Distance dependence of readout accuracy of intracellular $\text{Ca}^{2+}$ signaling

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$\text{Ca}^{2+}$ signaling is crucial for feedback of a living organism to external stimulation. In intracellular space, $\text{Ca}^{2+}$ signal propagates between organelles, and usually takes effect at a position far away from calcium pump. The readout accuracy of $\text{Ca}^{2+}$ signal is relevant to the spatial location of organelles involved. In this work, we develop a qualitative frame to study the distance dependence of readout accuracy of intracellular $\text{Ca}^{2+}$ signal. When $\text{Ca}^{2+}$ ion enters the system without velocity, the signal may become a global signal fast, and die away in the propagation. To keep the locality of $\text{Ca}^{2+}$ signal, the penetrability of $\text{Ca}^{2+}$ signal in intracellular space can be regulated through adjusting the initial speed of $\text{Ca}^{2+}$ ion. The result suggests that the distance between entrance and the position where the signal is read out should be considered to estimate the readout accuracy of signal.

I. INTRODUCTION

A living organism is a busy and orderly cell society. The maintenance of this society depends not only on material and energy transport, but also on cell communication and signal transmission extracellularly and intracellularly [1, 2]. The signal transmission system is the basis of adaptability of an organism to external stimuli, which coordinate cell behavior, and then adapt to external environment, such as cell growth, division, differentiation, low temperature, lighting, and mechanical damage [3, 4].

The extracellular stimulation regulates cell behavior by converting it into an intracellular signal response. Signal molecules are the key components of intracellular signaling, and their physical space constraints play an important role in cell signaling pathways. The receptor density, distribution, and clustering may be key spatial features influencing the physical and biochemical responses to many regulatory signals, among which receptor clusters have a certain effect on receptor-ligand binding [5–7]. Goyette et al. motioned that receptor aggregation affects the trigger of T cell receptor and transforms it into appropriate intracellular signal, and emerged as a key regulatory element in signal transduction of this archetypal immune receptor [8]. The relative position are also found important to the communication and material transport between membranes and organelles [9, 10]. Physical study has also revealed a new role of the endosomal network in signal processing by governing the spatio-temporal distribution of signaling molecules [11]. In addition, by measuring concentration of chemoattractants, it is possible to assess the number of specific receptors required and their effect on chemotaxis [12]. Hence, the extracellular and intercellular spatial locations are important in cell signal pathway, and its effect should be considered in relevant studies.

$\text{Ca}^{2+}$ is ubiquitous signal messenger in cell [1, 2]. It is generally believed that the response of cells to many external environment and hormone stimulation is through the change of free $\text{Ca}^{2+}$ concentration in cytoplasm. $\text{Ca}^{2+}$ ion can mediate phosphatidylinositol signaling pathway, $\text{IP}_3$-$\text{Ca}^{2+}$. $\text{IP}_3$ can mobilize the endogenous $\text{Ca}^{2+}$, transfer $\text{Ca}^{2+}$ stored in the endoplasmic reticulum to the cytoplasm, and increase intracellular $\text{Ca}^{2+}$ concentration. The PKC translocates in cytoplasm to the inner surface of plasma membrane, is activated by DAC, and then the substrate protein is phosphorylated. Calmodulin (CaM) is a common $\text{Ca}^{2+}$ responsive protein in eukaryotic cells. It can combine with $\text{Ca}^{2+}$ to form $\text{Ca}^{2+}$-CaM complex, and then combine with target enzyme (such as PKC) to activate it.

$\text{Ca}^{2+}$ enters cytoplasm from calcium pump, and diffuses intracellularly, and finally it will be read out. The readout of a $\text{Ca}^{2+}$ signal does not equal directly to the position of $\text{Ca}^{2+}$ ion. In Refs. [13, 14], the authors developed a frame to estimate the accuracy of the position of $\text{Ca}^{2+}$ signal by the spatial distribution of phosphorylation events. $\text{Ca}^{2+}$ ion can mediate phosphorylation events, which contribute to the readout of $\text{Ca}^{2+}$ signal. In their work, the propagation of $\text{Ca}^{2+}$ is simplified to a 1-dimensional diffusion while in a realistic cell $\text{Ca}^{2+}$ moves from calcium pump in 3-dimensional space. $\text{Ca}^{2+}$ ion enters cytoplasm from endoplasmic reticulum through a calcium pump, and the phosphorylation happens in plasma membrane. In this procedure, $\text{Ca}^{2+}$ ion need diffuse in cytoplasm when propagating from calcium pump to target enzyme. With the increasing of distance from calcium pump, the estimation error of position of $\text{Ca}^{2+}$ can be expected to become larger. It will lead to an interesting aftermath. If estimation error of readout of the position of $\text{Ca}^{2+}$ signal becomes very large to be comparable to the size of a cell, the effect of $\text{Ca}^{2+}$ is global. The velocity of $\text{Ca}^{2+}$ ion from calcium pump will affect readout accuracy also. One can expect that the locality of a $\text{Ca}^{2+}$ signal can be restored with a large speed of $\text{Ca}^{2+}$. However, there is no quantitative model to describe such phenomenon in the literature.

In this work, we will study the distance dependence of readout accuracy of intracellular $\text{Ca}^{2+}$ signaling. A toy scenario will be introduced first to show the basic frame to read out the 3-dimensional position of $\text{Ca}^{2+}$ by the phosphorylation events.
The effect of velocity are also discussed. Then, we will study the variation of spatial distribution of phosphorylation events in response to Ca\textsuperscript{2+} signal with the increase of distance for a cytosolic and a membrane binding kinase. One can find that with the increasing of distance it becomes more difficult to locate the position of Ca\textsuperscript{2+} while a large speed will slow it down obviously. And the results for cytosolic will trends to these for membrane binding kinase with small speed of Ca\textsuperscript{2+} and the increasing of distance.

