Noise Analysis in Ligand-Binding Reception for Molecular Communication in Nanonetworks

Massimiliano Pierobon, *Member, IEEE*, and Ian F. Akyildiz, *Fellow, IEEE*

***Abstract*—Molecular communication (MC) will enable the exchange of information among nanoscale devices. In this novel bio-inspired communication paradigm, molecules are employed to encode, transmit and receive information. In the most general case, these molecules are propagated in the medium by means of free diffusion. An information theoretical analysis of diffusion-based MC is required to better understand the potential of this novel communication mechanism. The study and the modeling of the noise sources is of utmost importance for this analysis. The objective of this paper is to provide a mathematical study of the noise at the reception of the molecular information in a diffusion-based MC system when the ligand-binding reception is employed. The reference diffusion-based MC system for this analysis is the physical end-to-end model introduced in a previous work by the same authors, where the reception process is realized through ligand-binding chemical receptors. The reception noise is modeled in this paper by following two different approaches, namely, through the ligand-receptor kinetics and through the stochastic chemical kinetics. The ligand-receptor kinetics allows to simulate the random perturbations in the chemical processes of the reception, while the stochastic chemical kinetics provides the tools to derive a closed-form solution to the modeling of the reception noise. The ligand-receptor kinetics model is expressed through a block scheme, while the stochastic chemical kinetics results in the characterization of the reception noise using stochastic differential equations. Numerical results are provided to demonstrate that the analytical formulation of the reception noise in terms of stochastic chemical kinetics is compliant with the reception noise behavior resulting from the ligand-receptor kinetics simulations.**

***Index Terms*—Chemical master equation, diffusion, ligand-receptor kinetics, molecular communication, nanonetworks, nanotechnology, reaction rate equation, stochastic chemical kinetics.**

I. Introduction

MOLECULAR COMMUNICATION (MC) is increasingly attracting the interest of the research community working in the field of information exchange at the nanoscale [1]. MC is a paradigm in which molecules are used to encode, transmit and receive information. This paradigm has been inspired by biology, where cells employ MC to establish both intracellular and intercellular information links [2].

Nanoscale devices are nowadays enabled by nanotechnology, which studies the realization of components in a scale ranging from one to a few hundred nanometers. Those components can be used to build basic structural and functional devices, i.e., nanomachines, which are able to perform tasks at nano-level, such as computing, data storing, sensing, actuation and communication. Once nanomachines can communicate between each other, they can be interconnected as a network, or nanonetwork [1], to execute more complex tasks and to expand their range of operation.

The application of MC to nanomachines stems from the possibility to satisfy constraints both in the apparatus size and in the communication medium. The former constraint is posed by the need to integrate molecular transceivers in the nanomachines. The latter constraint is given by the particular characteristics of the medium in which nanomachines can be immersed, such as in intra-body deployment or in other application scenarios. Some specific media, such as liquids, restrict the possibility of using other communication paradigms, i.e., the electromagnetic communication.

Different techniques can be used in molecular communication to exchange information. These range from the use of carriers, such as molecular motors [3] or bacteria [4], to the diffusion of the molecules in a fluid [5]. The focus of this paper is on diffusion-based techniques, since they can be considered the most common in nature. The calcium signaling among cells [6], the pheromonal communication [7]-[8] among animals and the synaptic transmission between neurons [2] are examples of these techniques, while they differ in the way molecules are diffused and received. The theory of turbulent diffusion [9] and the odorant-binding protein reception [10] can be applied to the pheromonal communication, while the theory of electro-diffusion [11] and the ligand-gated ion channel reception [12] are applicable to the calcium signaling. More general models for molecular diffusion and reception, which underlie all the other models, are based on the theory of the Brownian motion diffusion [13] and the ligand-binding reception [14] and they can be successfully applied, e.g., to the synaptic transmission of neurotransmitters in neurons. Further specifications of the system for the pheromonal communication case or the calcium signaling case depend from the general case treated in this work.

One of the main challenges in diffusion-based MC is the proper study and characterization of the noise. Most of the contributions from the literature to the noise analysis for diffusion-based MC are mainly based on the results of simulations

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M. Pierobon is with the Broadband Wireless Networking Laboratory, School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA 30332 USA (e-mail: maxp@ece.gatech.edu).

I. F. Akyildiz is with the Broadband Wireless Networking Laboratory, School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA 30332 USA. He is also with the NaNoNetworking Center in Catalunya (N3Cat), Universitat Politècnica de Catalunya (UPC), 08034 Barcelona, Catalunya, Spain (e-mail: ian@ece.gatech.edu).

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and do not provide closed-form solutions to the modeling of the noise sources. As an example, in [5] the results of simulations show a noise for the diffusion-based MC which follows a non-Gaussian statistics, although the analytical model for this statistics is not investigated. In [15] the noise effects on the diffusion-based MC are resulting only from simulation and there is no analytical model of diffusion-based noise and no stochastic study of its underlying physical phenomena. Moreover, in [15] there is no specific analysis of the noise sources which affect the reception side of a diffusion-based MC system. In [16], the diffusion-based MC reception noise is analyzed in terms of probability of having erroneous digital reception, under the assumption of a binary squared pulse code modulation signal. As a consequence, the work in [16] addresses the noise analysis for a diffusion-based MC system having specific characteristics in terms of modulation scheme and type of transmitted messages. In [17] we provided an analysis of the most relevant diffusion-based noise sources in the end-to-end MC system presented in [18]. Two noise sources are studied in [17], namely, the particle sampling noise and the particle counting noise, and they are related to the transmitter and to the signal propagation in the channel, respectively.

The objective of this paper is to analytically model the source of the reception noise due to the ligand-receptor binding at the *receiver* in diffusion-based MC. The goal of this analysis is to provide both mathematical expressions for the noise source simulation and closed-form solutions for the noise stochastic modeling. We follow the same methodology that we used in [17] for the noise sources at the transmitter and in the diffusion channel. The reference receiver for this analysis is described in [16] and in [18], and it is detailed in Section III. The ligand-receptor binding is modeled in this paper by following two different approaches, namely, through the ligand-receptor kinetics and through the stochastic chemical kinetics.

The ligand-receptor kinetics model stems from the classical chemical kinetics, which studies the mathematical description of time evolution of chemical reactions. Classical chemical kinetics has been successfully applied to the ligand-receptor binding analysis in biochemical signaling [19], although it is valid only where the random perturbations in the chemical reactions are negligible due to the large number of molecules, as stated in [20]. The ligand-receptor kinetics model in this paper is an extension of the classical chemical kinetics formulation that allows us to have a simulation model for the random perturbations in the ligand-receptor binding.

The stochastic chemical kinetics summarizes the noise generation by combining tools from chemistry and statistics. Works such as [21]–[23] provide us with the tools from stochastic chemical kinetics to derive a closed-form solution to the modeling of the reception noise, as we obtained in [17] with the stochastic models for the diffusion-based noise.

The remainder of the paper is organized as follows. In Section II, the existing solutions from the literature for the diffusion-based molecular communication architectures are presented and the specific architecture addressed in this paper is motivated with reference to them. In Section III, the assumptions for the molecular receiver model are introduced and the ligand-receptor binding at the MC reception is explained.

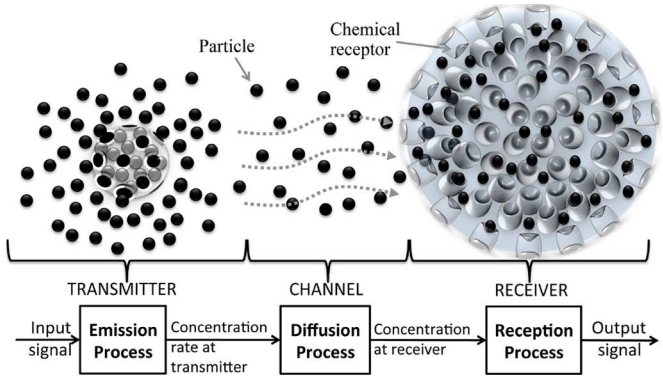

Fig. 1. Graphical representation of the end-to-end model, inspired by the work in [18].

The ligand-receptor kinetics is analyzed in Section IV for the ligand-receptor binding process, while the stochastic chemical kinetics model is treated in Section V. Simulation results are provided in Section VI to assess the validity of the reception noise model in terms of stochastic chemical kinetics and to compare them to the ligand-receptor kinetics simulations. Finally, in Section VII, we conclude the paper.

II. Diffusion-Based Molecular Communication Architecture

A. Proposed Architectures From the Literature

Different diffusion-based MC architectures have been proposed in the literature on the basis of the technique used to encode the information in the diffusing molecules. The three most referenced architectures encode the information in: i) the time of molecule release; ii) the type of each molecule; iii) the variations of the concentration of molecules in the space.

