreement has been found. In the absence of diffusion effects, the algorithm provides nice agreement with an ODE system describing dynamics of enzyme binding/dissociation and Ras transition.

Spatially-independent reactions

The computational procedure of the first module is built according to the recently developed rule-based approach (2), which is an efficient implementation of the well-known Gillespie method (3). All receptor sites and Ras molecules are labeled and classified in accordance with reaction types. Indices of molecules and sites are stored in the corresponding arrays. At each time step, only one reaction can occur. The method requires evaluation of macroscopic reaction rates before sampling every next reaction:

$$r_1 = k_{on,SE}\, N_{GDP}^{free} \quad \text{(GEF binding to Ras-GDP),} \qquad \text{(S1-1)}$$

$$r_2 = k_{off,SE}\, N_{SE} \quad \text{(dissociation of Ras-GDP/GEF complex),} \qquad \text{(S1-2)}$$

$$r_3 = k_{act}\, N_{SE} \quad \text{(GEF-catalyzed Ras activation),} \qquad \text{(S1-3)}$$

$$r_4 = k_{GAP}\, N_{GTP}^{free} \quad \text{(inactivation of Ras-GTP),} \qquad \text{(S1-4)}$$

$$r_5 = k_{on,SP}\, N_{GTP}^{free} \quad \text{(PI3K binding to Ras\_GTP),} \qquad \text{(S1-5)}$$

$$r_6 = k_{off,SP}\, N_{SP} \quad \text{(dissociation of Ras-GTP/PI3K complex),} \qquad \text{(S1-6)}$$

$$r_7 = k_{on,RE}\, N_{RE}^{free} \quad \text{(GEF binding to receptor sites),} \qquad \text{(S1-7)}$$

$$r_8 = k_{off,RE}\, N_{RE} \quad \text{(dissociation of receptor/GEF complex),} \qquad \text{(S1-8)}$$

$$r_9 = k_{on,RP}\, N_{RP}^{free} \qquad \text{(PI3K binding to receptor sites),} \qquad \text{(S1-9)}$$

$$r_{10} = k_{off,RP}\, N_{RP} \qquad \text{(dissociation of receptor/PI3K complex).} \qquad \text{(S1-10)}$$

Here, N_{GDP}^{free} and N_{GTP}^{free} denote the numbers of free Ras particles in the GDP and GTP states, respectively; N_{SE}, N_{SP}, N_{RE} and N_{RP} denote the numbers of molecular pairs (bonds) in complexes Ras-GDP/GEF, Ras-GTP/PI3K, receptor/GEF and receptor/PI3K, respectively; N_{RE}^{free} and N_{RP}^{free} are the numbers of free receptor sites available for an association reaction with GEF and PI3K, respectively. The concentration of each enzyme in the cytosol is assumed to be constant, and therefore, all bimolecular reactions with cytosolic enzymes are considered as pseudo-first order processes (cytosolic concentrations are lumped into binding rate constants).

In the system of spatially independent Poisson processes, the waiting time to the next reaction event is defined as

$$\Delta t_I = -\ln(z_1)/r_{tot}, \qquad \text{(S1-11)}$$

where $r_{tot} = \sum_{i=1}^{10} r_i$ and z_1 is a random number uniformly distributed on (0,1). To select the next reaction type (rule), the smallest integer J should be found satisfying the following condition:

$$\sum_{j=1}^{J} r_j > z_2 r_{tot}, \qquad \text{(S1-12)}$$

where z_2 is a second random number. Note that the final probability of the reaction to occur depends on the time step defined by the diffusion part (module II). Each accepted reaction is associated with a rule that updates arrays of receptor sites or Ras molecules; the index of receptor site or Ras molecule is picked randomly in the corresponding array, and shifted from the array of reactants to the array of products.