II. THE TOY SCENARIO

Due to the complexity of Ca\textsuperscript{2+} signal propagation, we first use a toy scenario to present the theoretical frame adopted in the current work (see Fig. 1). In toy scenario, Ca\textsuperscript{2+} ion enters the system from a calcium pump at \( r = (x, y, z) = 0 = (0, 0, 0) \) on endoplasmic reticulum, which is idealized as a large plane at \( x \) and \( y \) directions, and activates a kinase immediately. Here, we assume that the active kinase carrying an initial velocity \( v \), which is unchanged before the Ca\textsuperscript{2+} ion is lost. It is natural to assume that the velocity is in a direction along \( z \) direction perpendicular to the endoplasmic reticulum. Then, the active kinase phosphorylates at a rate of \( v_p \). At the same time, the Ca\textsuperscript{2+} ion detaches from the active kinase and leaves system at a rate of \( v_l \). Endoplasmic reticulum reflects kinase regardless of whether it is active. Such a scenario is also the simplest scenario for the signal propagation.

\[
\frac{\partial P_a[n(\xi); r, t]}{\partial t} = D(\nabla^2 - v\partial_z)P_a[n(\xi); r, t] - v_lP_a[n(\xi); r, t] + v_P[P_a[n(\xi) - \delta(\xi - r); r, t] - P_a[n(\xi); r, t]],
\]

The active kinase diffuses by constant \( D \) and is lost at a rate of \( v_l \), which is relevant to the former probability. The Dirac delta function \( \delta(\xi - r) \) means a phosphorylation event happens at \( r \), then, the distribution jumps from \( P_a[n(\xi) - \delta(\xi - r); r, t] \) to \( P_a[n(\xi); r, t] \) at a rate of \( v_P \). It makes two probabilities independent, so we have to adopt one probability function instead of the product of two independent probability functions to denote a state. Analogously, \( P_i[n(\xi); t] \) is for the distribution when the kinase is inactive.

Ca\textsuperscript{2+} ion enters system at position of \( r = 0 \), which leads to an initial condition as,

\[
P_a[n(\xi) = 0; r, t = 0] = \delta(\xi).
\]

Different from Refs. [13, 14], because active kinase will be reflected by boundary, we have an additional boundary condition at \( z = 0 \) as

\[
\partial_P[n(\xi); r, t] |_{z=0} = 0.
\]

After a dimensionless treatment, the time and space are scaled by \( v_l \) and \( \sqrt{v_l/D} \), respectively.

B. Stochastic simulation of the master equation

Because two independent possibilities involve in the function \( P_a[n(\xi); r, t] \), it is difficult to be solved analytically. However, the master equation can be simulated numerically. In the current work, we adopt the Gillespie algorithm to do the stochastic simulation [15] as in Refs. [13, 14] but in 3-dimensional space with a boundary at \( z = 0 \).

Ca\textsuperscript{2+} ion attached to a kinase enters system at \( r = 0 \). An event occurs to the active kinase in a step of time \( \Delta t = -\ln r/(1 + v_p) \) with \( r \) being a random number in a range from 0 to 1. This event is phosphorylation or inactivation, which is determined by drawing a random number from 0 to 1 + \( v_p \). The 1 is for the inactivation rate \( v_l \), which is scaled to 1, and the \( v_p \) is for scaled phosphorylation rate. If the random number is smaller than 1, simulation stops. If not, the position of active kinase is changed in three directions by drawing three independent random numbers \( \Delta x \) from the Gaussian distribution with zero mean and variance \( 2\Delta x \). For the position in the \( x \) or \( y \) direction, the \( \Delta x/\Delta y \) is added to the current position directly. But for the \( z \) direction, an additional change \( v_l\Delta t \) should be added for the velocity, and if new position \( z < 0 \), kinase should be reflected by endoplasmic reticulum as \( z \leq 0 \). Phosphorylation event happens in this step of time and the position is recorded as \( \xi_i \). The simulation continues, and a new time step is drawn for next loop. When simulation ends, we have a trajectory of \( n_0 \) phosphorylation events. With \( N \) simulations, we obtain \( n \) trajectories with phosphorylation events.

In Refs. [13, 14] where a one-dimensional study was performed, the mean position \( \bar{\xi} = \sum_{i=1}^{n_0} \xi_i/n_0 \) was used to estimate the position of Ca\textsuperscript{2+}. The estimation error \( \bar{\xi}^2 \) is calculated by the sum of mean position squares as \( \bar{\xi}^2 = \sum_{k=1}^{n} \xi_k^2/n \). We
would like to remind that if a simulation does not raise any phosphorylation event, we do not count it into the number of trajectories \( n \). In the current work, we will study the distance dependence of accuracy to estimate the position of \( \text{Ca}^{2+} \). In order to determine event distribution and estimation error at \( z \), we will collect all mean position of a simulation \( \xi \) which has \( z - \delta z / 2 < \xi < z + \delta z / 2 \), with a number \( n_z \). The number distribution is defined as \( P(z) = n_z / (n \delta z) \) and the estimation error as \( \ell^2(z) = \sum_{k=1}^{n_z} (\xi_{zk} - \xi_z)^2 / n_z \). Here, the number distribution \( \hat{P}(z) \) is for the phosphorylation trajectories, not for the phosphorylation events.

### C. Limitation of \( \nu_p << 1 \)

In one-dimensional case without velcity, the master equation can be solved analytically in the limitation of \( \nu_p << 1 \) where the probability of having a trajectory with two or more phosphorylation events is negligible [14]. In this case, the \( \xi \) tends to the position of kinase where the phosphorylation happens. In the followings, we will check if it is still valid in 3-dimensional case with a velocity.

The probability function of phosphorylation distribution is,

\[
P[n; t] = P_a[n; t] + \int dP_a[n; t]
\]

where \( P_a[n; t] \) or \( P_a[n; t] \) is the probability of having an active kinase at \( r \) (or after inactivation of the kinase) where a phosphorylation event had occurred at position \( \xi \).