The first type of architecture is theoretically analyzed in [24], where the authors focus on the mathematical modeling of the diffusion channel as a probabilistic contribution in the time of arrival of molecules at the receiver. The simulation results from [24] in terms of achievable information rate show that, due to the high uncertainty in the propagation time, this architecture is characterized by very low capacity.

The second type of architecture is analyzed in [15], where the diffusion channel part is modeled, together with other types of non-diffusive channels. Since each molecule carries information, a piece of information is received only if its carrier molecule reaches the receiver location. As a consequence, in [15] it is shown that the diffusion-based channel has very low performance for this architecture if compared to other non-diffusive techniques.

The third type of architecture is treated in [5], [18], [25], and [26]. In [5] a simplified receiver model of this architecture is studied, where the diffusion-based channel is coupled with an ideal molecule emitter at the transmitter location and a single molecule receptor at the receiver location. Although the simulation results in [5] show low values for the system capacity, the high similarity of this architecture to the cellular biological systems, which are characterized by much higher performance, encourages the investigation in this direction. In [25] and [26],

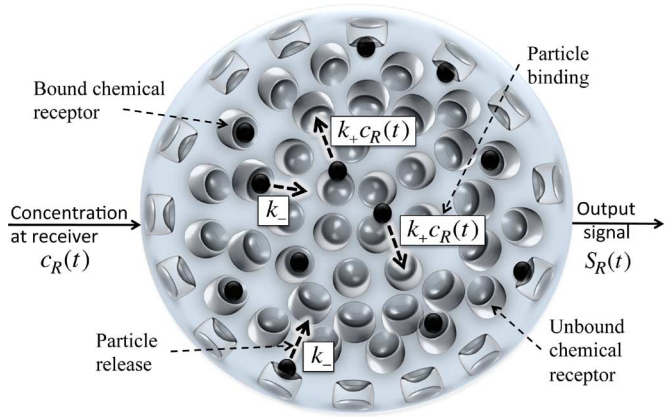

Fig. 2. Graphical sketch of the ideal ligand-receptor binding with the assumptions from [18].

a model of a diffusion-based MC receiver is developed by using multiple chemical receptors to read the molecule concentration at the receiver location. The results in terms of capacity with this model show relatively high values if compared to [5], especially when an error compensation technique is applied. Theoretical results from [27] confirm the high potential in terms of achievable information rates for this type of diffusion-based molecular communication system. Finally, a complete end-to-end physical model for the third architecture is proposed in [18]. Although capacity values are not provided in [18], a framework for the subsequent study of the performance of the complete end-to-end system is built.

B. Our Reference Architecture

The reference architecture for this paper is sketched in Fig. 1, where the diffusion-based MC is modeled in terms of transmission, propagation and reception of particles, as described in [18]. The **Emission Process** at the TRANSMITTER encodes the `Input signal` into variations in the particle concentration (`Concentration rate at the transmitter`). This encoding is achieved through the release/capture of particles into/from the environment. The particle concentration rate is the output of the transmitter and the input of the channel. The CHANNEL relies on the **Diffusion Process** of the particles in the environment to propagate the particle concentration variations to the receiver. The RECEIVER senses the particle `Concentration at the receiver` at its location and decodes the information into the `Output signal`. The **Reception Process** generates the output signal by means of chemical receptors through the ligand-receptor binding.

The result of the work in [18] is a mathematical analysis of the communication channel of Fig. 1, in terms of relation between the input signal and the output signal. The three processes, namely, the particle emission, diffusion and reception, are analyzed in terms of their contributions to the overall normalized gain and delay between inputs and outputs, as functions of the frequency and the transmission range. Noise effects arising from random perturbations in the three processes are not taken into account in [18].

In this paper, we focus on the analysis of the reception process and its related contribution to the random perturbation of the signal, as it is decoded by the chemical receptors through the ligand-receptor binding.

III. The Molecular Receiver Model

When a particle concentration $c_R(t)$, where t is the time variable, is present at the receiver location, the receiver modulates the output signal $s_R(t)$ according to the rate of change in the value of $c_R(t)$ itself. The reading of the concentration is achieved by means of the reception process, which is based on the chemical theory of the ligand-receptor binding [14]. The reception process of the end-to-end model from [18], sketched in Fig. 2, is based on the following assumptions:

- All the processes take place inside the space S, which contains a fluidic medium and it has infinite extent in all the three dimensions.
- A particle is an indivisible object that can be released to, or collected from, the space S.
- When a particle is not being released or collected, it is subject to the diffusion process in the fluidic medium contained in the space S.
- The measure of the particle concentration takes place inside the *receptor space*. The receptor space has a spherical shape of radius ρ.
- The input *particle concentration* $c_R(t)$ is considered homogeneous inside the receptor space and equal to the particle concentration value at the receiver location.
- The reception is realized by means of N_R *chemical receptors*.
- The chemical receptors are assumed to homogeneously occupy the volume of the receptor space.
- Each chemical receptor, at the same time instant t, is exposed to the same particle concentration $c_R(t)$.
- The chemical receptors, when exposed to the particle concentration $c_R(t)$, can remain in their state, namely, *bound* or *unbound*, or they can change their state by undergoing two possible chemical reactions: the *particle binding* reaction if the receptor was previously unbound, or the *particle release* reaction if the chemical receptor was previously bound to a particle.
- The particle binding occurs with a rate k_+, while the particle release occurs with the rate k_-.
- The output signal $s_R(t)$ of the reception process is the first time derivative in the number of bound chemical receptors, denoted as $n_b(t)$, as described in [18]

$$s_R(t) = \frac{dn_b(t)}{dt}. \tag{1}$$

The purpose of the above assumptions is to define a model inspired by the reception process in cellular systems from biology. According to this, the chemical receptors are models of the transmembrane receptors [2] embedded in the plasma membrane of living cells and involved in the signal transduction process. In this paper, we do not model the location of the chemical receptors as if they were on the plasma membrane, but we place them homogeneously in the receptor space. This allows us to simplify the treatment related to the chemical

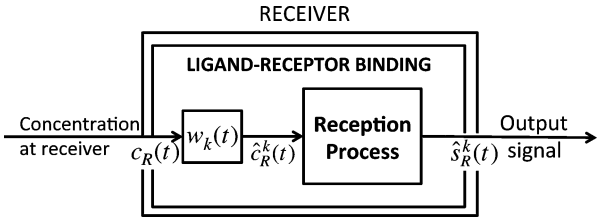

Fig. 3. Block scheme of the reception noise at the receiver.

changes which ultimately lead to the signal transduction. The signal transduction in biosignaling involves the conversion of a chemical change (e.g., the change in concentration of the chemical components in the surrounding environment) into information. From this point of view, the molecules of the biochemical components are modeled by the particles and the biological surrounding environment is the receptor space.

The reception noise affects the molecular receiver due to random fluctuations in the LIGAND-RECEPTOR BINDING process, represented by the block scheme in Fig. 3. Due to the effect of this noise contribution, denoted by $w_k(t)$, the particle concentration $c_R(t)$ is subject to an unwanted perturbation, resulting in $\hat{c}_R^k(t)$. As a consequence, this perturbation propagates to the output signal $\hat{s}_R^k(t)$ after the reception process.

IV. The Ligand-Receptor Kinetics

In this section, we first describe the classical formulation of the ligand-receptor binding according to the deterministic reaction rate equation. Second, we introduce the ligand-receptor kinetics equation as an extension of the reaction rate equation, which takes into account the randomness in the ligand-receptor binding process. Finally, we detail the ligand-receptor kinetics equation through the ligand-receptor kinetics block scheme, which incorporates all the mathematical relations necessary to model the random effects in the ligand-receptor kinetics.

A. The Reaction Rate Equation

The ligand-receptor kinetics stems from the definition of the binding and release reactions in the LIGAND-RECEPTOR BINDING. The binding reaction and the release reaction are considered by the assumptions given in Section III as happening only according to deterministic rates: k_+ and k_-, respectively. This is justified from the viewpoint of the classical chemical kinetics [19], which interprets the time evolution of a chemical system with deterministic reaction rate equations (RREs). The RRE of the chemical system defined by the assumptions from Section III is expressed as follows:

$$\frac{dn_b(t)}{dt} = k_+ c_R(t)\left(N_R - n_b(t)\right) - k_- n_b(t) \tag{2}$$

where $n_b(t)$ is the number of bound chemical receptors, k_+ is the rate of particle binding, $c_R(t)$ is the particle concentration at the receiver, N_R is the total number of chemical receptors at the receiver and k_- is the rate of particle release. In Appendix A, we detail the mathematical expressions of the particle binding and release rates.

