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Modeling of Ligand-Receptor Protein Interaction in Biodegradable Spherical Bounded Biological Micro-Environments

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ABSTRACT In this paper, we propose a generalized model for the Ligand-Receptor protein interaction in 3-D spherically bounded, diffusive biological microenvironments using molecular communication paradigm. Modeling a targeted cell as a receiver nano-machine, we derive analytical expressions for the Green's function as well as for the expected number of the activated receptors. The molecular degradation in the environment due to enzymatic effects and the changes in pH levels are included via the first-order degradation reaction mechanism. A second-order reversible reaction mechanism is employed to model the reception process that involve the reaction of ligands to activate the receptor proteins lying on the receiver surface to form ligand-receptor complexes. We also present a particle-based simulator that incorporates the reversible reaction of molecules with the receptors present on the surface of a receiver that is located inside a bounded, 3-D microfluidic environment. Our simulations also include molecular degradation and boundary absorption of the ligands due to collision. The simulation results show perfect agreement with the results obtained from the analytical, bounded, and 3-D spherical model of the medium. The proposed models can be used for accurate prediction of the drug concentration profiles and number of activated receptors at any targeted cell.

INDEX TERMS Biological microenvironment, molecular degradation, diffusion, nanomachines, ligand-receptor complexes, molecular communication, reversible reaction, particle-based simulator, concentration profile, 3-D spherical models, bounded environments, targeted cells.

I. INTRODUCTION

Molecular communication (MC) is an emerging biologically inspired paradigm that enables an understanding and modelling of the communication between biological and/or synthetic nano-machines within aqueous biological microenvironments over nanometer to micrometer scales [1], [2]. The molecular communication via diffusion (MCvD) is highly suitable for biomedical applications, e.g., targeted drug delivery, health monitoring, and lab-on-a-chip systems, due to its biocompatibility and low energy requirements [3]–[6]. In MCvD, the information between the bio-nano-machines (e.g., living cells) is exchanged via free diffusion of chemical molecules that propagate in fluidic biological microenvironments (e.g., biological tissues, blood vessels, etc.) following random Brownian motion [2], [7]–[12].

For performance evaluation and optimization of the molecular communication systems including the transmitter and receiver nano-machines, an accurate and realistic model of the biological medium (aka 'propagation channel') is required. The propagation channel model plays a significant role in predicting accurately the molecular concentration profile at any targeted cell which can be modelled as a receiver nano machine (RN). However, in the molecular communication literature, simplifying models of the diffusive biological media (channel models) have been widely employed that approximate the media to be unbounded extending to infinity in all directions [3], [7]–[16]. Although use of such an assumption simplifies the mathematical complexity, however, they may not predict the expected received molecular profile accurately at any targeted receiver nano-machine (RN) operating in realistic biological fluidic microenvironments, since such media are usually bounded.

The biological microfluidic environments inside any living organism are small and are usually bounded by biological

membranes, e.g., stomach, lungs, blood vessels, and capillaries, etc. In addition, when a drug delivery device or a nano robot acting as a transmitter nano machine (TN) is located near any terminating boundary of a medium, the boundary will have significant effect on the released molecules irrespective of the medium dimensions. As a result, a portion of the released information molecules may collide and react with the medium boundary (membranes). Due to this, a portion of the molecules may be transported into the surrounding environment via diffusion through the pores and some of them could either be reflected back or absorbed by the boundary surface, before reacting with the receptors located on the receiver, e.g., the targeted cells. Hence, modelling such bounded microenvironments using simplified unbounded media could lead to large errors in predicting the number of the received molecules [3], [17].

On-chip molecular communication system is one of the applications where the information can be transported using chemical molecules in a confined, bounded, microfluidic channel on a chip device [18]. Drug released into the perivascular space either by injection or drug delivery device such as a polymer coated drug eluting stent (DES), drug delivery via the gastrointestinal system, and pulmonary drug delivery throughout the lung are some of the important examples for bounded biological microfluidic environments where molecular communication paradigm could be gainfully employed [19]–[23]. The optimum design of drug delivery systems requires accurate modelling of the environment, the molecular degradation and reaction with the targeted cells for the precise prediction of the drug release pattern. Thus, if the effect of the medium boundary is ignored by assuming the medium to be unbounded, it can result in erroneous prediction of the drug concentration levels around the targeted cells which, may eventually lead towards poor therapeutic outcomes.

The binding/unbinding reaction process that the information molecules undergo with the receptor proteins on the target cells have been investigated extensively [24], [25]. The atherosclerosis is one of the examples, in which during the initial phases, the cytokine ligands (CD40L) that are released by platelets across the bloodstream in the blood vessel, bind with the CD40 receptors on the surface of the endothelial cells of the vessel wall. As a result, they express vascular cell adhesion molecules (VCAM-1) in response to cytokine stimuli [24], [26]. Also, it is possible to synthesize a biological cell to transmit specific type and amount of molecules and then receive them by specifically synthesized receptors on its surface [27], [28].

Another important mechanism that should be considered is the molecular degradation in biological environments [3], [29]. The molecular deformation and cleavage occur due to enzymatic attacks or changes in pH level in the biological environment and thus, do not contribute to the received signal [30], [31]. For example, ACh-hydrolyzing enzyme (AChE) degrades the acetylcholine (Ach) molecules, which diffuse into a small space (the synaptic cleft) between the axons and the dendrites of the brain neurons [31], [32].

In molecular communication, any targeted cells can be modelled as receivers. Many such receiver models exist, viz., passive, irreversible receiver either partially or fully absorptive, and a more realistic model of reversible receiver. The type and complexity of each receiver depends on the type of the targeted cell and determines the accuracy of the receiver model. The passive receiver is a sort of an ideal model and also is the simplest of all models which is, usually, assumed to have a capability of counting the number of molecules without either impeding their diffusion or creating any chemical reactions on its surface. Thus, it cannot accurately model any realistic biological reception mechanism [11]. Several works on MCvD that employ passive receiver models in unbounded biological media are reported in the literature [10]–[15]. Another commonly used receiver model is the irreversible receiver that is either partially or fully absorptive in which the molecules can irreversibly react and activate the protein receptors on the receiver surface via an irreversible reaction mechanism. The expressions for expected number of received molecules on the surface of an irreversible spherical receiver with both partial and full absorption in an unbounded propagation environment were first derived in [33] and [34]. Also, the impact of the size and density of absorbing receptors on the received signal has also been analyzed, but, all these works, approximate the medium to be unbounded [35]. For an unbounded medium, the expressions for molecular degradation have also been presented for a fully absorbing receiver model [29]. An equivalent discrete-time unbounded channel model for MCvD for a fully absorbing receiver is also available in the literature [36].

In order to accurately model the biological reception mechanism for molecular communications, realistic and reversible reaction receiver models are required. In the reversible reaction model, the information molecules (ligands) can activate the receptors on the receiver surface depending on the forward reaction constant. The activated receptors (i.e., ligand-receptor complexes) can dissociate and release the information molecules again into the environment depending on the backward reaction constant [37], [38]. When the net number of activated receptors reach a specific threshold value, a cascade of chemical reactions may be initiated inside the living cell which act as a receiver [24], [39]. However, the molecular concentration distributions for a reversible reaction receiver located in an unbounded medium are available for the steady state case [40]. The mean and covariance of the output signal for a reversible reaction receiver in an unbounded medium is obtained using reaction-diffusion master equation (RDME) [41]. Extension of this for a voxelated 3-D cubic bounded medium is reported in [42], however, only the first order reversible reaction is considered inside the receiver rather than on its surface. Although an improved model using the second-order reversible reaction mechanism at the receiver surface appeared in [37] and [38], however, the expressions for the expected received signal are

valid only for simplified, hypothetical, unbounded media. In some works, for example, [9]–[15], [34]–[41], the investigations have been restricted to only unbounded media that extend to infinity in all directions. All these works tend to ignore the effects of the medium boundaries on the molecular diffusion, and hence, may not correctly predict molecular concentration levels for realistic, bounded, biological micro-media.

To overcome these limitations, in this paper, we present a generalized analytical model for predicting the expected number of activated receptors (received signal), in a realistic 3-D bounded microfluidic environment considering both the second-order reversible reaction at the receiver and first-order degradation mechanisms within the bounded environment. Unlike some of the existing works [9]–[15], [34]–[41], here, we model the bounded medium using a 3-D spherical geometry and investigate the impact of the medium boundary on the expected number of activated receptors (or number of ligand-receptor complexes). It is well acknowledged that the analytical solution of the diffusion equation for a 3-D bounded medium can be extremely complex compared to its solution in unbounded medium. We derive the analytical solution as a convergent infinite series that converges fast for only a few number of terms, which will be discussed in later sections.