Surface diffusion module

The time step between matching points of the two modules is given by

$$\Delta t_{out} = \min\{\Delta t_I,\ \Delta t_{II}\}, \qquad \text{(S1-13)}$$

where Δt_{II} is a maximum allowed time step for random walks, specified according to $\Delta t_{II} = (\nu\, S)^2/(4D)$, with $\nu \sim O(10)$.

Within each time interval Δt_{out}, all particles are advanced iteratively. In the BD algorithm, we assume that the substrate particles do not interact with each other, and therefore, their lateral diffusion and interactions with receptor-bound enzymes can be modeled in two ways, as illustrated schematically in Fig. S1-1. In the first scheme (Fig.

S1-1a), within the specified time interval $(t, t + \Delta t_{out})$ all particles make random walks with the same radial displacement, $d_i = 2\sqrt{D\,\Delta t_i}$, where Δt_i is the i th elementary time step. In the second scheme (Fig. S1-1b), each particle is advanced with no connection to other particles until the time exceeds $t_{out} = t + \Delta t_{out}$. The simulations implementing both schemes have shown that the second scheme is more efficient. In both schemes, a new random walk position of the particle is chosen according to the circle point-picking algorithm (4).

According to the second propagation scheme (Fig. 1-1b), the time step for the i th random displacement of each particle is defined as

$$\Delta t_i = \min\{d_{\min}^2 / (4D), t_{out} - t_i\}; \qquad \sum_i \Delta t_i = \Delta t_{out}, \qquad \text{(S1-14)}$$

where $d_{\min}$ is the minimum receptor-particle distance and t_i is the moment in time before the next, $(i + 1)$ th step.

Formation of a receptor/enzyme/Ras complex is only possible when Ras reaches the encounter distance with the receptor bound enzyme, i.e., when the particle is inside the reactive layer of thickness delta, $d_{\min} \le \delta$. Once that happens, the time for this reaction is very short, much less than average times for interactions of cytosolic enzymes with receptors and Ras. The binding probability is calculated as

$$P(K, \Delta t_{RL}) = 1 - \frac{p_A(r_n, r_0, K, \Delta t_{RL})}{p_R(r_n, r_0, K, \Delta t_{RL})}, \qquad \text{(S1-15)}$$

where $K = K_{RM+S}$ or K_{R+MS}, r_0 and r_n are previous and new radial positions of the particle relatively the receptor/enzyme boundary, respectively; p_A and p_B are probability distributions, which describe particles diffusing near absorbing and reflection boundaries, respectively (1,5,6). Calculation of p_A requires evaluation of the complementary error function, $\mathrm{erfc}(x)$. To evaluate $\mathrm{erfc}(x)$ more efficiently, a lookup table was used. Inside the reactive layer, planar geometry is assumed ($\delta << S$), the time step is constant ($\Delta t_{RL} = 10^{-9}$ sec), and new particle coordinates are sampled from the Gaussian distribution using the Box-Muller method for generation of Gaussian deviates (7). Selection of any particular lateral interaction is made according to the following rule: if there are more than one possibility for a diffusing particle to bind receptor sites, a set of $P_j(K_j, \Delta t_{RL})$ is calculated (Eq. S1-15), and then, the receptor binding site is selected by sampling from the set of weighted probabilities (all sites may also be rejected). If the 2D binding is accepted, then the particle is assigned to the corresponding receptor/enzyme binding site.

The final probability of the event that has been selected among spatially independent reactions (module I) is calculated as

$$P_I = s \min\{1, \Delta t_{out} / \Delta t_I\}. \qquad \text{(S1-16)}$$

If the reactant selected in module I is also chosen to react through 2D interaction in module II, then $s = 0$, and the reaction selected in module II is accepted; otherwise, $s = 1$. If $P_I > z_3$, where z_3 is a uniform random deviate on (0,1), then the reaction selected in module I is accepted.

Dissociation of a receptor/enzyme/Ras complex takes place when either the receptor/enzyme or enzyme/Ras bond breaks, and the Ras particle in the enzyme-bound or free state is placed at a random position inside the reactive layer.