Given (1), the first time derivative in the number $n_b(t)$ of bound chemical receptors can be substituted with the output signal $s_R(t)$ of the reception process.

$$s_R(t) = \left(k_+ c_R(t)\right)\left(N_R - n_b(t)\right) - k_- n_b(t). \tag{3}$$

Equation (3) is a continuous function, which relates the output signal $s_R(t)$ of the reception process to the concentration $c_R(t)$ and the number of bound chemical receptors $n_b(t)$ at time t.

B. The Ligand-Receptor Kinetics Equation

The model of the reception process considered so far does not take into account the random fluctuations in the LIGAND-RECEPTOR BINDING, which stem from the Brownian motion, since the collision frequency averages the Brownian motion effects through the average particle velocity in (45); see Appendix A. We consider now the following additional assumptions:

- Particles inside the receptor space are discrete and they move according to the Brownian motion.
- The binding reaction can occur only when a particle, subject to the Brownian motion, collides with an unbound receptor.
- The binding reaction occurs only if the kinetic energy of the particle colliding with an unbound receptor is higher than the activation energy E_a. The kinetic energy $E_k^p(t)$ of a particle p at time t is expressed as follows:

$$E_k^p(t) = \frac{1}{2}\left|\overline{v}_p(t)\right|^2 m_p. \tag{4}$$

  $\overline{v}_p(t)$ is the velocity of the particle p at time t and m_p is its mass, while $|.|^2$ denotes the squared absolute value operator.
- Whenever a binding reaction occurs, there is a subtraction of a particle from the reception space. Whenever a release reaction occurs, there is an addition of a particle to the reception space.

As a result, the relation between the particle concentration $c_R(t)$ and the actual output signal of the reception process, denoted by $\hat{s}_R^k(t)$, is subject to random fluctuations due to the LIGAND-RECEPTOR KINETICS. During the LIGAND-RECEPTOR KINETICS, graphically sketched in Fig. 4, particles subject to the Brownian motion inside the reception space contribute to the number of bound chemical receptors, denoted with $\hat{n}_b(t)$, only at discrete time instants $t_n = t_1, t_2, \ldots$, which correspond to collision events between the particles themselves and the unbound receptors. Each collision event contributes to $\hat{n}_b(t)$ according to the coefficient k_n, which is a function of the kinetic energy of the collided particle at time t. The bound receptors can become unbound according to the particle release rate k_-, thus decreasing the actual number $\hat{n}_b(t)$. Therefore, we write a new equation, the ligand-receptor kinetics equation, by extending the RRE in (2) in order to account for the random effect of the collisions

$$\frac{d\hat{n}_b(t)}{dt} = \left(\sum_n k_n \delta(t - t_n)\right) - k_- \hat{n}_b(t), \quad t_n = t_1, t_2, \ldots \tag{5}$$

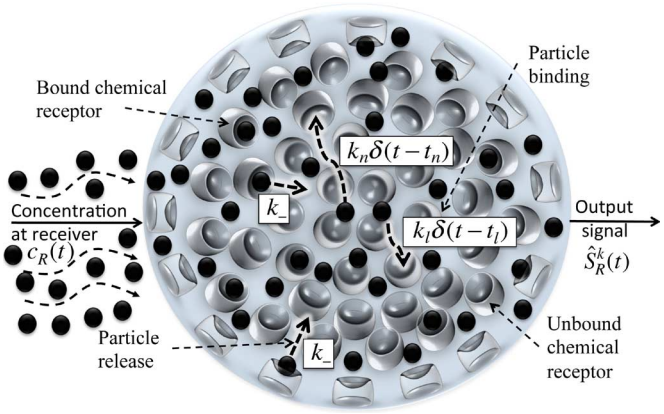

Fig. 4. Graphical sketch of the LIGAND-RECEPTOR KINETICS: the reception process and the reception noise $w_k(t)$ contribution. The time instant t_n is in general different from the time instant t_l, where $n \neq l$.

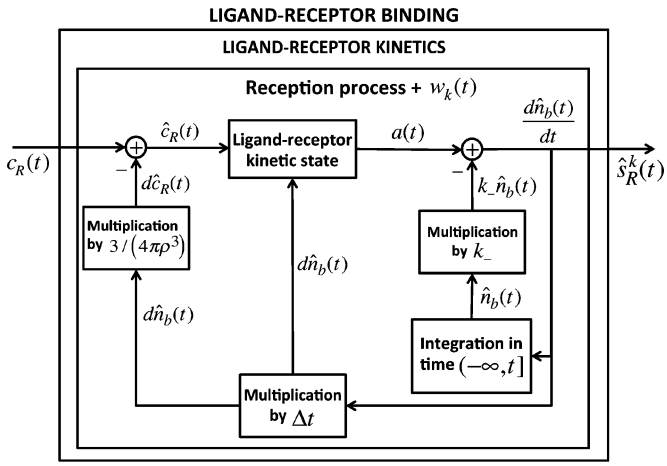

Fig. 5. Block scheme of the LIGAND-RECEPTOR KINETICS.

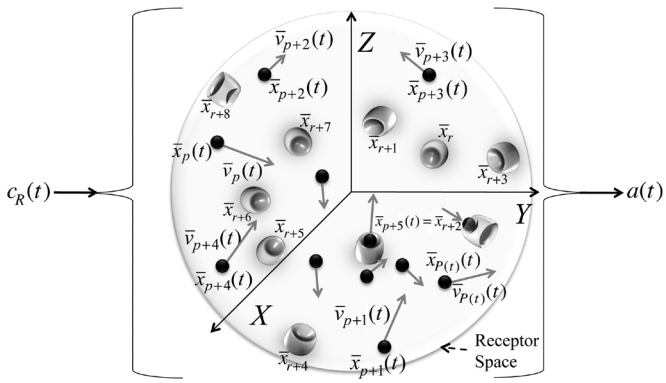

Fig. 6. Graphical sketch of the ligand-receptor kinetic state block. The number of particles $P(t)$ in the receptor space depends on the particle concentration $c_R(t)$ in input through the expressions in (8).

where $\hat{n}_b(t)$ is the number of bound chemical receptors, k_n is a coefficient related to the particle binding at time instant t_n, k_- is the rate of particle release and $\delta(.)$ is a Dirac delta function. Given (1), the first time derivative in the number $\hat{n}_b(t)$ of bound chemical receptors can be substituted with the output signal of the reception process, this time denoted as $\hat{s}_R^k(t)$

$$\hat{s}_R^k(t) = \left(\sum_n k_n \delta(t-t_n)\right) - k_- \hat{n}_b(t), \quad t_n = t_1, t_2, \ldots. \tag{6}$$

Equation (6) is not a continuous function with respect to the contribution of the binding reaction, which is expressed through the sum of Dirac deltas $\sum_n \delta(t-t_n)$ and the coefficient k_n of particle binding. As a consequence, the contribution of the LIGAND-RECEPTOR KINETICS creates fluctuations in the output signal $\hat{s}_R^k(t)$ that are not present in the previous formulation of the output $s_R(t)$ of the reception process through (3).

C. The Ligand-Receptor Kinetics Block Scheme

The LIGAND-RECEPTOR KINETICS is represented though the block scheme shown in Fig. 5. The particle concentration $c_R(t)$ is the input of the overall **Reception process** $+ w_k(t)$ block, whose output signal is $\hat{s}_R^k(t)$. The LIGAND-RECEPTOR KINETICS block is composed of the ligand-receptor kinetic state block, the integration block and three multiplication blocks.