The main contributions of this paper are: (i) Development of an analytical model for molecular communication via diffusion (MCvD) in a bounded, 3-D microfluidic environment by using a reversible spherical receiver. (ii) Inclusion of the impact of the medium boundary on the molecular diffusion in the prediction of the expected number of activated receptors at the receiver. (iii) Inclusion of the effects of the molecular degradation in the model via a first-order degradation reaction. (iv) Modelling of the reception mechanism at the receiver using a second-order reversible reaction mechanism. (v) Derivation of analytical expressions for the Green function (concentration profile) and expected received signal (i.e., number of activated receptors) in a 3-D bounded microenvironment including the effect of the medium boundary, the degradation, and the reversible reaction at the receiver. (vi) Development of a particle-based simulator for a 3-D bounded medium based on molecular diffusion via random Brownian motion considering the absorption by the medium boundary, the molecular degradation in environment, and the reversible reaction at the surface of the receiver. We also demonstrate analytically that our expressions for the expected received signal can be reduced to the special case of an unbounded medium, if the distance from the transmitter to the medium boundary is large enough.

The rest of the paper is organized as follows: in section II, the system model is introduced including the general mathematical formulation, derivation of the exact molecular distribution function (i.e., Green function), and an expression for expected received signal. In section III, the proposed simulation framework for the particle-based simulator is presented. We discuss the analytical and simulation results in section IV. Finally, conclusions are presented in section V.

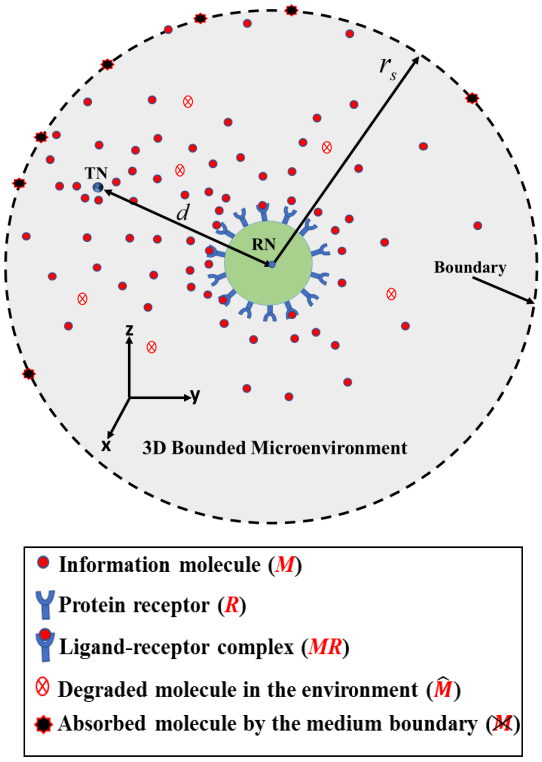

FIGURE 1. Graphical representation of the end-to-end MCvD model in 3-D bounded environment with degradation and reversible reaction mechanisms.

II. SYSTEM MODEL

The MCvD system considered in this paper consists of a transmitter nano machine (TN) which seeks to send chemical information molecules to a reversible (reactive) spherical receiver nano machine (RN) in a diffusive, 3-D spherically bounded, microfluidic molecular environment as shown in Fig. (1). The 3-D spherical bounded microfluidic diffusive medium has a finite radius (r_s) and is assumed to be isotropic i.e., it has a uniform diffusion coefficient (D) that is same in all the directions. A point source type transmitter (TN) is considered that is located at the position $\vec{r}_T = (x_T, y_T, z_T)$, which releases 'M' information molecules into the environment at time $t = t_0$. The information molecules are usually chemical compounds, e.g., antibodies, proteins, or ions, which are assumed to move randomly in the 3-D bounded medium following Brownian motion.

The 'M' information molecules that are emitted by TN may degrade in the environment with some finite probability to get transformed into a new molecule $\hat{M}$ that may not be recognized by the RN. This degradation follows a first-order degradation reaction mechanism given by

$$M \xrightarrow{k_d} \hat{M} \tag{1}$$

where, k_d is the degradation reaction constant in units of s^{-1}.

Moreover, we consider that the information molecules that collide with the medium boundary at $r = r_s$ will be absorbed

and removed from the environment with a probability of unity as follows

$$M \longrightarrow \not{M} \tag{2}$$

As indicated in Fig. 1, the receiver nano-machine (RN) is assumed to be a spherical reactive receiver that has a radius r_R which is positioned at the center of the coordinate system at a separation distance d from the TN. The reaction of the information molecules with the receptor proteins on the receiver surface is characterized via a second-order reversible reaction mechanism given by (3). We assume that the surface of the RN is fully covered by the receptor proteins and thus, there is no limit on the number of the activated receptors. The reaction of the information molecules (ligands) with the protein receptors on the surface of RN is a stochastic process, which may lead to either reflection or activation of the protein receptors, to produce the ligand-receptor complexes 'MR', depending on forward reaction rate constant k_f. However, some of the molecules that bind to the receptors tend to dissociate with some finite probability and will finally return to the environment depending on the backward reaction constant k_d. Here, we neglect effect of the angle of incidence of the molecules on the surface of the receiver due to the spherical symmetry.

$$M + R \underset{k_b}{\overset{k_f}{\rightleftarrows}} MR \tag{3}$$

where k_f and k_b are the forward and backward reaction constants in (m/s) and (s^{-1}), respectively. It is worth mentioning that the forward reaction constant k_f can be defined in different units, e.g., $m^3/(mol.s)$, depending on the adsorption model chosen. Furthermore, we assume that the ligand-receptor complexes 'MR' are independently formed on the surface of RN considering that the reaction can occur at any point on the surface with equal probability. As a special case, if $k_b = 0$, then the RN becomes irreversible which means that the absorbed molecules will not unbind from the receptors after the activation. Moreover, if k_f goes to infinity, then the RN becomes a fully absorber receiver where each reaction between the molecule and the receptor becomes deterministic which, then may activate the receptor protein. The RN is assumed to have the capability of counting the net number of activated receptors after each binding process. The expected number of activated receptors (or number of 'MR' complexes) is interpreted as the received molecular signal.

A. GENERAL MATHEMATICAL FORMULATION

Here, we formulate the mathematical approach including the equations and both the initial and boundary conditions, which would govern our proposed model. The concentration of the information molecules at the vicinity of the RN is affected by the molecular absorption and degradation in the environment as well as the binding process with the receptors on the RN surface. The molecular diffusion with degradation reaction can be described by Reaction-Diffusion Equation, given by [38]

$$\frac{\partial P_M(\vec{r}, t|\vec{r}_T, t_0)}{\partial t} = D\nabla^2 P_M(\vec{r}, t|\vec{r}_T, t_0) - k_d P_M(\vec{r}, t|\vec{r}_T, t_0) \tag{4}$$

where, $P_M(\vec{r}, t|\vec{r}_T, t_0)$ is a molecular distribution function that represents the probability of finding a molecule 'M' at any arbitrary position $\vec{r} = (x, y, z)$ at a time t given that it was released at the transmitter position $\vec{r}_T = (x_T, y_T, z_T)$ and at time t_0, ∇^2 is the Laplacian operator in three-dimensional (3-D) spherical coordinate system, and D is the medium diffusion coefficient in (m^2/s).

We employ the spherical coordinate system. Since the molecular distribution is assumed to have spherical symmetry, it depends only on the radial distance r. For this case, the Reaction-Diffusion Equation (4) can be modified as

$$\frac{\partial (rP_M(r, t|r_T, t_0))}{\partial t} = D\frac{\partial^2 (rP_M(r, t|r_T, t_0))}{\partial r^2} - k_d rP_M(r, t|r_T, t_0) \tag{5}$$

In the proposed model, the solution of the diffusion equation (5), i.e., the molecular distribution $P_M(r, t|r_T, t_0)$, should satisfy the following initial and boundary conditions:

$$P_M(r, t \to t_0|r_T) = \frac{1}{4\pi r_T^2}\delta(r - r_0) \tag{6}$$

$$P_M(r \to r_s, t|r_T, t_0) = 0 \tag{7}$$

The initial condition (6) represents the instantaneous emission of the information molecules by a point-like TN located at any position $\vec{r}_T$ on the surface of a virtual sphere of radius r_T which is normalized with its area $4\pi r_T^2$. The boundary condition (7) characterizes the absorption of molecules at the finite boundary of a three-dimensional (3-D) bounded medium. Use of (7) differentiates our paper from other reported works, e.g., [9]–[15], [34]–[41], which all assume unbounded, open medium.