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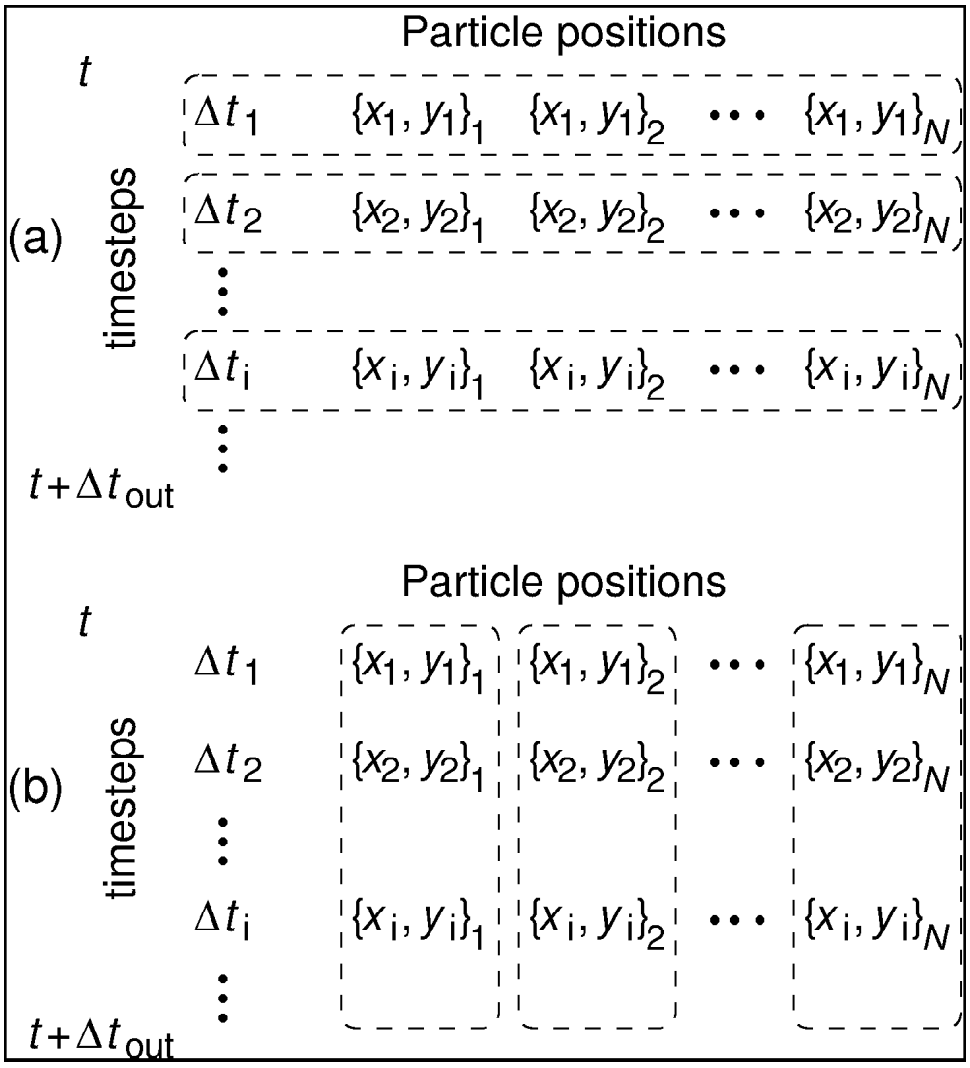

Figure S1-1. Illustration of two distinct particle advancement schemes. *a*. In the first scheme, within specified time interval $(t, t + \Delta t_{out})$ all particles make random walks with the same radial displacement, $d_i = 2\sqrt{D\,\Delta t_i}$, where Δt_i is ith elementary time step, until the specified time $t_{out} = t + \Delta t_{out}$ is reached. *b*. In the second scheme, each particle is advanced with no connection to other particles until the time exceeds $t_{out} = t + \Delta t_{out}$.