The **ligand-receptor kinetic state** block, as shown in Fig. 6, takes as input the concentration $\hat{c}_R(t)$ of the particles inside the receptor space and returns the signal $a(t)$ as output. The ligand-receptor kinetic state block keeps track of the locations $\bar{x}_p(t)$ of all the particles present inside the receptor space at time t through the set $K_P(t)$:

$$K_P(t) = \{\bar{x}_p(t) | p = 1, \ldots, P(t)\} \tag{7}$$

where $P(t)$ is the number of particles in the receptor space at time t and it is expressed as follows:

$$P(t) = round\left(\hat{c}_R(t)\frac{4}{3}\pi\rho^3\right) \tag{8}$$

where $\hat{c}_R(t)$ is the particle concentration at the receiver and $\left(\frac{4}{3}\right)\pi\rho^3$ is the size of the receptor space. ρ is the radius of the receptor space, and $round(.)$ is the operator that rounds the operand to the nearest integer. In order to realistically simulate the evolution of $K_P(t)$, we consider the Brownian motion contribution at every time instant t. The expression of the particle location $\bar{x}_p(t)$ is written as follows:

$$\bar{x}_p(t) = \bar{x}_p(t-\Delta t) + b_x(\Delta t)\hat{i} + b_y(\Delta t)\hat{j} + b_z(\Delta t)\hat{k} \tag{9}$$

where the Brownian motion components, namely, $b_x(\Delta t)$, $b_y(\Delta t)$, and $b_z(\Delta t)$, are random variables with normal distribution, zero mean value and variance equal to $2D\Delta t$, according to the expression of the Wiener process [28]

$$b_x(\Delta t), b_y(\Delta t), b_z(\Delta t) \sim \mathcal{N}(0, 2D\Delta t) \tag{10}$$

along the directions of the Cartesian axes, namely, $\hat{i}$, $\hat{j}$ and $\hat{k}$. D is the diffusion coefficient and Δt is the simulation time step and it depends on how the ligand-receptor kinetics block samples the evolution of $K_P(t)$ during the physical model simulation. The smaller is the time step Δt, the closer is the simulation to the real physical phenomenon of the particle Brownian motion. Despite in the simulation we are sampling the Brownian dynamics, the time variable of the number of bound chemical

receptor $n_b(t)$ is kept continuous. This is due to the fact that while collisions between particles and unbound receptors can occur only every Δt time steps, the unbinding reaction occurs continuously according to (5). The ligand-receptor kinetic state block keeps also memory of the locations $\bar{x}_r(t)$ of the unbound chemical receptors through the set $K_R(t)$

$$K_R(t) = \{\bar{x}_r(t), r = 1, \ldots, n_u(t)\} \tag{11}$$

where $n_u(t)$ corresponds to the number of unbound chemical receptors present in the receptor space at time t. The number $n_u(t)$ is computed by taking into account the time differential $dn_b(t-\Delta t)$ in the number of bound chemical receptors coming from the lower branch of the block scheme at time $t - \Delta t$. The resulting number of unbound chemical receptors $n_u(t)$ at time t is recursively computed as follows:

$$n_u(t) = round\,(n_u(t - \Delta t) - dn_b(t - \Delta t)) \tag{12}$$

where $round(.)$ is the operator that rounds the operand to the nearest integer. Since for every time instant we assume to have a uniform distribution of both particles and receptors inside the receptor space, the probability of having a collision between a particle and an unbound receptor is uniform. As a consequence, for every time instant, every unbound receptor has the same probability of having a collision with a particle. Whenever there is a collision between a particle and an unbound chemical receptor, which means that the spherical volume of a particle of radius r_p from the set $K_P(t)$ has a non-void intersection with the volume of a receptor of radius r_R from the set $K_R(t)$, then the ligand-receptor kinetic block contributes to the output $a(t)$ with a Dirac delta $\delta(t - t_n)$ multiplied by the coefficient k_n. The coefficient k_n is equal to 1 when the kinetic energy of the colliding particle $E_k^p(t)$ is higher than the activation energy E_a, and it is 0 otherwise. In case of k_n equal to 1, then the collision successfully results in a binding reaction (non-elastic collision). If k_n is equal to 0, then the binding reaction does not take place and the particle resumes its Browinan motion from the location of the collision with the same kinetic energy as before the collision occurred (elastic collision). The coefficient k_n is computed through the following expression:

$$k_n = \begin{cases} 1 & \text{if } E_k^p(t_n) > E_a \\ 0 & \text{otherwise.} \end{cases} \tag{13}$$

The kinetic energy $E_k^p(t_n)$ of the colliding particle p at time t_n is computed through (4), where the velocity $\bar{v}_p(t_n)$ of the particle p at time t_n is computed with the following expression:

$$\bar{v}_p(t_n) = \frac{\bar{x}_p(t_n - \Delta t) - \bar{x}_p(t_n)}{\Delta t} \tag{14}$$

where $\bar{x}_p(t_n - \Delta t)$ and $\bar{x}_p(t_n)$ are the particle location at time $t_n - \Delta t$ and time t_n, respectively. The activation energy E_a is computed as a function of the rate k_+ of particle binding by rearranging (43) and (44) from Appendix A as follows:

$$E_a = -k_B T \ln\left(\frac{k_+}{Z}\right) \tag{15}$$

where Z is computed through (43). The time instant t_n corresponds to the moment when a collision between a particle and an unbound receptor occurs. As a consequence, the output $a(t)$ of the ligand-receptor kinetic block is a sum of Dirac deltas $\delta(t - t_n)$, each one at a different time instant t_n:

$$a(t) = \sum_n k_n \delta(t - t_n); t_n \in \left\{ t_i \middle| \left(K_P(t_i) \bigcap K_R(t_i) \right) \neq \oslash \right\} \tag{16}$$

where $K_P(t_i) \bigcap K_R(t_i)$ is the intersection between the set $K_P(t_i)$ and the set $K_R(t_i)$, which contains elements only if there are particle locations with the same value as the locations of unbound receptors. $\oslash$ is the void set.

The **multiplication by Δt** block receives as input the first time derivative $\frac{d\hat{n}_b(t)}{dt}$ at time t of the number of bound chemical receptors and returns as output its time differential $d\hat{n}_b(t)$. The time differential $d\hat{n}_b(t)$ corresponds, when positive, to the number of particles subtracted from the receptor space due their binding to previously unbound receptors; when negative, it corresponds to the number of particles added to the receptor space due to their release from previously bound receptors.

The **multiplication by $\frac{3}{(4\pi\rho^3)}$** block receives as input the time differential $d\hat{n}_b(t)$ at time t in the number of bound receptors, and it outputs the concentration differential $d\hat{c}_R(t)$ of bound receptors at time t. The value of $d\hat{c}_R(t)$ corresponds to the variation in the concentration of particles inside the receptor space given by the binding or the release of particles to/from chemical receptors. The true concentration $\hat{c}_R(t)$ of particles present at time t inside the receptor space is given by the following expression:

$$\hat{c}_R(t) = c_R(t) - d\hat{c}_R(t) \tag{17}$$

where $d\hat{c}_R(t)$ is the time differential of the particle concentration $c_R(t)$ in input to the LIGAND-RECEPTOR KINETICS.

The **integration** block receives as input the first time derivative $\frac{d\hat{n}_b(t)}{dt}$ in the number of bound chemical receptors and gives as output the number $\hat{n}_b(t)$ of bound chemical receptors at time t. The output of the integration block $\hat{n}_b(t)$ is therefore the time integral

$$\hat{n}_b(t) = \int_{-\infty}^{t} \frac{\hat{n}_b(t')}{dt'} dt'. \tag{18}$$

The **multiplication by k_-** block receives as input the number $\hat{n}_b(t)$ of bound receptors at time t and multiplies it by the rate k_- of release reaction. The output of the multiplication block is then subtracted from the output $a(t)$ of the ligand-receptor kinetics block. The result of the subtraction is the first time derivative in the number $\hat{n}_b(t)$ of bound receptors

$$\frac{d\hat{n}_b(t)}{dt} = a(t) - k_- \hat{n}_b(t) \tag{19}$$

where $a(t)$ is computed through (16).

Since it is not possible to always have the knowledge of the ligand-receptor kinetic state due to the huge amount of information and to the randomness in the particle motion, we cannot analytically compute the value of $\hat{S}_R^k(t)$ as a function of $c_R(t)$ through the ligand-receptor kinetics model of the reception noise. Using the physical model provided here, we can only simulate numerically the behavior of the reception noise $w_k(t)$.

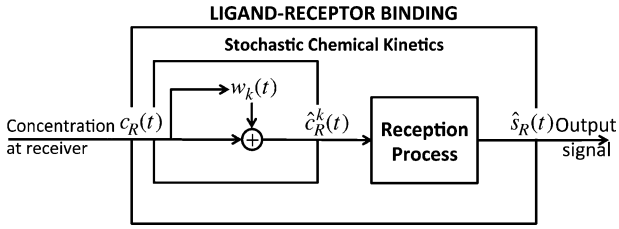

Fig. 7. Block scheme of the stochastic chemical kinetics applied to the LIGAND-RECEPTOR BINDING process.

V. The Stochastic Chemical Kinetics

The reception noise can also have another formulation, through the stochastic chemical kinetics, which is suitable when theoretical studies require an analytical expression of the noise. For this, the reception noise $w_k(t)$ is generated by a random process, whose contribution corresponds to

$$w_k(t) = \hat{c}_R^k(t) - \left\langle \hat{c}_R^k(t) \right\rangle \tag{20}$$

where $\hat{c}_R^k(t)$ is the actual particle concentration in input of the reception process and $\langle \hat{c}_R^k(t) \rangle$ is the expected particle concentration, where $\langle . \rangle$ denotes the ensemble average operator. The expected particle concentration $\langle \hat{c}_R^k(t) \rangle$ corresponds to the particle concentration that we would expect in input to the reception process in the absence of the reception noise

$$\left\langle \hat{c}_R^k(t) \right\rangle = c_R(t). \tag{21}$$

In this section, we provide the necessary assumptions underlying the stochastic models of the reception noise: the reversible second-order reaction and the reversible first-order reaction stochastic models. As we explain in the following, the latter allows also to find a closed-form solution for the variance $Var(\hat{c}_R^k(t))$ of the perturbed particle concentration.