The forward and backward reactions of molecules with the receptors on the RN surface are characterized via Robin boundary condition (or radiation boundary condition) given by [37], [40]

$$D\frac{\partial P_M(r, t|r_T, t_0)}{\partial r}\bigg|_{r=r_R} = k_f P_M(r_R, t|r_T, t_0) - k_b P_{MR}(t|r_T, t_0) \tag{8}$$

where, $P_M(r_R, t|r_T, t_0)$ is the molecular distribution function at the sensing area of RN and $P_{MR}(t|r_T, t_0)$ is the average surface concentration distribution of the activated receptor proteins (ligand-receptor complexes) on RN surface at time t.

The solution for the molecular distribution $P_M(r_R, t|r_T, t_0)$ due to the instantaneous release of the information molecules by a point-like TN at time $t = t_0$ and at a radial distance $r = r_0$ in a three-dimensional spherical bounded medium represents the Green's function. The Green's function $P_M(r, t|r_T, t_0)$ can be expressed as a superposition of

two solutions as [37],

$$rP_M(r,t|r_T,t_0) = rC(r,t|r_T,t_0) + rV(r,t|r_T,t_0) \quad (9)$$

The first term $rC(r,t|r_T,t_0)$ on the r.h.s is the solution of the radial Reaction-Diffusion Equation (10) with the initial condition (11) for unbounded spherical medium ($r_s \to \infty$), assuming that the RN is removed from the environment, i.e., without applying the boundary condition (8). It is given by

$$\frac{\partial(rC(r,t|r_T,t_0))}{\partial t} = D\frac{\partial^2(rC(r,t|r_T,t_0))}{\partial r^2} - k_d rC(r,t|r_T,t_0) \quad (10)$$

$$rC(r,t\to t_0|r_T) = \frac{1}{4\pi r_T}\delta(r-r_T) \quad (11)$$

We require two boundary conditions to obtain an exact solution for (10). Assuming the molecular distribution to be finite at the center of the medium (i.e., $r \to 0$) and vanishes at a distance $r \gg r_T$ (i.e., $r \to \infty$) leads to

$$\left|C(r\to 0,t|r_T,t_0)\right| < \infty, \quad t > t_0 \quad (12)$$

$$C(r\to\infty,t|r_T,t_0) = 0 \quad (13)$$

The second term, $rV(r,t|r_T,t_0)$, at the r.h.s of (9) is the solution of the radial reaction-diffusion equation (14) that initially vanishes at time $t = t_0$, as given in eq. (15) below. The terms $rV(r,t|r_T,t_0)$ and $rC(r,t|r_T,t_0)$ together satisfy the boundary conditions (7)-(8) for a bounded medium.

$$\frac{\partial(rV(r,t|r_T,t_0))}{\partial t} = D\frac{\partial^2(rV(r,t|r_T,t_0))}{\partial r^2} - k_d rV(r,t|r_T,t_0) \quad (14)$$

$$rV(r,t\to t_0|r_T) = 0 \quad (15)$$

B. GREEN'S FUNCTION: MOLECULAR CONCENTRATION DISTRIBUTION

Now, we will derive a closed-form expression for Green's function by solving a system of the diffusion equations, with the initial and the boundary conditions given in the previous subsection. The Green's function (9) can be obtained after solving (10) and (14). We will first solve the diffusion equation (10) in the Laplace transform domain then substitute the initial condition (11) to get

$$\frac{\partial^2 r\tilde{C}(r,s|r_T,t_0)}{\partial r^2} - \frac{(s+k_d)}{D}r\tilde{C}(r,s|r_T,t_0) = -\frac{1}{4D\pi r_T}e^{-st_0}\delta(r-r_T) \quad (16)$$

where, $\tilde{C}(s)$ is the Laplace transform of $C(t)$.

The general solution of a second order inhomogeneous differential equation (16) can be expressed as a superposition of homogeneous solution ($\tilde{C}_h$) and particular solution ($\tilde{C}_p$):

$$r\tilde{C}(r,s) = \underbrace{c_1e^{ru} + c_2e^{-ru}}_{\tilde{C}_h} - \underbrace{\frac{e^{-st_0}}{8D\pi r_T u}\left(e^{(r-r_T)u} - e^{-(r-r_T)u}\right)H(r-r_T)}_{\tilde{C}_p} \quad (17)$$

where, the parameter u is defined as

$$u = \sqrt{(s+k_d)/D} \quad (17.a)$$

The Heaviside function $H(r-r_T)$ is given as

$$H(r-r_T) = \begin{cases} 1, & r \ge r_T \\ 0, & r < r_T \end{cases} \quad (17.b)$$

Then, by applying the conditions (12)-(13) to (17), we get

$$c_1 = -c_2 = \frac{e^{-st_0}e^{-r_T u}}{8D\pi r_T u} \quad (17.c)$$

Now, substituting the values of c_1 and c_2 from (17.c) in (17), and with some algebraic manipulations, we get the general solution of (16) as

$$r\tilde{C}(r,s|r_T,t_0) = \frac{e^{-st_0}}{4\pi D r_T u} \times \begin{cases} e^{-ru}\sinh(r_T u), & r \ge r_T \\ e^{-r_T u}\sinh(ru), & r < r_T \end{cases} \quad (18)$$

where, $\sinh(\cdot)$ is the hyperbolic sine function. Now, to find the solution of (14)-(15) in the Laplace domain, i.e., $r\tilde{V}(r,s|r_T,t_0)$, we first apply the Laplace transform to (14) and then substitute the initial condition (15), to get

$$\frac{\partial^2\left(r\tilde{V}(r,s|r_T,t_0)\right)}{\partial r^2} - \frac{s+k_d}{D}r\tilde{V}(r,s|r_T,t_0) = 0 \quad (19)$$

Eq. (19) is a homogeneous second order differential equation with two distinct roots, i.e., $\pm\sqrt{(s+k_d)/D}$, and thus its solution can be expressed in terms of hyperbolic functions as

$$r\tilde{V}(r,s|r_T,t_0) = A\sinh(ru) + B\cosh(ru) \quad (20)$$

where, A and B are functions of(s, r_R, r_s, r_T).

Taking the Laplace transform of (9), the total solution can be expressed as a superposition of (18) and (20) in the Laplace domain as

$$r\tilde{P}(r,s|r_T,t_0) = r\tilde{C}(r,s|r_T,t_0) + A\sinh(ru) + B\cosh(ru) \quad (21)$$

where, $r\tilde{C}(r,s|r_T,t_0)$ can be chosen from (18) depending on the value of radial distance r chosen.

At the RN surface, the distribution of activated receptor proteins 'MR' over the time is equal to the flux of information molecules in the receiver vicinity and towards its surface. Recognizing that the distribution of the activated receptor proteins 'MR' on the RN surface is zero at the initial time instant, i.e., $P_{MR}(t_0|r_T) = 0$, the conservation identity [37, eq. 6], can be expressed in Laplace domain as

$$\tilde{P}_{MR}(s|r_T,t_0) = \frac{D}{s}\left.\frac{\partial\tilde{P}_M(r,s|r_T,t_0)}{\partial r}\right|_{r=r_R} \quad (22)$$

Substituting (22) in the Laplace domain version of the boundary condition (8), we get

$$\left.\frac{\partial \tilde{P}_M(r,s|r_T,t_0)}{\partial r}\right|_{r=r_R} = \frac{sk_f}{D(s+k_b)}\tilde{P}_M(r_R,s|r_T,t_0) \quad (23)$$

Using the product rule of derivatives, the derivative of $r\tilde{P}_M(r,s|r_T,t_0)$ with respect to r at $r=r_R$ can be expressed as

$$\left.\frac{\partial (r\tilde{P}_M(r,s|r_T,t_0))}{\partial r}\right|_{r=r_R} = r_R \left.\frac{\partial \tilde{P}_M(r,s|r_T,t_0)}{\partial r}\right|_{r=r_R} + \tilde{P}_M(r_R,s|r_T,t_0) \quad (24)$$

Now, substituting (23) in (24), we get

$$\left.\frac{\partial r\tilde{P}_M(r,s|r_T,t_0)}{\partial r}\right|_{r=r_R} = r_R\tilde{P}_M(r_R,s|r_T,t_0)\frac{\omega_1}{\omega_2} \quad (25)$$

where,

$$\begin{aligned}\omega_1 &= s(r_Rk_f+D)+Dk_b\\ \omega_2 &= r_RD(s+k_b)\end{aligned} \quad (26)$$