The \( P_a[n; t] \) and \( P_a[n; t] \) are connected into the \( P_a[n; t] \), which is the probability of having, at time \( t \), an active kinase at \( r \) without any phosphorylation, as

\[
\partial_t P_{a[s]}(\xi; t) = (\nabla^2 - \nu \partial_z) P_{a[s]}(\xi; t) + \nu_p \delta(\xi - r) P_{a[s]}(r; t) - P_{a[s]}(\xi; t).
\]

After integrating above equation and inserting it into Eq. (4), we can obtain the probability function of phosphorylation distribution as

\[
P(\xi) = \nu_p \int_{0}^{\infty} \partial_t P_{a[s]}(\xi; t') dt',
\]

where we take time to \( \infty \), which means phosphorylation have finished.

Under the limitation of \( \nu_p << 1 \), the master equation for \( P_a(r; t) \) is reduced to

\[
\partial_t P_a(r; t) = (\nabla^2 - \nu \partial_z) P_a(r; t) - (1 + \nu_p) P_a(r, t),
\]

with initial condition \( P_a(r; 0, t) = \delta(r) \). We integrate above equation in respect to time \( t \) and have

\[
\nu_p \delta(r) = (\nabla^2 - \nu \partial_z) P(r) - (1 + \nu_p) P(r).
\]

We make the Fourier and Laplace transformation with respect to \( x/y \) and \( z \) directions, respectively, and it yields,

\[
P(\hat{q}, z) = \frac{v_p}{\omega_+ (q)} e^{-\omega_+ (q) z}
\]

with \( \omega_+ (q) = \sqrt{v^2/4 + q^2} + v_p / 2 \). Here, \( q^2 \equiv q_x^2 + q_y^2 \) with \( q = (q_x, q_y) \) for the Fourier transformation in the \( x/y \) direction. Refer to Appendix for the explicit method.

Distribution of number in \( z \) direction can be obtained as,

\[
\hat{n}(\xi_z) = \int d\xi_x d\xi_y P(\xi) = P(\hat{q}_z, \xi_z)_{\hat{q}_x = 0} = \frac{v_p e^{-\omega_+ \xi_z}}{\omega_+},
\]

with \( \omega = \sqrt{1 + v_p} \). The results with a rate of \( v_p = 0.05 \) are presented in Fig. 2 and compared with results from \( 10^7 \) stochastic simulations.

![FIG. 2. The simulation points, estimation error \( \ell^2(\xi_z) \) and number of the phosphorylation events \( \hat{n}(\xi_z) \) with a small rate of \( v_p = 0.05 \) from \( 10^7 \) stochastic simulations in toy scenario. The upper two panels are for the simulations with the horizontal and vertical coordinates are for the \( \xi_z \) and \( \xi_x \), respectively. The lower two panels are for the \( z \) dependence of the error \( \ell^2(\xi_z) \) and number \( \hat{n}(\xi_z) \). The left and right two panels are for speed \( v = 0 \) and 5, respectively.](image.png)

As expected, under the limitation of \( \nu_p << 1 \), the analytical results fit the stochastic simulation very well. The simulation events exhibit the effect of velocity obviously. With zero speed, the events condensate near the position where \( \text{Ca}^{2+} \) enters system. If the \( \text{Ca}^{2+} \) ion attached to a kinase has a non-
zero speed, the events spread further in the direction of velocity. Moreover, the estimation error $\ell^2(z)$ decreases obviously slower than the case with zero speed.

### D. Mean-field ansatz

Now we consider the mean-field ansatz where the phosphorylation rate at position $x$ is assumed to be proportional to the probability of finding a kinase at this position. Let $p_a(r, t) = \int Dn(\hat{q}) n(\hat{q}, r, t) d\hat{q}$ denotes the probability of finding an active kinase at $r$, where the functional integral extends over all possible phosphorylation distributions $n(\hat{q})$ with $n(\xi) \geq 0$ for all $\xi$.

The probability of having $n$ phosphorylation events at position $r$ at time $t$, $P(n, r, t)$ is determined by

$$P(0, r, t) = -\nu_p p_a(r, t) P(0, r, t),$$

$$\dot{P}(n, r, t) = \nu_p p_a(r, t)[P(n - 1, r, t) - P(n, r, t)],$$

with initial condition as $P(0, r, 0) = \delta(r)$. It yields $P(n, r, t) = \frac{\nu_p}{n!} p_a(r, t)^n e^{-\nu_p \bar{p}_a(r, t)}$ with $\bar{p}_a(r, t) = \int_0^t dt' p_a(r, t')$ which is similar to the results in Ref. [14]. The mean number of phosphorylation events at $r$ is $\bar{n}(r, t) = \sum_{n=0}^\infty n P(n, r, t) = \nu_p \bar{p}_a(r, t)$. The time evolution of $p_a$ obeys

$$\hat{\partial}_t p_a(r, t) = (\nabla^2 - v^2) p_a - p_a(r, t).$$

After integrating on the time $t$ from 0 to $\infty$, we have,

$$-\hat{\partial}(r, t) = (\nabla^2 - v^2) \bar{p}_a(r) - \bar{p}_a(r).$$

By making a Fourier and cosine transformation with respect to $x/y$ and $z$, respectively, and it yields,

$$\bar{n}(\hat{q}, z) = \nu_p \bar{p}_a(\hat{q}, z) = \frac{\nu_p}{\omega_+} e^{-\omega_+ |z|},$$

with $\omega_+ = \sqrt{v^2 + 4 + 1 \pm v/2}$. We can obtain the distribution in the $z$ direction,

$$\bar{n}(z) = \bar{n}(\hat{q}, z)|_{q=0} = \frac{\nu_p}{\omega_+} e^{-\omega_+ z},$$

In the spirit of the mean-field ansatz, we replace the expression for the estimation error by

$$\ell^2(z) = \frac{\int dxdy (x^2 + y^2) \bar{n}(x, y, z)}{\int dxdy \bar{n}(x, y, z)}
= \frac{1}{\bar{n}(z)} \nabla^2 \bar{n}(\hat{q}, z)|_{q=0} = \frac{2(1 + z \omega_+)}{\omega_+}.$$

One can find that the result in the mean-field ansatz is close to that under small $\nu_p$ limit. In fact, the mean-field equations can only be expected to work well in the cases when the number of phosphorylation events in a trajectory is small, that is, when two or more phosphorylation events for a single Ca$^{2+}$ ion are rare. The realistic phosphorylation rate $\nu_p$ is about $2/s$ [16] while the $\nu_1 = 40/s$ [17], which leads to a scaled $\nu_p \approx 0.05$, which is sufficient to apply the mean filed ansatz.