A. Stochastic Model Assumptions

In Fig. 7 we show the main block scheme of the LIGAND-RECEPTOR BINDING process when the stochastic chemical kinetics is applied to model the reception noise. The random process $w_k(t)$, as it is proved in the following, depends on the value of the particle concentration $c_R(t)$ itself, output from the diffusion process. The sum of the random process $w_k(t)$ and the particle concentration $c_R(t)$ is the particle concentration affected by the reception noise $\hat{c}_R^k(t)$.

In order to properly model the random process $w_k(t)$ we consider the following assumptions:

- The particles and the chemical receptors inside the receptor space are considered as two different types of molecules (chemical species). For these two chemical species, we assume that the system is "well stirred", which means that the particles and the chemical receptors have uniformly random distributed locations inside the receptor space.
- The assumption of having a "well stirred" system allows us to describe the ligand-receptor binding process only accounting for the populations of the chemical species. We can therefore ignore the description of the system through the ligand-receptor kinetic state defined in Section IV, which was composed by the locations of the chemical receptors and the locations and velocities of the particles inside the receptor space.
- The populations of the chemical species are described through two quantities: the number of particles $P(t)$ in the receptor space and the number of bound receptors $\hat{n}_b(t)$ at each time instant t. The number of unbound receptors is computed by subtracting the number $\hat{n}_b(t)$ of bound receptors from the total number N_R of chemical receptors, namely $N_R - \hat{n}_b(t)$.
- As a consequence of the first assumption, the binding reaction rate is considered as a constant equal to k_+, since, without accounting for the ligand-receptor kinetic state, it is not possible to know either the kinetic energy of a particle colliding with an unbound chemical receptor, nor when the collision occurs.

Under these assumptions, the value of the population for each chemical species is never known deterministically, but only in probability. The stochastic chemical kinetics studies how the populations of the chemical species evolve in a system due to chemical reactions. This is achieved by the formulation of the chemical system through the chemical master equation (CME) [20]. The CME is a stochastic differential equation that binds together the populations of the chemical species involved in the chemical reactions. In the following, we consider two different CMEs, namely, the **reversible second-order reaction** and the **reversible first-order reaction**. Although both of them can represent the ligand-receptor binding, the former CME is the most complete formulation but, due to its complexity, it does not easily provide a closed-form solution. On the contrary, the latter CME is based on further assumptions and it allows for a closed-form solution to the problem of the stochastic modeling of the ligand-receptor kinetics.

B. The Reversible Second-Order Reaction

The **reversible second-order reaction** is able to model the changes both in the number of bound receptors $\hat{n}_b(t)$ and in the number of particles $P(t)$ in the receptor space occurring due to the binding and release reactions. Whenever a binding/release reaction occurs, there is a subtraction/addition of a particle from/to the reception space, and this is taken into account in the perturbation of the value of the particle concentration $c_R(t)$ inside the receptor space. Given this assumption, we can write the reversible second-order reaction CME for the ligand-receptor binding, whose schematic relation is

$$N_R - \hat{n}_b(t) + P(t) \underset{k_-}{\overset{\frac{k_+}{(4/3)\pi\rho^3}}{\rightleftarrows}} \hat{n}_b(t) \tag{22}$$

where $\hat{n}_b(t)$ is the number of bound chemical receptors, $P(t)$ is the number of particles in the receptor space, and $N_R - \hat{n}_b(t)$ is the number of unbound chemical receptors, as defined above. $\left(\frac{4}{3}\right)\pi\rho^3$ is the size of the receptor space and it divides the binding reaction rate k_+ since here we are dealing with the number of particles in the receptor space rather than with the particle concentration $c_R(t)$. The formulation of the CME for the ligand-receptor binding states that the first time derivative of the probability of having n_b bound receptors is equal to the sum of different terms: the probability $P_{n_b-1}(t)$ of having $n_b - 1$ bound chemical receptors and having a binding reaction, the

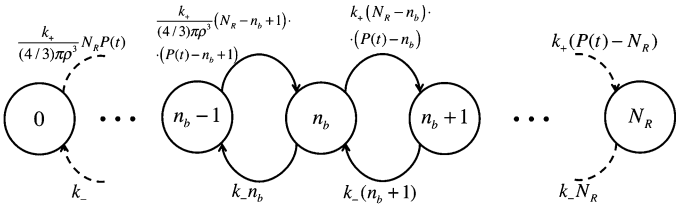

Fig. 8. Graphical representation of (23) as a Markov chain.

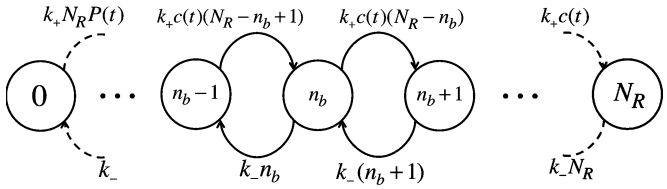

Fig. 9. Graphical representation of (25) as a Markov chain.

probability $P_{n_b+1}(t)$ of having n_b+1 bound chemical receptors and having a release reaction, the negative of the probability $P_{n_b}(t)$ of having n_b chemical receptors and having either a release reaction or a binding reaction.

$$\begin{aligned}\frac{dP_{n_b}(t)}{dt} =& \frac{k_+}{((4/3)\pi\rho^3)}(N_R-n_b+1)\,(P(t)-n_b+1)\\ &\times P_{n_b-1}(t)+k_-(n_b+1)P_{n_b+1}(t)\\ &-[k_-n_b+k_+(N_R-n_b)\,(P(t)-n_b)]\\ &\times P_{n_b}(t)\end{aligned} \tag{23}$$

where $\frac{k_+}{\left(\left(\frac{4}{3}\right)\pi\rho^3\right)(N_R-n_b+1)(P(t)-n_b+1)}$ is the rate of having a binding reaction with N_R-n_b+1 available unbound receptors and $P(t)-n_b+1$ available particles; $k_-(n_b+1)$ is the rate of having a release reaction with n_b+1 bound receptors; k_-n_b is the rate of having a release reaction with n_b bound receptors and $k_+(N_R-n_b)(P(t)-n_b)$ is the rate of having a binding reaction with N_R-n_b available unbound receptors and $P(t)-n_b$ available particles. Equation (23) can be schematically interpreted in terms of Markov chains [28], as shown in Fig. 8. According to the theory of Markov chains, each possible value of the number n_b of bound chemical receptors can represent a finite state in a state chain. In the Markov chain of Fig. 8, the probability of having a transition to a higher state number is given by the probability of being in that state and having a binding reaction, while the probability of having a transition to a lower state number is given by the probability of being in that state and having a release reaction. In order to find a closed-form solution to the problem of the stochastic modeling of the ligand-receptor kinetics it is necessary to add a further assumption to the stochastic model and to interpret the system through the reversible first-order reaction CME, which is explained in the following.

C. The Reversible First-Order Reaction and Closed-Form Solution

The **reversible first-order reaction** is based on a further assumption which is formulated as follows:

- The number of particles $P(t)$ in the receptor space for any time instant t is much higher than the number N_T of chemical receptors.