The functions, A and B, in (21) are obtained by applying the boundary conditions (7) and (25) to (21),

$$A = \frac{e^{-st_0}}{4\pi Dr_Tu}\times\left[\frac{e^{-r_su}\sinh\left(r_Tu\right)f_2(u)-e^{-r_Tu}\cosh\left(r_su\right)f_1(u)}{f_3(u)}\right] \quad (27)$$

$$\begin{aligned}B = -\frac{e^{-st_0}}{4\pi Dr_Tu}\frac{1}{f_3(u)\cosh\left(r_su\right)}&\left[e^{-r_su}f_3(u)\sinh\left(r_Tu\right)\right.\\ &+e^{-r_Tu}\sinh\left(r_su\right)\cosh\left(r_su\right)f_1(u)\\ &\left.-e^{-r_su}\sinh\left(r_Tu\right)\sinh\left(r_su\right)f_2(u)\right]\end{aligned} \quad (28)$$

where,

$$f_1(u) = u\omega_2\cosh\left(r_Ru\right)-\omega_1\sinh(r_Ru) \quad (29)$$
$$f_2(u) = u\omega_2\sinh\left(r_Ru\right)-\omega_1\cosh(r_Ru) \quad (30)$$
$$f_3(u) = \omega_1\sinh\left((r_s-r_R)u\right)+u\omega_2\cosh\left((r_s-r_R)u\right) \quad (31)$$

The number of the ligand-receptor complexes on the RN surface can be obtained by substituting (18) and (27)-(28) in (21) for $r<r_T$. Replacing the exponential terms by their equivalent hyperbolic functions along with some algebraic manipulations, we finally obtain

$$\begin{aligned}\tilde{P}_M(r,u|r_T,t_0) = \frac{e^{-st_0}}{4\pi Drr_T}\frac{1}{uf_3(u)}&\left[\sinh\left((r-r_T)u\right)f_3(u)\right.\\ &+\sinh\left((r_s-r)u\right)\left(\omega_1\sinh\left(\left(r_T-r_R\right)u\right)\right.\\ &\left.\left.+u\omega_2\cosh\left(\left(r_T-r_R\right)u\right)\right)\right]\end{aligned} \quad (32)$$

The inverse Laplace transform of (32) can be evaluated using the residue theorem [43] as

$$\tilde{P}_M(r,s|r_T,t_0) = \sum_{\substack{poles\ of\\ \tilde{P}_M(r,s|r_T,t_0)}} \mathrm{Res}\left(\tilde{P}_M(r,s|r_T,t_0)e^{st}\right) \quad (33)$$

where, Res $(F(s))$ is the residue of $F(s)$.

Although the function (32) includes a square root of s (i.e., $u=\sqrt{(s+k_d)/D}$), it is a meromorphic as well as even function in u which does not have a branch point at $u=0$ (i.e., at $s=-k_d$). Hence, for this case, we can directly use the residue theorem. Now, the expression (32) has simple pole at $u=0$ and infinite number of simple poles at the roots of $f_3(u)$. The residues at these poles are evaluated in Appendix. The spatio-temporal distribution $P_M(r,t|r_T,t_0)$ can be expressed as

$$\begin{aligned}&P_M(r,t|r_T,t_0)\\ &= \frac{1}{2\pi rr_T}\sum_{n=1}^{\infty}e^{-(\alpha_n+k_b)(t-t_0)}\frac{\sin\left((r_s-r)\kappa_n\right)}{\sin\left(\left(r_s-r_R\right)\kappa_n\right)}\\ &\times\frac{\alpha_n\beta_n\lambda_n\sin\left(\left(r_T-r_R\right)\kappa_n\right)+\alpha_n^2\lambda_n^2\cos\left(\left(r_T-r_R\right)\kappa_n\right)}{\left(r_s-r_R\right)\left(\lambda_n^2\alpha_n^2+\beta_n^2\right)+\alpha_n\beta_nDr_R+2\lambda_n^2k_fk_b}\end{aligned} \quad (34)$$

where, κ_n for $n=1,\ldots,\infty$, are the n^{th} positive root of the following identity (35). See Appendix.

$$\tan\left(\left(r_s-r_R\right)\kappa_n\right) = -\frac{\lambda_n\alpha_n}{\beta_n} \quad (35)$$

The parameters α_n, β_n, and λ_n for $n=1,\ldots,\infty$ are defined as

$$\begin{aligned}\alpha_n &= D\kappa_n^2+k_d-k_b\\ \beta_n &= \alpha_n(r_Rk_f+D)+r_Rk_fk_b\\ \lambda_n &= Dr_R\kappa_n\end{aligned} \quad (36)$$

Eq. (35) has infinite number of simple roots along the positive real axis. In addition, depending on the system parameters, it is possible to have another simple imaginary root present on the positive imaginary axis. This additional imaginary root can have a significant effect on the behavior of the model, especially on the reversible reaction process at the RN. Hence, it is important to determine the additional imaginary root by precisely scanning the region around the positive zeros of β_n in (36). For this, we propose an algorithm and implemented it in MATLAB to find the first N roots, which provide very accurate results to ensure that the remaining roots will have a negligible effect on the total summation in (35).

C. THE RECEIVED SIGNAL: EXPECTED NUMBER OF ACTIVATED RECEPTORS

The cumulative expected number of the activated receptors (i.e., number of ligand-receptor complexes) on the surface of the RN represents the channel impulse response (CIR), which can be expressed as

$$\begin{aligned}N(t) &= N_m\int_{t_0}^{t}R(\tau|r_T,t_0)d\tau\\ &= N_mA_{RN}D\int_{t_0}^{t}\left.\frac{\partial P_M(r,t|r_T,t_0)}{\partial r}\right|_{r=r_R}d\tau\end{aligned} \quad (37)$$

where, $R(t|r_T, t_0)$ is the coupling reaction rate which provides the number of the activated receptor proteins per second on the RN surface, and $A_{RN} = 4\pi r_R^2$ is its surface area.

Substituting the derivative of (34) in (37) and using (35), we get

$$N(t) = \frac{2N_m k_f r_R}{r_T} \sum_{n=1}^{\infty} \left[1 - e^{-(\alpha_n + k_b)(t-t_0)}\right] \times \frac{\beta_n \lambda_n \sin((r_T - r_R)\kappa_n) + \alpha_n \lambda_n^2 \cos\left((r_T - r_R)\kappa_n\right)}{\left(r_s - r_R\right)\left(\beta_n^2 + \alpha_n^2 \lambda_n^2\right) + r_R D \alpha_n \beta_n + 2\lambda_n^2 k_f k_b} \quad (38)$$

Eq.(38) is the most generalized expression for the received molecular signal by a reversible receiver in a spherically bounded biological MCvD medium. It can be reduced for the following special cases:

(i) *Irreversible fully absorber receiver with/without degradation in the environment* ($k_f \to \infty, k_b = 0$):
Multiplying both the numerator and denominator of (38) by $1/k_f^2$, and taking the limit as $k_f \to \infty$, we get the expected received signal for a fully absorber receiver (RN) with molecular degradation ($k_d \neq 0$) as

$$N_{FD}(t) = \frac{2DN_m r_R}{\left(r_s - r_R\right) r_T} \times \sum_{n=1}^{\infty} \frac{\kappa_n \sin\left(\left(r_T - r_R\right)\kappa_n\right)}{\kappa_n^2 D + k_d} \times \left(1 - e^{-(\kappa_n^2 D + k_d)(t-t_0)}\right) \quad (39)$$

where, κ_n is the n$^{\text{th}}$ positive root of (35) when $k_f \to \infty$ given as $\kappa_n = n\pi/(r_s - r_R)$ and $n = 1, 2, \ldots, \infty$.
From (39), we can easily obtain the expected received signal without molecular degradation $N_{FA}(t)$ by substituting $k_d = 0$.

(ii) *Irreversible partially absorber receiver with/without degradation* ($k_b = 0$):
To get the expected received signal for a partially absorber RN with degradation ($k_d \neq 0$), substitute $k_b = 0$ in the general expression (38) which results in

$$N_{PD}(t) = \frac{2N_m k_f r_R}{r_T} \sum_{n=1}^{\infty} \left(1 - e^{-(\kappa_n^2 D + k_d)(t-t_0)}\right) \times \frac{\lambda_n q \sin\left(\left(r_T - r_R\right)\kappa_n\right) + \lambda_n^2 \cos\left(\left(r_T - r_R\right)\kappa_n\right)}{\left(\kappa_n^2 D + k_d\right)\left(\left(r_s - r_R\right)\left(q^2 + \lambda_n^2\right) + D r_R q\right)} \quad (40)$$

where, $q = D + r_R k_f$ and κ_n is the n^{th} positive root of $\tan\left(\left(r_s - r_R\right)\kappa_n\right) = -\lambda_n/q$ which can be calculated by substituting $k_b = 0$ in (35).
For the same case, but, without degradation $N_{PA}(t)$, the expected received signal can be derived by substituting $k_d = 0$ in (40).