### E. Dependence on the $\nu_p$

As analyzed above, the mean field ansatz is only valid in the cases for a small phosphorylation rate $\nu_p$. However, the stochastic simulation works at all $\nu_p$. In Fig. 3, we present the results for different values of $\nu_p$ from 0.01 to 100.

![FIG. 3. The estimation error $\ell(z)$ and number $n(z)$ with different phosphorylation rates. The lines for $\nu_p = 0.01$ and 0.1 are drawn by using Eq. (10) and Eq. (11). Other lines are obtained by fitting the simulation results linearly and exponentially for $\ell(z)$ and $\bar{n}(z)$, respectively.](image)

For all values of the $\nu_p$, without velocity the estimation error $\ell^2(z)$ increases rapidly with the increasing of distance from entrance. If the Ca$^{2+}$ ion attached to the kinase has a velocity, the increase of estimation error against distance becomes slower, which indicates higher readout accuracy of the position of Ca$^{2+}$ ion. Besides, with the increasing of speed, the number decreases much slower along the $z$ direction, which suggests that the signal penetrates further in intracellular space and can be read out more easily.

With the increasing of the $\nu_p$, the estimation error $\ell^2(z)$ reduces and reaches a minimum. And a large rate leads to a large number $\bar{n}(z)$. For the $\nu_p = 0.01$ and 0.1, we use Eq. (10) and Eq. (11) to give the analytical results, and one can find that these lines fit the simulation very well. For larger $\nu_p$, the small $\nu_p$ approximation becomes invalid. We give linear and exponential fits for estimation error and number, respectively. The results suggest that estimation error and number still vary with distance linearly and exponentially, respectively.

### III. THE CAM SCENARIO

Now, we turn to a more realistic scenario. In CaM scenario, the kinase will be activated when Ca$^{2+}$ diffuses in cytoplasm (see Fig. 4). Ca$^{2+}$ ion enters system at $r = 0$ on endoplasmic reticulum with an initial velocity $v$. Here, we still assume the
velocity is along the z direction perpendicular to the endoplasmic reticulum, which reflects Ca\(^{2+}\) ion and kinase regardless of whether it is active. If not losing into cytosolic, the moving Ca\(^{2+}\) ion attaches and activates the kinase. After attachment, the velocity of combined kinase and Ca\(^{2+}\) ion is assumed to disappear due to their large mass difference. Then, the active kinase phosphorylates at a rate of \(v_p\). At the same time, the Ca\(^{2+}\) ion may detach form active kinase at a rate of \(v_d\). The detached Ca\(^{2+}\) ion may leave the system at a rate of \(v_l\), or attach a kinase and begin a new loop again.

**A. Master equation**

Since Ca\(^{2+}\) ion does not attach and active a kinase immediately, we should introduce a function to describe such state. As the \(P_a[(n(\xi); r, t)] \) is defined as the probability distribution, when Ca\(^{2+}\) is present, but not attached to the kinase. Different from Refs. [13, 14], Ca\(^{2+}\) ion enters system with a velocity \(v\), and after an attachment, the velocity is lost. We should distinguish the states with and without velocity. As in toy scenario, we adopt the Gillespie algorithm to do stochastic simulation. After Ca\(^{2+}\) ion entering system, an event, attachment or leaving system, occurs and is determined by drawing a random number from \(0\) to \(v_l + v_d\). The position of Ca\(^{2+}\) ion is changed in three directions randomly. In the z direction, an additional movement from velocity as \(v\Delta t\) should be added in the first loop. Besides, if new position \(z < 0\), the kinase should be reflected by boundary as \(|z|\). The kinase may phosphorylate target protein or inactivate in a new step of time. The type of event is still determined by drawing a random number. At the same time, if phosphorylation happens, the position is recorded. If the Ca\(^{2+}\) ion detaches from the active kinase, simulation continues to a new loop.

In Fig. 5, we present the results for the simulation points, estimation error and number for phosphorylation trajectories with \(v_l=10,\ v_d=10,\ v_p=20,\) and \(D_K=0.02\) from 10\(^7\) stochastic simulations. Here, the values of parameters are cited from Refs. [16–19].

**B. Stochastic simulation of the master equation**

As in toy scenario, the explicit description is presented in text.
signal has large penetrability, and the simulation points spread farther along the $z$ direction, which leads to slow increase of the estimation error and slow decrease of the number.