As a consequence, the particle concentration $c_R(t)$ in input to the ligand-receptor binding process is not affected by the binding or release reactions occurring between the particles and the chemical receptors. For this, even if, whenever a binding/release reaction occurs, there is a subtraction/addition of a particle from/to the reception space, the perturbation in the value of the particle concentration $c_R(t)$ inside the receptor space is negligible. Given this assumption, we can write the CME for the ligand-receptor binding process as a reversible first-order reaction, whose schematic relation is

$$N_R-\hat{n}_b(t) \underset{k_-}{\overset{c_R(t)k_+}{\rightleftarrows}} \hat{n}_b(t) \tag{24}$$

where $\hat{n}_b(t)$ is the number of bound chemical receptors and $N_R-\hat{n}_b(t)$ is the number of unbound chemical receptors, as defined above. The formulation of the CME for the ligand-receptor binding states that the first time derivative of the probability of having n_b bound receptors is equal to the sum of different terms: the probability $P_{n_b-1}(t)$ of having n_b-1 bound chemical receptor and having a binding reaction, the probability $P_{n_b+1}(t)$ of having n_b+1 bound chemical receptors and having a release reaction, the negative of the probability $P_{n_b}(t)$ of having n_b chemical receptors and having either a release reaction or a binding reaction

$$\begin{aligned}\frac{dP_{n_b}(t)}{dt} =& c_R(t)k_+(N_R-n_b+1)P_{n_b-1}(t)\\ &+k_-(n_b+1)P_{n_b+1}(t)\\ &-[k_-n_b+c_R(t)k_+(N_R-n_b)]\,P_{n_b}(t)\end{aligned} \tag{25}$$

where $c_R(t)k_+(N_R-n_b+1)$ is the rate of having a binding reaction with N_R-n_b+1 available unbound receptors; $k_-(n_b+1)$ is the rate of having a release reaction with n_b+1 bound receptors; k_-n_b is the rate of having a release reaction with n_b bound receptors, and $c_R(t)k_+(N_R-n_b)$ is the rate of having a binding reaction with N_R-n_b available unbound receptors. Equation (23) can be schematically interpreted in terms of Markov Chains [28], as shown in Fig. 9. We can interpret the Markov chain of Fig. 9 in the same way as we did for Fig. 8, where, this time, the probability of having a transition to a higher state number does not account for the number of particles $P(t)$ in the receptor space, but only for the value of the particle concentration $c_R(t)$. The solution to the problem of the stochastic modeling of the ligand-receptor kinetics can be found through a similar procedure as in [21]. We express (25) in terms of Probability Generating Function [28] $F(s,\tau)$, which is defined as follows:

$$F(s,\tau)=\sum_{n_b=0}^{N_R}P_{n_b}(\tau)s^{n_b} \tag{26}$$

where s is an auxiliary variable and τ is a time variable which is ranging from t to $\frac{t+1}{(2B_c)}$. B_c is the bandwidth of the particle concentration $c_R(t)$ in input to the stochastic model. According to the Nyquist theorem [29], we can sample the particle concentration $c_R(t)$ with a rate equal to $2B_c$ without loss of information. During a sampling time interval from t to $\frac{t+1}{(2B_c)}$ spanned by τ, we can consider only one sample of the concentration signal $c_R(t)$. As a consequence, we can solve (25) treating $c_R(t)$ as a

constant parameter. The CME in (25) can be expressed in terms of Probability Generating Function as follows:

$$\frac{\partial F(s,\tau)}{\partial \tau} = \left[k_- + (c_R(t)k_+ - k_-)\, s - k_- s^2\right] \frac{\partial F(s,\tau)}{\partial s} + N_R c_R(t) k_+ (s-1) F(s,\tau). \quad (27)$$

We impose to the Probability Generating Function to have at $\tau = t$ a number of bound receptors $\hat{n}_b(\tau = t)$ equal to the number of bound receptors $n_0(t)$ that we would expect in the absence of noise and at chemical equilibrium, given the particle concentration $c_R\left(\frac{t-1}{(2B_c)}\right)$ in the receptor space from the previous time interval $\frac{t-1}{(2B_c)}$, which is computed by setting to zero the derivative $\frac{dn_b(t)}{dt}$ of the RRE in (2) and solving for $n_b(t)$:

$$\hat{n}_b(\tau = t) = n_0(t) = \frac{N_R c_R\left(t - 1/(2B_c)\right) k_+}{c_R\left(t - 1/(2B_c)\right) k_+ + k_-} \quad (28)$$

which means that the probability of having n_0 bound receptors at time $\tau = 0$ is equal to 1. As a consequence, the Probability Generating Function assumes at time $\tau = 0$ the value $s^{n_0(t)}$

$$F(s,0) = s^{n_0(t)}. \quad (29)$$

Accounting for (29), we can solve (27) with respect to the Probability Generating Function $F(s,\tau)$: [see (30) at the bottom of the page] where $k_- = k_1$, $c_R(t)k_+ = k_2$, $\lambda = \frac{k_1}{k_2}$, and $K = k_1 + k_2$. This allows to find the average value $\langle \hat{n}_b(t) \rangle$ and the variance $Var(\hat{n}_b(t))$ of the number $n_b(\tau)$ of bound receptors at time τ according to the properties [28] of the Probability Generating Function as follows:

$$\langle \hat{n}_b(\tau) \rangle = \left.\frac{\partial F(s,\tau)}{\partial s}\right|_{s=1} \quad (31)$$

$$Var\left(\hat{n}_b(\tau)\right) = \left.\frac{\partial^2 F(s,\tau)}{\partial s^2}\right|_{s=1} + \left.\frac{\partial F(s,\tau)}{\partial s}\right|_{s=1} - \left(\left.\frac{\partial F(s,\tau)}{\partial s}\right|_{s=1}\right)^2. \quad (32)$$

The final expressions for the average value $\langle n_b(\tau) \rangle$ and the variance $Var(n_b(\tau))$ become

$$\langle \hat{n}_b(\tau) \rangle = \frac{n_0(t)}{K}\left(k_1 e^{-K(\tau - t)} + k_2\right) \quad (33)$$

$$Var\left(\hat{n}_b(\tau)\right) = \frac{n_0(t)\left(\lambda e^{-K(\tau-t)} + 1\right)}{1+\lambda} \times \left(1 - \frac{\lambda e^{-K(\tau-t)} + 1}{1+\lambda}\right) \quad \tau \in [t, t + 1/(2B_c)]. \quad (34)$$

The perturbed particle concentration $\hat{c}_R^k(t)$ is computed from the value of the number of bound receptors through the steady-state solution of the RRE in (2)

$$\hat{c}_R^k(t) = \frac{k_- \hat{n}_b(\tau)}{k_+\left(N_R - \hat{n}_b(\tau)\right)} \quad (35)$$

which is computed from (28) by substituting $n_0(t)$ with $\hat{n}_b(t)$ and $c_R(t)$ with $\hat{c}_R^k(t)$ and by solving for $\hat{c}_R^k(t)$. By substituting the value of $n_0(t)$ from (28) into (33) and by applying the approximation $\exp(-K(\tau - t)) \approx 1$, the average value of the perturbed particle concentration $\langle \hat{c}_R^k(t) \rangle$ computed by averaging (35) is equal to the particle concentration $c_R(t)$ that we would expect in input to the reception process without the contribution of the reception noise

$$\langle \hat{c}_R^k(t) \rangle = c_R(t) \tau \in [t, t + 1/(2B_c)]. \quad (36)$$

The variance $Var(\hat{c}_R^k(t))$ of the perturbed particle concentration can be approximated through the formula for the variance of a function of a random variable of known variance and average [28]

$$Var\left(\hat{c}_R^k(t)\right) \approx \left[\frac{N_R k_-}{k_+\left(N_R - \langle \hat{n}_b(\tau) \rangle\right)^2}\right]^2 Var\left(\hat{n}_b(\tau)\right) \quad (37)$$

valid for $\tau \in \left[\frac{t, t+1}{(2B_c)}\right]$, and where $\langle \hat{n}_b(\tau) \rangle$ and $Var(\hat{n}_b(\tau))$ are computed through (33) and (34), respectively, N_R is the total number of chemical receptors, k_+ is the rate of the binding reaction and k_- is the rate of the release reaction.

VI. Numerical Results

In this section, we present a numerical analysis of the reception noise models. Sets of noise data realizations are generated through simulation of both the **ligand-receptor kinetics model** and the **stochastic chemical kinetics model**. The sets of noise data realized using the ligand-receptor kinetics model are then used to assess the performance of the analytical formulations of the reception noise in terms of stochastic chemical kinetics.

A. Ligand-Receptor Binding Simulations

The simulations of the ligand-receptor kinetics are computed by applying a sinusoidal signal in the particle concentration $c_R(t)$ to the scheme in Fig. 5

$$c_R(t) = A \sin(2\pi f_a t) + A \quad (38)$$

where f_a is the frequency of the sinusoid in Hz, $2A$ is the value of the maximum particle concentration, expressed in particles $\mu\mathrm{m}^{-3}$, and t is the simulation time index in msec.

$$F(s,\tau) = \left\{ \frac{\left[k_2 s^2 + (k_1 - k_2)s - k_1\right]\left(\lambda e^{-K(\tau-t)}(s-1) + \lambda + s\right)^2}{(s-1)(s+\lambda)K(1+\lambda)} \right\}^{\frac{n_0(t)}{2}} \quad (30)$$

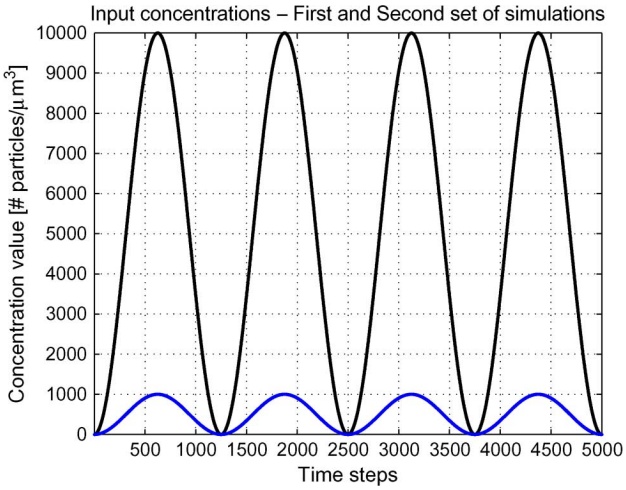

Fig. 10. The input of the ligand-receptor kinetics and stochastic chemical kinetics simulations in terms of particle concentration.