(iii) *Steady state case* ($t \to \infty$):
The expected number of received molecules on the surface of the RN at the equilibrium (steady state) can be obtained by evaluating (38) in the limit as $t \to \infty$ to get

$$N(t \to \infty) = \frac{2N_m k_f r_R}{r_T} \times \sum_{n=1}^{\infty} \frac{\beta_n \lambda_n \sin((r_T - r_R)\kappa_n) + \alpha_n \lambda_n^2 \cos((r_T - r_R)\kappa_n)}{(r_s - r_R)(\beta_n^2 + \alpha_n^2 \lambda_n^2) + D r_R \alpha_n \beta_n + 2\lambda_n^2 k_f k_b} \quad (41)$$

Using a similar procedure, the asymptotic steady-state expressions for other special cases given by (39)-(40) can also be derived.

(iv) *Unbounded medium* ($r_s \to \infty$):
The molecular received signal for an unbounded medium can be analytically obtained by substituting a very large value for r_s in (38). A comparison of results will be discussed in section IV.

Thus, the expressions derived in this paper for a spherically bounded medium can be reduced to the special case of an unbounded medium if the separation distance between TN-RN is quite small (e.g., in micrometer scale) compared to the medium radius (e.g., in millimeter range).

III. SIMULATION FRAMEWORK

In this section, we will introduce a 3D particle-based simulator to verify the accuracy of the proposed analytical expressions derived in section II. The simulation is conducted using MATLAB software package. In this simulation framework, the total simulation time T is divided into N small time steps Δt. The number of remaining information molecules and their precise locations are tracked and recorded at each time step during the simulation. The simulation procedure can be described throughout the following processes:

- *Signal transmission*: The information molecules 'M' are instantaneously released by a point-like TN at the time t_0 and at the location (x_T, y_T, z_T) in 3D spherical bounded medium.
- *Diffusion*: The information molecules move randomly and independently of each other according to Brownian motion in every direction and the precise position of each molecule is tracked and updated at each time step as follows [44]:

$$(x_i, y_i, z_i) = (x_{i-1}, y_{i-1}, z_{i-1}) + (\Delta x_i, \Delta y_i, \Delta z_i) \quad (42)$$

where, $i = 1, 2, \ldots, \mathrm{N}$, N is the total number of the simulation time steps, the coordinate (x_i, y_i, z_i) is the new position of the molecule at the i^{th} time step, the coordinate $(x_{i-1}, y_{i-1}, z_{i-1})$ is the previous position of molecule at the $(i-1)^{th}$ time step, and $(\Delta x_i, \Delta y_i, \Delta z_i)$ is the random displacements over each spatial axis at i^{th} time step which follows the normal distribution $N(0, \sigma^2)$ with zero-mean and variance $\sigma^2 = 2D\Delta t$.
- *Degradation*: The degradation of molecules in the environment is modelled by first-order degradation reaction [38]. At each time step, a uniformly distributed random number a_d between 0 and 1 is assigned for each

molecule, and if the degradation probability, evaluated using (43) [38], is greater than a_d, then this molecule will be removed from the environment.

$$P_d = 1 - e^{-k_d \Delta t} \tag{43}$$

- *Absorption by the medium boundary*: At the end of each time step, the position of each molecule is checked and if it reaches the medium boundary (r_s), then it will be removed from the environment.
- *Forward reaction with the receiver*: The reaction of molecules with the receptors on the RN surface is modelled by the second-order reversible reaction mechanism. If the molecule falls in the sensing region of the RN, it will either activate the receptor on the surface of the RN or reflect back to the environment depending on the forward reaction probability P_f which is given in (44), [37]. At the end of each time step, a uniformly distributed random number a_f between 0 and 1 is assigned for each molecule, and if P_f is greater than a_f, the receptors on the RN gets activated by the molecules. On other hand, if P_f is less than a_f, the molecules will revert back to their previous location at the beginning of the simulation time step. The forward reaction probability P_f is given by

$$P_f = k_f \sqrt{\pi \Delta t / D} \tag{44}$$

However, if the final location of the absorbed molecules during each simulation time step falls inside the receiver volume (i.e., not exactly on the receiver surface), then the molecules should be repositioned to their correct location on the receiver surface. Thus, the location in the current time step $[t_{j-1} t_j]$ is the intersection point between the receiver surface and line passing through the location of molecule at beginning of the current simulation time step $(x_{j-1}, y_{j-1}, z_{j-1})$ and the final location of molecule at the end of the current simulation time step (x_j, y_j, z_j).

- *Backward reaction with the receiver*: Each ligand-receptor complex 'MR' on the RN surface has a probability of dissociation (unbound) and thus the information molecule 'M' may be released again to the environment depending on the backward reaction probability P_b [37], [38], given by

$$P_b = 1 - e^{-k_b \Delta t} \tag{45}$$

At each time step, a uniformly distributed random number a_b between 0 and 1 is assigned for each ligand-receptor complex 'MR' and if the P_b is greater than a_b, the ligand-receptor complex 'MR' will get unbounded and the molecule (ligand) will return to the medium to an approximate location given by [37]

$$(x, y, z) = (x_{j-1}, y_{j-1}, z_{j-1}) + (\Delta x_R, \Delta y_R, \Delta z_R) \tag{46}$$

where, $\Delta m_R = sgn(m_{j-1} - m_R) p(a_m)$ for $m = \{x, y, z\}$ and

$$p(a_m) = \frac{\sqrt{2D\Delta t}\left(0.571825 a_m - 0.552246 a_m^2\right)}{1 - 1.53908 a_m + 0.546424 a_m^2} \tag{47}$$

TABLE 1. The system parameters (unless stated otherwise).

Parameters	Value	Description
N_m	10^5 *mol.*	No. of released molecules.
D	1×10^{-9} m^2/s	Diffusion coefficient.
r_R	5 μm	Radius of RN.
r_T	7 μm	Radius of TN.
r_s	10 μm	Radius of the medium.
Δt	10^{-6} s	Simulation time step.
T_s	0.2 s	Total simulation time.
# of realizations	100	-

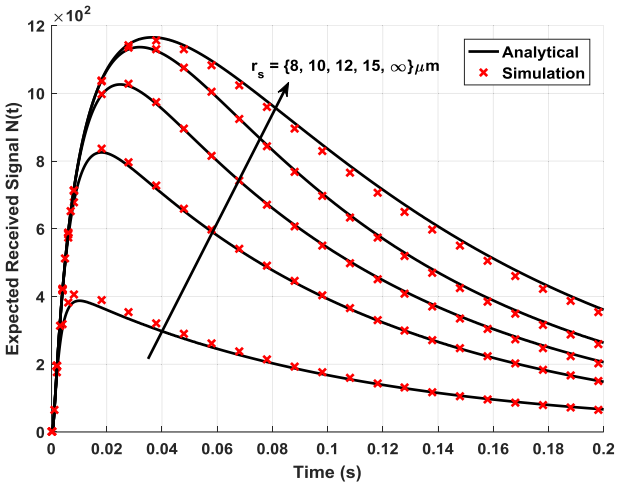

FIGURE 2. Expected received signal as a function of time for various boundary radiuses r_s when the reaction parameters are $k_f = 50\mu m/s$, $k_b = 5s^{-1}$, and $k_d = 200s^{-1}$.

The random numbers a_m for $m = \{x, y, z\}$ are uniformly distributed between 0 and 1 and $sgn(.)$ is the signum function.

- *Signal reception*: At the end of each time step, the total change in the number of ligand-receptor complexes 'MR' on the receiver surface represents the expected received signal.

IV. ANALYTICAL AND SIMULATION RESULTS

The analytical and simulation results for the expected received signal by a reversible RN in a 3-D spherically bounded microfluidic environment, are plotted and compared here. We can observe that the analytical results match well with the simulation results. Furthermore, it is demonstrated that by making the radius of the bounded medium very large, the expected received signal can be analytically reduced to that of an unbounded medium. All the simulation results presented here are averaged over 100 independent realizations. The common system parameters used are listed in Table-1 and any other specific parameters will be discussed separately for each case.

Fig. 2 shows the analytical and simulation results for the molecular received signal (i.e., expected number of 'MR' complexes on the RN surface) as a function of time for different radii of the bounded spherical medium for the following fixed reaction parameters: $k_f = 50\mu m/s$, $k_b = 5s^{-1}$, and $k_d = 200s^{-1}$. This figure clearly shows that with the increase in the medium radius, there is a corresponding increase in the

amplitude and peak time of the expected received signal. This occurs because as the radius of the bounded medium becomes smaller, a portion of the released molecules will quickly reach the medium boundary and hence, the probability that they be absorbed by the boundary is quite high. As a result, they will be removed from the environment before reaching the receptors on the receiver surface as indicated in (2). The absorbed molecules by the medium boundary will not contribute to the received signal and therefore one can see a reduction in the expected received signal. However, as the radius of the bounded medium increases, the molecules have higher chances to react with the receptors on the receiver surface before being absorbed by the medium boundary. This reaction may then lead to binding between the information molecules and the receptors on the receiver surface to form 'MR' complexes. The peak time increases with increase in the radius of the bounded medium because the molecules that travel far away from the RN will take longer time to reach the RN and contribute to the received signal. It is worth repeating here that for relatively large radius of the bounded medium, our expressions can be reduced for unbounded medium which will be used for comparison with published results in the literature [33], [37], [38].