C. Mean-field ansatz

Now we give analytical results in the mean-field ansatz. As in the toy scenario, the expected number $\hat{n}$ of phosphorylation trajectories in the limit $t \to \infty$ is $\hat{n} = \bar{P}_d(r)$. where the barred quantities indicate as above time-integrated quantities. To obtain the distribution of the expected phosphorylation trajectories, we are then left with solving,

$$\begin{align*}
-\delta(r) &= (\nabla^2 - vi\partial_z)\bar{P}_d(r) - (\nu_a + \nu_i)\bar{P}_a(r), \\
0 &= \nabla^2 \bar{P}_a(r) + \nu_d\bar{P}_a(r) - (\nu_a + \nu_i)\bar{P}_i(r), \\
0 &= D_K \nabla^2 \bar{P}_d(r) - \nu_d\bar{P}_d(r) + \nu_a[\bar{P}_i(r) + \bar{P}_o(r)].
\end{align*}$$

(21)

As presented explicitly in Appendix, we make a Fourier and Laplace transformation with respect to $x/y$ and $z$ directions, respectively, and it yields,

$$\begin{align*}
\hat{n}(z) &= \frac{\nu_a}{D_K} \frac{\omega_x}{\omega_z} \left[ \frac{\omega^2 - \lambda_+^2}{\lambda_+(\lambda_+^2 - \omega_x^2)(\lambda_+^2 - \lambda_-^2)} e^{-\lambda_+ z} + \frac{\omega^2 - \omega_x^2}{\omega_x(\omega_x^2 - \lambda_+^2)(\omega_x^2 - \lambda_-^2)} e^{-\omega_x z} + \frac{\omega^2 - \lambda_-^2}{\lambda_-(\lambda_-^2 - \omega_x^2)(\lambda_-^2 - \lambda_+^2)} e^{-\lambda_- z} \right],
\end{align*}$$

(22)

where $\omega_{\pm} = \sqrt{(\nu_a + \nu_i) + \nu_d} \pm \nu_d/2$ and $\omega = \sqrt{\nu_a + \nu_i}$. $\lambda_{\pm} = \sqrt{(a \pm \sqrt{a^2 - 4b})/2}$ with $a = (\nu_a + \nu_i) + \nu_d/D_K$ and $b = \gamma \nu_d/D_K$. The analytical expression for the estimation error $\ell^2(z)$ is very complicated and given in Appendix. As discussed in the toy scenario, the realistic value of the $\nu_p$ is very small, which suggests the mean-field ansatz workable with such parameters. In Fig. 5, we compare the simulation results with the results obtained by Eqs. (22) and (A11). The mean field ansatz describes simulation results quite well for both estimation error and number.

In Fig. 6, we present the dependence of estimation error and number on distance $z$ and speed $v$, respectively. As shown in left panels, if Ca$^{2+}$ enters system without velocity, the estimation error increases rapidly with the increasing of distance. With large speed of Ca$^{2+}$, the gradient of curves for estimation error against $z$ becomes small. For a speed of 50, the estimation error is only about 0.8 at a distance $z$ of about 9. With a large speed of several hundreds, the estimation error is very small and almost unchanged with the variation of distance. The number also decreases with the increasing of distance, but large velocity will slow down such decrease as for the estimation error.

In right panels, for a certain distance $z$, the estimation error first decreases very rapidly, and then slowly with the increasing of speed. Finally it becomes stable at large speed. For larger distance, larger speed is needed to get a stable estimation error. Difference of estimation error for different distances becomes small at large distance. The number tends to a stable value also with the increase of speed.

For both estimation error and number, analytical results with the mean-field ansatz fit the simulation well. And as in the toy scenario, velocity makes signal propagate to further distance. For example, for Ca$^{2+}$ ion without velocity, the estimation error will increase to 1 at $z$ of about 2, which corresponds to 15.8 $\mu$m at 31.6 $\mu$m. With a large speed, the error with the current parameters keeps about 5$\mu$m even at a distance larger than 100 $\mu$m, which is a standard size of a cell.

D. Dependence of the parameters

In above figure, we adopt the values of parameters suggested in the literature [16–19]. It is interesting to discuss the uncertainty from the different values of the parameters. In Fig. 7, we present the variation of the estimation error against the distance with different parameters.

A large attachment rate $\nu_a$ will increase the possibility to produce a trajectory of phosphorylation event. However, the variation of estimation error is obviously smaller than expected. The results with $\nu_a$ of 50 is about 0.2 larger than the one of 0.5. The effect of detachment rate variation is smaller. The result with $\nu_d$ of 50 is only about 0.05 larger than the one of 0.5. The variation of the estimation error is more sensitive to the last rate $\nu_i$ and the diffuse constant $D_K$. It is interesting to see that though larger $\nu_a$ and $D_K$, smaller $\nu_d$ and $\nu_i$, lead to more phosphorylations, the error decreases instead. Besides, one can find that the results with smaller $\nu_a$ and $D_K$, larger $\nu_d$ and $\nu_i$, fit the simulation better. All these cases mean few phosphorylations, which is more consistent with the mean field ansatz as discussed in the toy scenario.
IV. THE PKC SCENARIO

Now, we turn to the PKC scenario, that is, phosphorylation happens when active kinase is bound into plasma membrane (see Fig. 8). In Refs. [13, 14], the propagation along the vertical direction of the membrane was neglected, and Ca\(^{2+}\) ion enters and binds to the same plane. In the current work, we consider a more realistic scenario. Ca\(^{2+}\) ion enters from endoplasmic reticulum as an infinite plane and propagates to plasma membrane as another plane at a distance.

![Diagram](image)

FIG. 8. The PKC scenario for Ca\(^{2+}\) signal propagation. The explicit description is presented in text.

We describe the scenario more explicitly in followings. Ca\(^{2+}\) ion enters system at \( r = 0 \) on endoplasmic reticulum with an initial velocity \( v \). Here, we still assume the velocity along \( z \) direction perpendicular to endoplasmic reticulum, which is parallel to the plane for plasma membrane. Endoplasmic reticulum will reflect Ca\(^{2+}\) ion and kinase regardless of whether it is active, while plasma membrane reflects Ca\(^{2+}\) and inactive kinase. Different from inactive kinase, active kinase has a possibility to be bound onto plasma membrane at a rate of \( v_a \). Active kinase phosphorylates target protein at a rate of \( v_p \). At the same time, the bound kinase may unbind from plasma membrane at a rate of \( v_d \). After unbinding from plasma membrane, Ca\(^{2+}\) ion may detach from active kinase at a rate of \( v_{d} \). The detached Ca\(^{2+}\) ion may leave the system, or attach a kinase and begin a new loop again.