We used a simple modulation waveform, a sinusoid, to produce easy to read graphical results. Moreover, the sinusoidal waveform spans the concentration values from 0 to the maximum value $2A$ and it allows for the computation of the noise contribution for all the values in this range. Since we do not account for a time correlation model in the noise statistical parameters of the stochastic chemical kinetics, in this paper we are not interested in the analysis of different waveforms in input to the receiver and on their distortion due to the reception noise.

The input of the ligand-receptor kinetics simulation is the particle concentration $c_R(t)$ in (38), sum of a sinusoid and a constant value A, since $c_R(t)$ cannot have negative values. The sinusoid has frequency f_a equal to 4/5 Hz. We carried out two sets of simulations: in the first set, the amplitude of the input sinusoid is equal to the value A of 5000 particles $\mu\mathrm{m}^{-3}$, while for the second set, the value of A is 500 particles $\mu\mathrm{m}^{-3}$, as shown in Fig. 10. The values for the particle concentration $c_R(t)$ are quantized with respect to the number of particles ranging from 0 to $2A$, even if, due to the high values of the parameter A, the quantization of the sinusoidal curves is not clearly visible in Fig. 10. These two different values in the simulations enable to validate the property of the reversible first-order reaction model to approximate the output of the reversible second-order reaction model when the number of particles inside the receptor space is much higher than the number of chemical receptors, which is a valid assumption only for the first set of simulations. All the simulations run for 5 sec by steps of $\Delta t = 1$ msec.

The simulations are carried out using the following values for the system parameters: the radius of the reception space is $\rho = 10\ \mu\mathrm{m}$, the binding reaction rate is set to $k_+ = 0.2\ [\mu\mathrm{m}^3/\mathrm{sec}]$, and the release reaction rate is set to $k_- = 10$ [1/s], with reference to [14]; the number of receptors present inside the receptor space is set to $N_R = 500$, while the particle diffusion coefficient, used in the ligand-receptor kinetics, is set to $D \sim 10^{-6}\ \mathrm{cm}^2\mathrm{sec}^{-1}$ of calcium molecules diffusing in a biological environment (cellular cytoplasm, [30]). The radii of a particle r_p and a chemical receptor r_R are set equal to 1 nm.

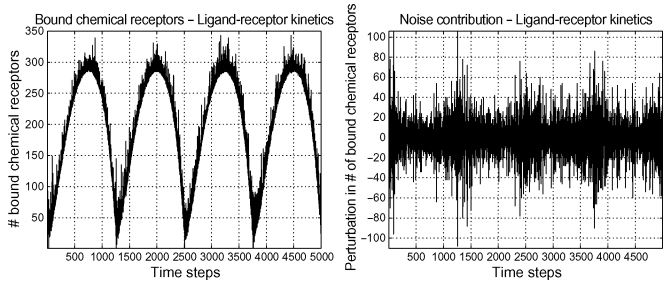

Fig. 11. The output of the first set of simulations of the ligand-receptor kinetics model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

The ligand-receptor binding is simulated through two different models, namely, the ligand-receptor kinetics and the stochastic chemical kinetics. The former is simulated through the LIGAND-RECEPTOR KINETICS, schematically represented in Fig. 5, while the latter is simulated through the CME of the reversible second-order reaction from (23) and Fig. 8 and through the CME of the reversible first-order reaction from (25) and Fig. 9.

In the simulation of the **ligand-receptor kinetics model** particles are generated inside the receptor space at random locations whenever the particle concentration $c_R(t)$ increases. Particle deletion is randomly performed inside the receptor space whenever $c_R(t)$ decreases. Through particle generation and particle deletion, we control the number of particles $P(t)$ in the receptor space, which is a parameter of the ligand-receptor kinetic state block shown in (7). The number of particles $P(t)$ in the receptor space depends from the particle concentration $c_R(t)$ through the relation in (8). The Brownian motion of the particles is modeled according to (9). Samples contributing to the value of the number $\hat{n}_b(t)$ of bound chemical receptors are generated by applying (13) and (16) with the knowledge of the results from (4) and (14). The final results in terms of $\hat{n}_b(t)$ is achieved by applying (18) and (19).

The results of the first set of simulations of the ligand-receptor kinetics model are shown in Fig. 11 in terms of the number $\hat{n}_b(t)$ of bound chemical receptors (left) and in terms of the perturbation of $\hat{n}_b(t)$ around the average value (right), which corresponds to the isolated noise contribution. Fig. 11 shows how the LIGAND-RECEPTOR KINETICS affects the value of $\hat{n}_b(t)$ more heavily when the input particle concentration $c_R(t)$ and the resulting $\hat{n}_b(t)$ have a lower value. This result is a consequence of the fact that when there are fewer particles inside the receptor space, the fluctuations in the number of bound chemical receptors are comparable in magnitude to the average number of bound receptors itself.

For the **stochastic chemical kinetics model**, we reproduce the behavior of the Chemical Master Equations studied in Section V through simulations of the Markov chains sketched in Fig. 8 and Fig. 9, respectively. For the **reversible second-order reaction** we use (23), while for the **reversible first-order reaction** we use (25).

The results of the first set of simulations of the stochastic chemical kinetics model are shown in Fig. 12 and Fig. 13 in terms of the number $\hat{n}_b(t)$ of bound chemical receptors (left)

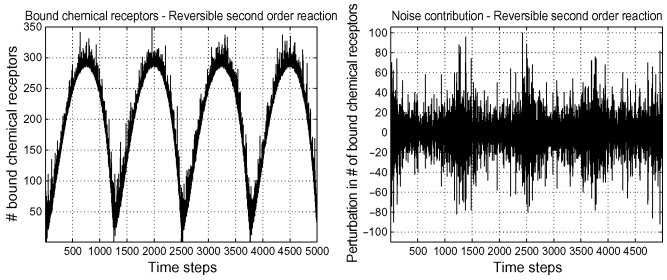

Fig. 12. The output of the first set of simulations on the reversible second-order reaction model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

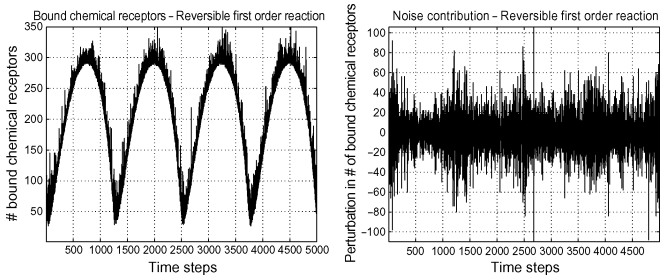

Fig. 13. The output of the first set of simulations on the reversible first-order reaction model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

and the perturbation of $\hat{n}_b(t)$ around the average value (right) for the reversible second-order reaction and the reversible first-order reaction, respectively. The results for the two types of reactions show similar values to the results of the model of the ligand-receptor kinetics, shown in Fig. 11.

The results of the second set of simulations for the ligand receptor kinetics, the reversible second-order reaction and the reversible first-order reaction are shown in Fig. 14, Fig. 15 and Fig. 16, respectively. The reversible second-order reaction has values closer to the model of the ligand-receptor kinetics if compared to the reversible first-order reaction. This is a consequence of the fact that the reversible second-order reaction model accounts for the effects of the binding or release reactions on the input particle concentration $c_R(t)$. The reversible first-order reaction is an approximation of the real behavior of the ligand-receptor kinetics: the higher is the number of particles inside the receptor space than the number of chemical receptors, the closer is the reversible first-order reaction to reality. Since for the second set of simulations we used a number of particles inside the receptor space closer to the number of chemical receptors, the difference of the results from the reversible first-order reaction with respect to the results from the ligand-receptor kinetics are more evident. The reversible first-order reaction model overestimates the number of particles present inside the receptor space, while the reversible second-order reaction model realistically accounts for a depletion of the particles when these bind to the receptors.