Moreover, the initial increasing trend of expected received signal with time as seen in all the figures could be due to forward reaction process that contributes to the increase of the total cumulative number of activated receptors (i.e., ligand-receptor complexes) on the receiver surface. Also, the decreasing trend seen in the same figures at later times may be due to backward reaction process, which tends to reduce the total number of activated receptors on the surface of the RN via dissociation of the ligand-receptor complexes into 'M' molecules. Both the forward and backward reaction processes are modeled via second-order reaction process as indicated in (3). As shown in Fig. 2, after a lapse of long time interval (i.e., at steady state), the expected received signal becomes very small due to the backward reaction which causes most of the ligand-receptor complexes to become deactivated at the steady state.

The impact of the forward reaction constant k_f on the expected received signal is shown in Fig. 3 for fixed values of $k_b = 5s^{-1}$, $k_d = 200s^{-1}$, and the radius of the bounded medium $r_s = 10\mu m$. We can see from this figure that as the forward reaction constant increases, the probability of forming new 'MR' complexes (i.e., number of activated receptors) increases. On other hand, if the forward reaction constant decreases, the molecules that hit the receiver receptors will have increased probability to reflect back to the environment without forming a ligand-receptor complexes 'MR'. These molecules may move away and do not react again with the receiver receptors and thus there is a corresponding decrease in the expected received signal.

Fig. 4 shows the expected received signal as a function of time with varying backward reaction constant k_b for the following parameters: $r_s = 10\mu m$, $k_f = 50\mu m/s$, and $k_d = 200s^{-1}$. We can see from

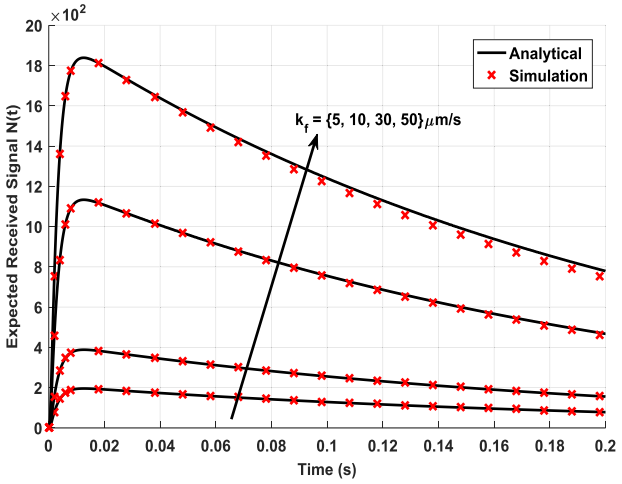

FIGURE 3. Expected received signal as a function of time for various values of forward reaction constant k_f when $k_b = 5s^{-1}$, $k_d = 200s^{-1}$ and $r_s = 10\mu m$.

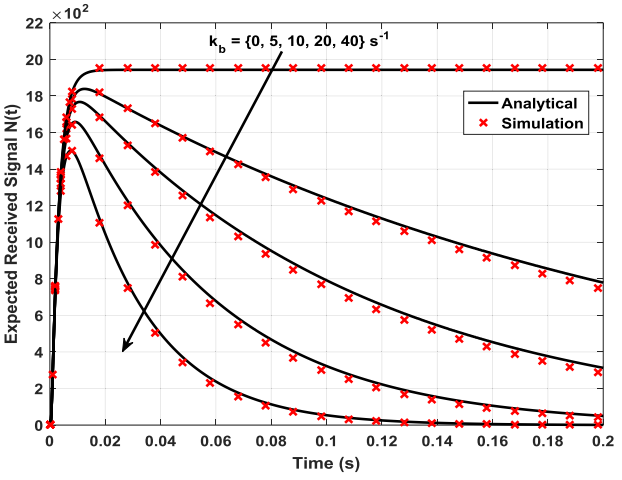

FIGURE 4. Expected received signal as a function of time for various values of backward reaction constant k_b when $k_f = 50\mu m/s$, $k_d = 200s^{-1}$ and $r_s = 10\mu m$.

this figure that the expected received signal decreases with increase in the backward reaction constant, due to increased probability of dissociation of the ligand-receptor complexes 'MR' on the receiver surface. As a result, the deactivated receptors will release the information molecules 'M' to the environment. The newly dissociated molecules will diffuse in the environment with the other molecules, which may either react again with the receiver receptors to possibly activate them or move away without visiting the receiver again. In addition, the results in Fig. 4 indicate that with the increase in the backward reaction constant, there is a faster decreasing trend in the expected received signal with time (i.e., it decreases with higher slope). This could be attributed to the faster dissociation process and as a result, the ligand-receptor complexes get deactivated quickly as soon as they are formed. However, the increasing and decreasing trends of the expected received signal with time are mainly due to forward and backward reaction processes, respectively, as discussed earlier.

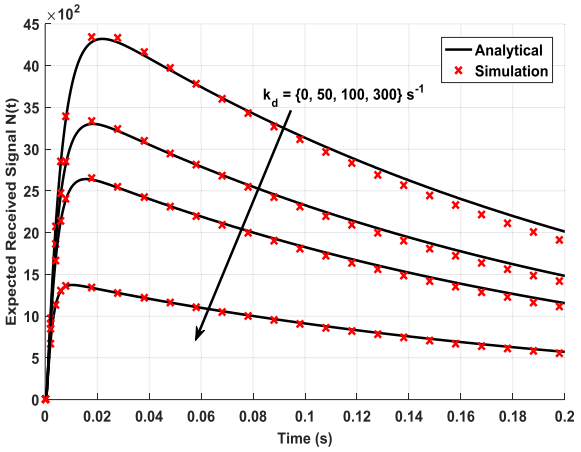

FIGURE 5. Expected received signal as a function of time for various values of degradation constant k_d when $k_f = 50\mu m/s$, $k_b = 5s^{-1}$ and $r_s = 10\mu m$.

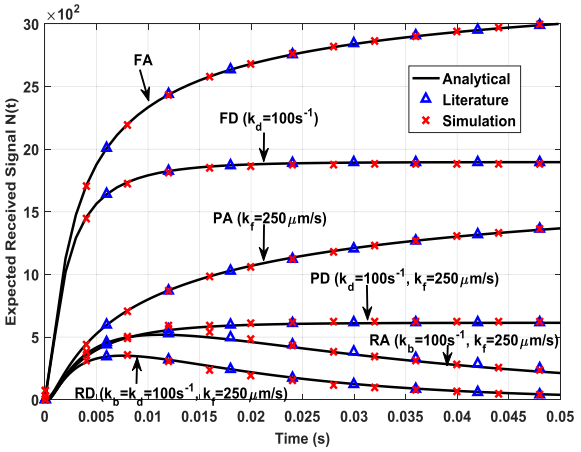

FIGURE 6. Expected received signal in unbounded (infinite) environment as special case for N_m=5000.

The effect of the degradation reaction in the bounded environment can be seen in Fig. 5 for various values of the degradation reaction constant and for fixed $k_f = 50\mu m/s$, $k_b = 5s^{-1}$, and $r_s = 10\mu m$. The molecular degradation in the bounded environment is modeled via first-order reaction process (1). As expected, the received signal decreases with the increase in the degradation reaction constant. This could be because due to an increase in the number of molecules that get degraded in the environment. The degraded molecules will not be recognized by the receiver thereafter and will neither react nor activate the receptors on the receiver surface, and thus the received signal will be decreased.

Now, we will demonstrate how our results reduce to the case of unbounded medium [33], [38]. Fig. 6 shows the simulation and analytical results for the expected received signal with reversible reaction and degradation when the radius $r_s \to \infty$ is substituted in our expressions which leads to unbounded medium, which can be considered as special case of our work. As shown in this figure, the analytical and simulation results for the special cases agree well with the results in the published literature [33], [38]. In addition, the expected received signal with molecular degradation in the environment is lower than when there is no molecular degradation.

However, to compare with results in [38], we firstly multiply the forward reaction constant in this paper (k_f) by the receiver surface area ($4\pi r_R^2$) and then, calculate the dimensionless parameters using [38, eq. (11)]. This conversion is needed because the boundary condition in [38, eq. (9)] differs from the boundary condition (8) used in this paper by a factor equal to the receiver surface area.