A. Master equation

Besides the state functions in the CaM scenario, a new state function \( \mathcal{P}_b[n(\bar{\xi}); \bar{r}, t] \) is defined as the probability distribution, when Ca\(^{2+}\) attaches to a kinase and binds into plasma membrane. Because plasma membrane is at a fixed distance from endoplasmic reticulum, we adopt \( \bar{r} \) to denote the \( r \) with \( z \) equaling to the distance \( l \). They obey the following master equation:

\[
\begin{align*}
\frac{\partial}{\partial t}\mathcal{P}_a[r, t] &= D_C(\nabla^2 - v_\partial)\mathcal{P}_a[r, t] \\
\frac{\partial}{\partial t}\mathcal{P}_i[n(\bar{\xi}); r, t] &= D_N(\nabla^2 - v_\partial)\mathcal{P}_i[n(\bar{\xi}); r, t] \\
\frac{\partial}{\partial t}\mathcal{P}_a[n(\bar{\xi}); r, t] &= D_N(\nabla^2 - v_\partial)\mathcal{P}_a[n(\bar{\xi}); r, t] \\
\frac{\partial}{\partial t}\mathcal{P}_b[n(\bar{\xi}); \bar{r}, t] &= v_p\mathcal{P}_a[n(\bar{\xi}); \bar{r}, t] - v_p\mathcal{P}_b[n(\bar{\xi}); \bar{r}, t] \\
\frac{\partial}{\partial t}\mathcal{P}_0[n(\bar{\xi}); r, t] &= v_f \int dxdy \int_0^{\infty} dz \mathcal{P}_a[n(\bar{\xi}); r, t].
\end{align*}
\]

The initial condition is

\[ \mathcal{P}_a[n(\bar{\xi})] \equiv 0; r, t = 0 \] and all other probabilities are zero, reflecting that Ca\(^{2+}\) ion enters system at \( r = 0 \). Because Ca\(^{2+}\) ion and active kinase will be reflected by the boundary, we have boundary conditions as

\[
\begin{align*}
\frac{\partial}{\partial n}\mathcal{P}_a[n(\bar{\xi}); r, t]|_{n=0} &= 0, \\
\frac{\partial}{\partial n}\mathcal{P}_a[r, t]|_{n=0} &= 0, \\
\frac{\partial}{\partial n}\mathcal{P}_i[n(\bar{\xi}); r, t]|_{n=0} &= 0, \\
\frac{\partial}{\partial n}\mathcal{P}_a[n(\bar{\xi}); r, t]|_{n=1} &= 0, \\
\frac{\partial}{\partial n}\mathcal{P}_a[r, t]|_{n=1} &= 0.
\end{align*}
\]

The boundary condition for the kinase accounts for its binding to and unbinding from the membrane is [20],

\[
-D_N\frac{\partial}{\partial n}\mathcal{P}_a[n(\bar{\xi}); \bar{r}, t] = -v_p\mathcal{P}_a[n(\bar{\xi}); \bar{r}, t] + v_p\mathcal{P}_b[n(\bar{\xi}); \bar{r}, t].
\]

After a dimensionless treatment, the time and space are scaled by \( v_p / \sqrt{D_C} \), respectively.

B. Mean-field ansatz

Now we give the analytical results in the mean field ansatz. As in the CaM scenario, the distribution of the phosphorylation events at time \( t \to \infty \) is given by \( \hat{n} = \bar{P}_b(\bar{r}) \), which is related to the kinase distribution as,

\[
\hat{n} = v_p\mathcal{P}_a(\bar{r}) - v_p\mathcal{P}_b(\bar{r}).
\]

![Graph](image)

FIG. 7. The variation of estimation error against distance with different parameters from \( 10^3 \) stochastic simulations. The results are obtained by varying one of the parameters, \( v_a = 10, v_d = 10, v_i = 20 \), and \( D_N = 0.02 \).

![Graph](image)

FIG. 8. The PKC scenario for Ca\(^{2+}\) signal propagation. The explicit description is presented in text.
After integrating, we have

$$p_b(\bar{r}) = \frac{v_b}{v_a} p_a(\bar{r}).$$

(28)

To obtain the distribution of phosphorylation trajectories, we are then left with solving,

$$\delta(r) = (\nabla^2 - v_\partial) \tilde{p}_a(r) - (v_a + v_l) \tilde{p}_a(r),$$

$$0 = \nabla^2 \tilde{p}_l(r) + v_l \tilde{p}_a(r) - (v_a + v_l) \tilde{p}_l(r),$$

$$0 = D_K \nabla^2 \tilde{p}_b(r) - v_d \tilde{p}_b(r) + v_a (\tilde{p}_a(r) + \tilde{p}_b(r)).$$

(29)

One can finds that above equations are the same as Eq. (21) in the CaM scenario. The difference is that the current problem has additional boundary conditions at $z = l$. It makes the Laplace transformation adopted in the toy and CaM scenario failure to solve these differential equations because it only works in a region from 0 to $\infty$. Hence, in this work, we do not try to give the analytical results. However, for large $l$ the effect of boundary at $z = l$ on the above equations becomes small. Hence, the $p_b(\bar{r})$ can be solved as in the CaM scenario. Combined with Eq. (28), one can expect a similar result of estimation error for PKC scenario at large $l$. It can be used to check our simulation results.