The results on expected received signal for fully absorber RN with/without degradation (FD, FA) computed using (39) agrees well with the available results in the literature [38, eq. (31)], [33, eq. (116)]. The fully absorber receiver without degradation (FA) has the largest expected received signal compared to other receiver types because the forward reaction constant is infinity with backward and degradation reaction constants equal to zero, which causes each molecule that hit the receptor on the receiver surface to activate the receptor without dissociation. The expected received signal for partially absorber RN with/without degradation (PD, PA) obtained from (40) is always less than the received signal for both fully absorber receivers (FA and FD) which agree well with the results available in the literature [38, eq. (30)], [33, eq. (114)]. This may be due to the fact that the forward reaction constants for PA and PD receivers are finite and thus not the all reactions lead to activation of the receptors on the surface of the receiver.

Eq. (38) provides a generalized case of reversible reaction receiver with/without degradation (RD, RA) which when reduced to special cases of unbounded medium also obtained accurate results which match well with the corresponding published for unbounded medium as plotted in Fig. 6. The irreversible receiver has increasing received signal with time and after some specific time period reaches a fixed value. This means that there are no further molecules to react with the receptors on the receiver surface. However, in case of the reversible reaction receiver, the signal level starts to decrease after reaching the peak value. This may be due to effect of the reverse reaction where some of the ligand-receptor complexes on the receiver surface get deactivated and the information molecules revert back to the environment.

V. CONCLUSION

In this paper, we propose novel and accurate analytical and simulation models for MCvD systems operating in 3D spherically bounded biological microenvironments involving reversible receiver nanomachines. The reception is modelled by a second-order reversible reaction mechanism where the information molecules can reversibly react with as well as activate the receptors on the receiver surface to form ligand-receptor complexes. Furthermore, the degradation of the information molecules during the diffusion in the propagating environment is modelled via a first-order reaction mechanism. The medium in which molecules are transported is modelled as a bounded spherical medium, and

those molecules that collide with the boundary are removed from the environment. In addition, we presented a particle-based simulator to model bounded medium including the reversible reaction at the RN together with molecular degradation and absorption at the medium boundary. The analytical results agree well with the simulations.

We also have shown that the expressions derived for the bounded medium can be reduced to other special cases mentioned in the literature for an unbounded environment. The results indicate that the radius of the bounded medium affects the amplitude and time characteristics of the received signal. This clearly demonstrates the inadequacy of unbounded medium assumption to accurately model the molecular communication system in realistic biological microfluidic environments especially for small bounded environments found inside the human body or when the TN located near the medium boundary. The impact of other system parameters, e.g., forward reaction constant (k_f), backward reaction constant (k_b), and degradation reaction constant (k_d), on the expected received signal are examined. The proposed model can be used in certain biomedical applications, for predicting the drug concentration profile and the molecular reaction over time at any targeted cell e.g., tumor cells.

APPENDIX
THE INVERSE LAPLACE TRANSFORM VIA RESIDUES THEOREM (34)-(35)

The expression (32) has simple pole at $u = 0$ and infinitely simple poles at the roots of $f_3(u)$ given by (31). Using L'Hospital's rule, we get zero residue at the simple pole $u = 0$ (i.e., $s = -k_d$) while the residue at infinitely simple poles at the roots of $f_3(u)$ can be obtained by substituting the value of ω_1 and ω_2 from (26) in (31), then we get

$$f_3(u) = (s(r_R k_f + D) + Dk_b)\sinh((r_s - r_R)u) + ur_R D(s + k_b)\cosh((r_s - r_R)u) \quad (48)$$

Now, replacing the parameter "s" in (48) by its equivalent $s = u^2 D - k_d$ where $u = \sqrt{(s + k_d)/D}$ and let (48) equal to zero, we get

$$\tanh((r_s - r_R)u) = -\frac{ur_R D(u^2 D - k_d + k_b)}{(u^2 D - k_d)(r_R k_f + D) + Dk_b} \quad (49)$$

Now, converting the hyperbolic tangent function in (49) to its equivalent trigonometric tangent function and let the parameter $\kappa_n = iu$, we get

$$\tan\left(\left(r_s - r_R\right)\kappa_n\right) = -\frac{\kappa_n r_R D(\kappa_n^2 D + k_d - k_b)}{(\kappa_n^2 D + k_d)(r_R k_f + D) - Dk_b} \quad (50)$$

Rewrite (50) in terms of the parameters α_n, β_n, and λ_n from (36), then we get (35).

The residues at the n$^{\text{th}}$ simple pole κ_n can be derived as

$$\begin{aligned}&\mathrm{Res}_{s=-(\kappa_n^2 D+k_d)}\\ &= \frac{1}{2\pi r r_T}\lim_{s\to-(\kappa_n^2 D+k_d)} e^{s(t-t_0)}\sinh\left(\left(r_s - r\right)u\right)\\ &\quad\times\left(\omega_1\sinh\left(\left(r_T - r_R\right)u\right) + u\omega_2\cosh\left(\left(r_T - r_R\right)u\right)\right)\\ &\quad\times\left[\sinh((r_s - r_R)u)\left(2Du\frac{d\omega_1}{ds} + (r_s - r_R)u\omega_2\right)\right.\\ &\quad\left.+\cosh((r_s - r_R)u)\left((r_s - r_R)\omega_1 + \left(\omega_2 + 2Du^2\frac{d\omega_2}{ds}\right)\right)\right]^{-1}\end{aligned} \quad (51)$$

By substituting the value of ω_1 and ω_2 from (26) and their derivative w.r.t "s" in (51), then converting the hyperbolic functions in (51) to their equivalent trigonometric functions, we get

$$\begin{aligned}\mathrm{Res}_{s=-(\kappa_n^2 D+k_d)} &= \frac{1}{2\pi r r_T}e^{-(\alpha_n+k_b)(t-t_0)}\frac{\sin\left(\left(r_s - r\right)\kappa_n\right)}{\sin\left(\left(r_s - r_R\right)\kappa_n\right)}\\ &\times\frac{\alpha_n\beta_n\lambda_n\sin\left(\left(r_T - r_R\right)\kappa_n\right) + \alpha_n^2\lambda_n^2\cos\left(\left(r_T - r_R\right)\kappa_n\right)}{\left(r_s - r_R\right)\left(\lambda_n^2\alpha_n^2 + \beta_n^2\right) + \alpha_n\beta_n D r_R + 2\lambda_n^2 k_f k_b}\end{aligned} \quad (52)$$

where, the parameters α_n, β_n, and λ_n are defined in (36).

We use the fact that $f_3(u) = 0$, to get the identity $\cos\left(\left(r_s - r_R\right)\kappa_n\right) = -(\beta_n/(\lambda_n\alpha_n))\sin\left(\left(r_s - r_R\right)\kappa_n\right)$ and then using it in deriving the final expression (52).

Since, the residue at the simple pole $s = -k_d$ is equal to zero, then the inverse Laplace transform of expression (32) can be expressed as the summation of the residue at the infinitely simple poles κ_n for $n = 1, 2, \ldots, \infty$. which give us the spatiotemporal distribution $P(r, t|r_T, t_0)$ in (34).

REFERENCES

[1] I. F. Akyildiz, J. M. Jornet, and M. Pierobon, "Nanonetworks: A new frontier in communications," *Commun. ACM*, vol. 54, no. 11, pp. 84–89, Nov. 2011.

[2] T. Nakano, A. W. Eckford, and T. Haraguchi, *Molecular Communication*. Cambridge, U.K.: Cambridge Univ. Press, 2013.

[3] N. Farsad, H. B. Yilmaz, A. Eckford, C.-B. Chae, and W. Guo, "A comprehensive survey of recent advancements in molecular communication," *IEEE Commun. Surveys Tuts*, vol. 18, no. 3, pp. 1887–1919, 3rd Quart., 2016.

[4] Y. Chahibi, M. Pierobon, S. O. Song, and I. F. Akyildiz, "A molecular communication system model for particulate drug delivery systems," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 12, pp. 3468–3483, Dec. 2013.

[5] Y. Chahibi, I. F. Akyildiz, S. Balasubramaniam, and Y. Koucheryavy, "Molecular communication modeling of antibody-mediated drug delivery systems," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 7, pp. 1683–1695, Jul. 2015.

[6] T. Nakano, M. J. Moore, F. Wei, A. V. Vasilakos, and J. Shuai, "Molecular communication and networking: Opportunities and challenges," *IEEE Trans. Nanobiosci.*, vol. 11, no. 2, pp. 135–148, Jun. 2012.