C. Stochastic simulation of the master equation

The stochastic simulation of master equation is similar to the CaM scenario with some changes made for two boundaries. After Ca$^{2+}$ ion enters system with a velocity and moves a step, if the new position $z_{\text{new}} = z_{\text{old}} + \Delta z$ is not in the range of $0 < z_{\text{new}} < l$, Ca$^{2+}$ ion will be reflected by two boundaries to a position in this range. After the kinase is active, the situation is more complex because it has possibility to be bound onto plasma membrane. Let us consider an active kinase in $z_{\text{old}}$, which certainly locates between two boundaries, goes to a new position $z_{\text{new}}$ after a random movement at time $\Delta t$. If the $z_{\text{new}}$ is still between the two boundaries, we draw a random number $r$ between 0 and 1. If $r < e^{-(l-z_{\text{new}})/(l-z_{\text{old}}))}/(D_K \Delta t)$, the kinase is bound to the membrane. If the $z_{\text{new}}$ is larger than $l$, the kinase is bound if $r > 1 - v_b \sqrt{\pi \Delta t}/(2 \sqrt{D_K})$. Otherwise, it will be reflected. If the $z_{\text{new}}$ is smaller than 0, kinase is reflected only. If after reflecting, the kinase is still out of the boundaries, the above step should be repeated until it goes to a position between the boundaries. After binding to the membrane, a random number is drawn to determine whether phosphorylation happens or kinase unbinds from the membrane as before.

In Fig. 9, we present the simulation results with $v_a=10, v_d=10, v_l=20, v_b = 1$, and $D_K=0.02$ from 10$^4$ stochastic simulations, and compare it with the analytical results with Eqs. (22) and (A11) in the CaM scenario.

D. Dependence of the parameters

Now, we consider the effect of variation of the parameters on the estimation error. Based on the results with $v_a=10, v_d=10, v_l=20, v_b = 1$, and $D_K=0.02$, we vary each parameter, and give the results with a speed of 200 in Fig. 10. Here, we still give the analytical results in CaM scenario for reference. One can find that with the increasing of speed, the analytical lines fit the simulation better.

As in the CaM scenario, the increase of the $v_a$ and $D_l$ leads to larger estimation error while small $v_d$ and $v_l$ leads to small estimation error. For two new parameters, $v_b$ and $v_d$, the simulation results are nearly not affected by their variation in a range from 0.1 to 10. It is consistent with Eq. (28), where these two rates will be canceled when obtaining the estimation error. Such conclusion should not depend on distance and speed.
of Ca

ν

from the entrance. Hence, in this work, we develop a quanti-

2

ty of intracellular Ca

ν

ferent parameters from 10

2

phorylation trajectories. With the parameters in Refs. [1, and

2

signal dies away due to rapid decrease of the number of phosphorylation trajectories. With a large speed, one can find that the estimation error is stable at about 5~10 μm with the increasing of distance, which suggests a local signal compared with the size of a cell.

The current results suggest that the distance between calcium pump and the position where the signal is read out should be considered to estimate readout accuracy of Ca

2

signal. And initial velocity can regulate the penetrability of Ca

2

signal. In the current work, we do not consider the e

ACKNOWLEDGMENTS

This project is partially supported by the National Natu-

r

ral Science Foundation of China under Grants No. 11675228 and China postdoctoral Science Foundation under Grants No. 2015M572662XB.

Appendix A: Explicit solution of master equation in the CaM scenario with mean-field ansatz

In this appendix, we will give the explicit to obtain estimation error in the CaM scenario in the mean-field limit. The master equation is rewritten as

\[
\dot{p}_\nu(r,t) = (\nabla^2 - v_\nu \partial_r) p_\nu(r,t) - (v_a + v_i) p_\nu(r,t),
\]

\[
\dot{p}_i(r,t) = \nabla^2 p_i(r,t) + v_\nu p_\nu(r,t) - (v_a + v_i) \tilde{p}(r,t),
\]

\[
\dot{p}_0(r,t) = D_K \nabla^2 \tilde{p}(r,t) - v_a \tilde{p}(r,t) + v_\nu p_\nu(r,t) + p_{\nu 0}(r,t),
\]

\[
\dot{p}_{\nu 0}(r,t) = v_i \int dr [p_i(r,t) + p_{\nu i}(r,t)].
\]

After integrating the above equation from \( t \) = 0 to \( \infty \), we have

\[
-\delta(r) = (\nabla^2 - v_\nu \partial_r) \tilde{p}(r) - (v_a + v_i) \tilde{p}(r),
\]

\[
0 = \nabla^2 \tilde{p}(r) + v_\nu \tilde{p}(r) - (v_a + v_i) \tilde{p}(r),
\]

\[
0 = D_K \nabla^2 \tilde{p}(r) - v_a \tilde{p}(r) + v_\nu p_\nu(r) + P_{\nu 0}(r). \tag{A3}
\]

Eq. (A2) is only for the \( \tilde{p}_\nu(r) \), and does not couple with other equations, which can be solved first. We would like to remind that the \( x/y \) is from \( -\infty \) to \( \infty \) while the \( z \) is from 0 to \( \infty \). Due to the existence of velocity \( v \), we can not extend \( z \) to full range from \( -\infty \) to \( \infty \). Here, we perform the Fourier transformation for \( x/y \) but the Laplace transformation for \( z \), which yields

\[
\tilde{p}_\nu(\vec{q}, k) = \frac{1 + (k - v_i) \tilde{p}_\nu(\vec{q}, 0) + \tilde{p}_\nu(\vec{q}, 0)}{k^2 - \vec{q}^2 - v_k - v_i} = \frac{-1 + (k - v_i) \tilde{p}_\nu(\vec{q}, 0) + \tilde{p}_\nu(\vec{q}, 0)}{[k - \omega_q(\vec{q})][k + \omega_q(\vec{q})]]. \tag{A4}
\]
Then, we preform an inverse Laplace transformation on \( k \),
\[
\bar{p}_n(q, z) = \frac{-1 + [\omega_+(q) - v][\bar{p}_n(q, 0) + \bar{p}_n'(q, 0)]}{\omega_+(q) + \omega_-(q)} e^{\omega_+(q)z} + \frac{1 + [\omega_+(q) + v][\bar{p}_n(q, 0) - \bar{p}_n'(q, 0)]}{\omega_+(q) + \omega_-(q)} e^{-\omega_+(q)z}, \tag{A5}
\]
with \( \tilde{\omega}_n(q) = \sqrt{v^2/4 + q^2} \mp i/2 \). Now we need to determine \( \bar{p}_n(q, 0), \bar{p}_n'(q, 0) \). Since the \( \bar{p}_n(q, z) \) should converge at \( z \to \infty \), we have
\[
\bar{p}_n(q, z) = \bar{p}_n(q, 0)e^{-\omega_+(q)z}. \tag{A6}
\]
Inserting the above result to Eq. \( (A3) \), we can determine \( \bar{p}_n(q, 0) = 1/\omega_+(q) \). The above method can be also used to the toy scenario.