[7] P.-C. Yeh *et al.*, "A new frontier of wireless communication theory: Diffusion-based molecular communications," *IEEE Wireless Commun.*, vol. 19, no. 5, pp. 28–35, Oct. 2012.

[8] M. S. Kuran, H. B. Yilmaz, T. Tugcu, and B. Özerman, "Energy model for communication via diffusion in nanonetworks," *Nano Commun. Netw.*, vol. 1, no. 2, pp. 86–95, Jun. 2010.

[9] M. Pierobon and I. F. Akyildiz, "A statistical–physical model of interference in diffusion-based molecular nanonetworks," *IEEE Trans. Commun.*, vol. 62, no. 6, pp. 2085–2095, Jun. 2014.

[10] M. H. Bazargani and D. Arifler, "Deterministic model for pulse amplification in diffusion-based molecular communication," *IEEE Commun. Lett.*, vol. 18, no. 11, pp. 1891–1894, Nov. 2014.

[11] A. Noel, K. Cheung, and R. Schober, "Optimal receiver design for diffusive molecular communication with flow and additive noise," *IEEE Trans. Nanobiosci.*, vol. 13, no. 3, pp. 350–362, Sep. 2014.

[12] A. Aijaz and A. H. Aghvami, "Error performance of diffusion-based molecular communication using pulse-based modulation," *IEEE Trans. Nanobiosci.*, vol. 14, no. 1, pp. 146–151, Jan. 2015.

[13] D. Kilinc and O. B. Akan, "Receiver design for molecular communication," *IEEE J. Sel. Areas Commun.*, vol. 31, no. 12, pp. 705–714, Dec. 2013.
[14] X. Wang, M. D. Higgins, and M. S. Leeson, "Relay analysis in molecular communications with time-dependent concentration," *IEEE Commun. Lett.*, vol. 19, no. 11, pp. 1977–1980, Nov. 2015.
[15] M. U. Mahfuz, D. Makrakis, and H. T. Mouftah, "A comprehensive study of sampling-based optimum signal detection in concentration-encoded molecular communication," *IEEE Trans. Nanobiosci.*, vol. 13, no. 3, pp. 208–222, Sep. 2014.
[16] B.-H. Koo, C. Lee, H. B. Yilmaz, N. Farsad, A. Eckford, and C.-B. Chae, "Molecular MIMO: From theory to prototype," *IEEE J. Sel. Areas Commun.*, vol. 34, no. 3, pp. 600–614, Mar. 2016.
[17] B. Alberts *et al.*, *Essential Cell Biology*. New York, NY, USA: Garland, 2013.
[18] N. Farsad, A. W. Eckford, S. Hiyama, and Y. Moritani, "On-chip molecular communication: Analysis and design," *IEEE Trans. Nanobiosci.*, vol. 11, no. 3, pp. 304–314, Sep. 2012.
[19] M. A. Lovich, L. Brown, and E. R. Edelman, "Drug clearance and arterial uptake after local perivascular delivery to the rat carotid artery," *J. Amer. College Cardiol.*, vol. 29, no. 7, pp. 1645–1650, 1997.
[20] S. McGinty and G. Pontrelli, "A general model of coupled drug release and tissue absorption for drug delivery devices," *J. Controlled Release*, vol. 217, pp. 327–336, Nov. 2015.
[21] S. McGinty, S. McKee, R. M. Wadsworth, and C. McCormick, "Modeling arterial wall drug concentrations following the insertion of a drug-eluting stent," *SIAM J. Appl. Math.*, vol. 73, no. 6, pp. 2004–2028, 2013.
[22] R. Del Cont *et al.*, "A physiologically-oriented mathematical model for the description of *in vivo* drug release and absorption," *ADMET DMPK*, vol. 2, no. 2, pp. 80–97, 2014.
[23] J. U. Menon *et al.*, "Dual-drug containing core-shell nanoparticles for lung cancer therapy," *Sci. Rep.*, vol. 7, no. 1, p. 13249, Oct. 2017.
[24] L. Felicetti, M. Femminella, G. Reali, P. Gresele, M. Malvestiti, and J. N. Daigle, "Modeling CD40-based molecular communications in blood vessels," *IEEE Trans. Nanobiosci.*, vol. 13, no. 3, pp. 230–243, Sep. 2014.
[25] C. M. Groh *et al.*, "Mathematical and computational models of drug transport in tumours," *J. Roy. Soc. Interface*, vol. 11, no. 94, p. 20131173, 2014.
[26] V. Henn *et al.*, "CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells," *Nature*, vol. 391, no. 6667, pp. 591–594, 1998.
[27] S. Basu, Y. Gerchman, C. H. Collins, F. H. Arnold, and R. Weiss, "A synthetic multicellular system for programmed pattern formation," *Nature*, vol. 434, no. 7037, pp. 1130–1134, 2005.
[28] O. Mondragón-Palomino, T. Danino, J. Selimkhanov, L. Tsimring, and J. Hasty, "Entrainment of a population of synthetic genetic oscillators," *Science*, vol. 333, no. 6047, pp. 1315–1319, 2011.
[29] A. C. Heren, H. B. Yilmaz, C.-B. Chae, and T. Tugcu, "Effect of degradation in molecular communication: Impairment or enhancement?" *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, vol. 1, no. 2, pp. 217–229, Jun. 2015.
[30] S. Hiyama and Y. Moritani, "Molecular communication: Harnessing biochemical materials to engineer biomimetic communication systems," *Nano Commun. Netw.*, vol. 1, no. 1, pp. 20–30, 2010.
[31] L. S. Goodman, *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York, NY, USA: McGraw-Hill, 1996.
[32] K. Tai, S. D. Bond, H. R. MacMillan, N. A. Baker, M. J. Holst, and J. A. McCammon, "Finite element simulations of acetylcholine diffusion in neuromuscular junctions," *Biophys. J.*, vol. 84, no. 4, pp. 2234–2241, 2003.
[33] K. Schulten and I. Kosztin, "Lectures in theoretical biophysics," Ph.D. dissertation, Dept. Phys. Beckman Inst., Univ. Illinois, Urbana, IL, USA, 2000, vol. 117.
[34] H. B. Yilmaz, A. C. Heren, T. Tugcu, and C.-B. Chae, "Three-dimensional channel characteristics for molecular communications with an absorbing receiver," *IEEE Commun. Lett.*, vol. 18, no. 6, pp. 929–932, Jun. 2014.
[35] A. Akkaya, H. B. Yilmaz, C.-B. Chae, and T. Tugcu, "Effect of receptor density and size on signal reception in molecular communication via diffusion with an absorbing receiver," *IEEE Commun. Lett.*, vol. 19, no. 2, pp. 155–158, Feb. 2015.
[36] M. Damrath, S. Korte, and P. A. Hoeher, "Equivalent discrete-time channel modeling for molecular communication with emphasize on an absorbing receiver," *IEEE Trans. Nanobiosci.*, vol. 16, no. 1, pp. 60–68, Jan. 2017.
[37] M. Elkashlan, "Modeling and simulation of molecular communication systems with a reversible adsorption receiver," *IEEE Trans. Mol. Biol. Multi-Scale Commun.*, vol. 1, no. 4, pp. 347–362, Dec. 2015.
[38] A. Ahmadzadeh, H. Arjmandi, A. Burkovski, and R. Schober, "Comprehensive reactive receiver modeling for diffusive molecular communication systems: Reversible binding, molecule degradation, and finite number of receptors," *IEEE Trans. Nanobiosci.*, vol. 15, no. 7, pp. 713–727, Oct. 2016.
[39] D. Holcman, A. Marchewka, and Z. Schuss, "Survival probability of diffusion with trapping in cellular neurobiology," *Phys. Rev. E, Stat. Phys. Plasmas Fluids Relat. Interdiscip. Top.*, vol. 72, no. 3, p. 031910, 2005.
[40] S. S. Andrews, "Accurate particle-based simulation of adsorption, desorption and partial transmission," *Phys. Biol.*, vol. 6, no. 4, p. 046015, 2009.
[41] C. T. Chou, "Extended master equation models for molecular communication networks," *IEEE Trans. Nanobiosci.*, vol. 12, no. 2, pp. 79–92, Jun. 2013.
[42] C. T. Chou, "Impact of receiver reaction mechanisms on the performance of molecular communication networks," *IEEE Trans. Nanotechnol.*, vol. 14, no. 2, pp. 304–317, Mar. 2015.
[43] S. G. Krantz, *Handbook of Complex Variables*. Springer, 2012.
[44] Y. Lu, M. D. Higgins, A. Noel, M. S. Leeson, and Y. Chen, "The effect of two receivers on broadcast molecular communication systems," *IEEE Trans. Nanobiosci.*, vol. 15, no. 8, pp. 891–900, Dec. 2016.

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