Now, we solve the left two equations which are coupled to each other. The \( z \) is still larger than zero for these two equations. However, due to the boundary at \( z = 0 \) is reflective, it is reasonable to make an even extension. Hence, we can preform the Fourier transformation for three direction as,
\[
0 = -D_k(q^2 + k^2)\bar{p}_n(q, k) + v_\alpha \bar{p}_a(q, k) + v_\beta \bar{p}_\beta(q, k) + \bar{p}_n(q, \bar{k}),
0 = -(q^2 + k^2)\bar{p}_n(q, k) + v_\alpha \bar{p}_a(q, k) + \bar{p}_n(q, k). \tag{A7}
\]
It is easy to obtain,
\[
\bar{p}_n(q, k) = \frac{v_\alpha[q^2 + k^2 + v_\alpha + v_\gamma][D_k(q^2 + k^2) + v_\alpha] - v_\alpha v_\gamma}{[q^2 + k^2 + v_\alpha + v_\gamma][D_k(q^2 + k^2)]} \tag{A8}
\]
An inverse Fourier transformation yields,
\[
\bar{p}_n(q, z) = \frac{v_\alpha}{D_k} \frac{\omega_+(q)}{\omega_+(q)} e^{-\omega_+(q)z}. \tag{A9}
\]

\[
\frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} + \frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} + \frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} \tag{A10}
\]
where \( \lambda_n = \sqrt{v^2 + (b + \sqrt{b^2 - 4c})/2} \) with \( b = (v_\alpha + v_\gamma) + v_\delta \) and \( c = v_\delta^2/v_\alpha \). \( \omega_+ = \sqrt{q^2 + (v_\alpha + v_\gamma) + v_\delta^2/4} \pm v/2 \). \( \omega_- = \sqrt{q^2 + (v_\alpha + v_\gamma)} \). The number distribution is
\[
\hat{n}(z) = \bar{p}_n(q, z) \bar{p}_n(q, z). \tag{A11}
\]
The results can be obtained easily by taking all \( q \) in Eq. \( (A9) \) to zero and given in Eq. \( (22) \). The estimation error can be obtained as
\[
\frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} + \frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} + \frac{\omega^2(q) - \lambda_n^2(q)}{\lambda_n(q)[\lambda_n^2(q) - \lambda_n^2(q)]^2} e^{-\lambda_n(q)z} \tag{A10}
\]
Here, \( \omega = \sqrt{(v_\alpha + v_\gamma) + v_\delta^2/4} \).

[1] E. Brown, R. Macleod, Physiol. Rev. 81 (2001) 239-297.
[2] D. E. Clapham, Cell 131(2017)10471058.
[3] M. Berridge, Michael, Physiol. Rev. 96 (2016) 1261-1296.
[4] G. Gutas, R. A. Hallett, S. P. Zimmerman, T. Williams, H. Yumerefeudi, J. E. Bear, B. Kuhlman, Proc. Natl. Acad. Sci. USA 112 (2015) 112-117.
[5] T. A. Duke and D. Bray, Proc. Natl. Acad. Sci. USA 96 (1999) 10104.
[6] B. A. Mello and Y. H. Tu, Proc. Natl. Acad. Sci. USA 100 (2003) 8223.
[7] B. A. Mello, L. Shaw, and Y. H. Tu, Biophys. J. 87 (2004) 1578.
[8] J. Goyette J. D. Nieves, Y. Ma, K. Gaus, J Cell Sci 132(2019) jcs226423.
[9] A. Jha, W. Y. Chung, L. Vachel, J. Maledt, S. Lake, G. Zhang, M. Ahuja, S. Muallhem, EMBO J. 17 (2019) 38.
[10] Y. Saheki, Adv Exp Med Biol 997 (2017) 83-93.
[11] R. Villaseñor, Y. Kalaidzidis, M. Zerial, Curr Opin Cell Biol. 39 (2016) 53-60.
[12] P. J. M. Van Haastert and P. N. Devreotes, Nat. Rev. Mol. Cell Bio. 5 (2004) 626.
[13] V. H. Wasnik, P. Lipp, and K. Kruse, Phys. Rev. Lett. 123 (2019) 058102.
[14] V. H. Wasnik, P. Lipp, and K. Kruse Phys. Rev. E 100 (2019) 022401.
[15] D. T. Giuespie, J Phys. Chem. 81 (1977) 25.
[16] E. A. Nalefski and A. C. Newton, Biochemistry 40 (2001) 13216.
[17] G. D. Smith, J. E. Keizer, M. D. Stern, W. J. Lederer, and H. Cheng, Biophys. J. 75 (1998) 15.
[18] B. S. Donahue and R. F. Abercrombie, Cell Calcium 8 (1987) 437.
[19] M. Schaefer, N. Albrecht, T. Hofmann, T. Gudermann, and G. Schulz, FASEB J. 15 (2001) 1634.
[20] J. Crank, 1975, The Mathematics of Diffusion (Oxford: Oxford University Press)
[21] R. Erban and S. J. Chapman, Phys. Biol. 4 (2007) 16.
[22] S. S. Andrews and D. Bray, Phys. Biol. 1 (2004) 137.