B. The Statistical Likelihood Test

The statistical likelihood test is applied to prove that the analytical formulation of the reception noise in terms of stochastic

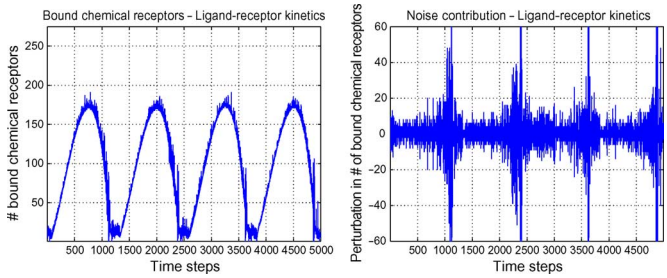

Fig. 14. The output of the second set of simulations on the ligand-receptor kinetics model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

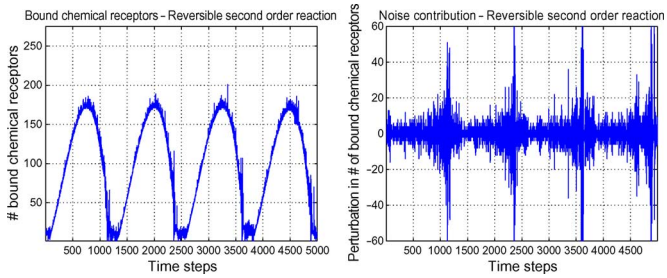

Fig. 15. The output of the second set of simulations on the reversible second-order reaction model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

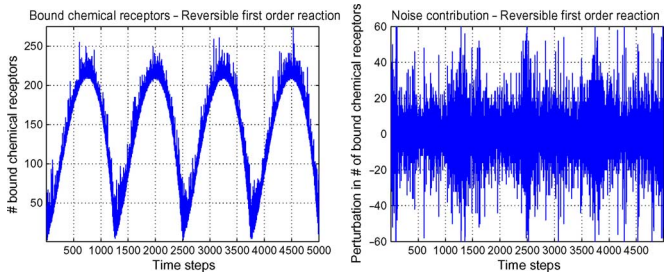

Fig. 16. The output of the second set of simulations on the reversible first-order reaction model in terms of number of bound chemical receptors (left) and isolated noise contribution (right).

chemical kinetics provides a good model of the behavior of the ligand-receptor kinetics. For this, we compute the likelihood, that is, the probability of having a number of bound chemical receptors n_b, given a stochastic chemical kinetics models defined in Section V, and then we compare the results with the value of the number of bound receptors from the simulation of the ligand-receptor kinetics model.

The likelihood of the stochastic chemical kinetics models is evaluated for a range of different values for the number of bound chemical receptors n_b as follows:

$$\text{likelihood}_{StoChemKin} = Pr\left(n_b | \text{StoChemKin}\left(\hat{n}_b(t)\right)\right) \quad (39)$$

where n_b ranges from 1 to N_R bound chemical receptors for every time instant t and $\hat{n}_b(t)$ is the result of the simulation of the model of the ligand-receptor kinetics. The results are

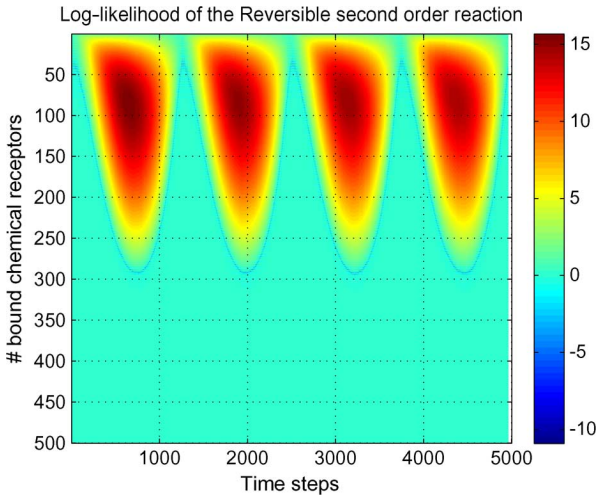

Fig. 17. The reversible second-order reaction log-likelihood for the first set of simulations.

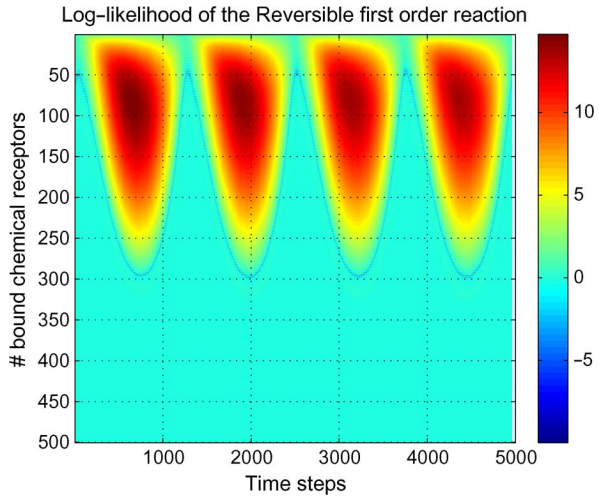

Fig. 18. The reversible first-order reaction log-likelihood for the first set of simulations.

shown for the reversible second-order reaction and for the reversible first-order reaction in Fig. 17 and Fig. 18, respectively, for the first set of simulations. The highest likelihood value corresponds, for every time instant t, to the value of the number of bound receptors in Fig. 11 (left), thus visually confirming that the best particle concentration model parameter for the stochastic chemical kinetics model is actually the number $\hat{n}_b(t)$ of bound chemical receptors in output from the model of the ligand-receptor kinetics. A noticeable characteristic in Fig. 17 and Fig. 18 is the asymmetry of the values between a time interval where the input sinusoid increases and a time interval where it decreases. This is also evident in Fig. 14, Fig. 15 and Fig. 16. This phenomenon is created by the difference between the values of the rates k_+ and k_-, where $k_+ < k_-$, which results in a slower increase in the number of bound chemical receptors than a corresponding decrease. This is even more evident for a lower number of particles in the receptor space.

These statistical likelihood test results shown in Fig. 17 and Fig. 18 are compared to the results obtained through

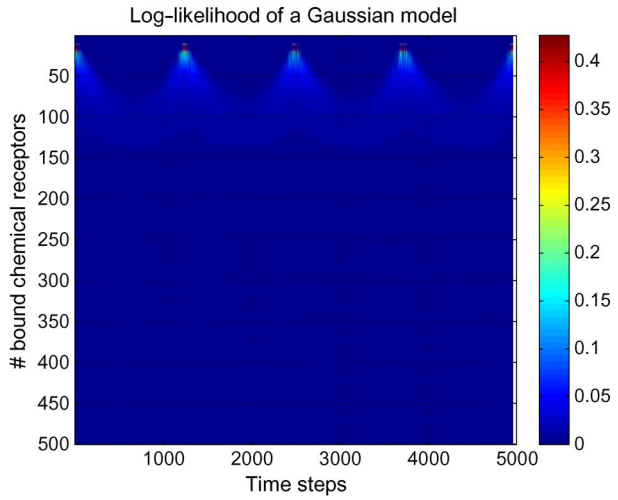

Fig. 19. The log-likelihood of a Gaussian model for the first set of simulations.

the use of a Gaussian model in place of the stochastic chemical kinetics model. The Gaussian model, denoted by $\mathcal{N}(\langle n_b(\tau)\rangle, Var(n_b(\tau)))$, has the same expected value and the same variance as the stochastic chemical kinetics model for the reversible first-order reaction, from (33) and (34), respectively. The likelihood formula is

$$\text{likelihood}_{\text{Gaussian}} = Pr\left(n_b | \mathcal{N}\left(\langle n_b(\tau)\rangle, Var\left(n_b(\tau)\right)\right)\right) \tag{40}$$

where n_b ranges from 1 to N_R bound chemical receptors for every time instant t. $n_b(\tau)$ is the result of the simulation of the model of the ligand-receptor kinetics, where $\tau \in \left[t, \frac{t+1}{2B_c}\right]$. When the Gaussian model is applied, the likelihood shows lower values than when using the stochastic chemical kinetics model. On average, the likelihood values shown in Fig. 19 are much lower than the values in Figs. 17 and 18, and this proves that the stochastic chemical kinetics model performs better than the Gaussian model. These results confirm the validity of the stochastic chemical kinetics model presented in this paper.

The results of the second set of simulations in terms of statistical likelihood are shown for the reversible second-order reaction, the reversible first-order reaction and the Gaussian model in Figs. 20, 21, and 22, respectively. The same conclusions as for the first set of simulations can be drawn from these results, even if now the likelihood values for the reversible second-order reaction are noticeably different from the reversible first-order reaction. This is given by the fact that for the second set of simulations the number of particles inside the receptor space is not consistently higher than the number of chemical receptors, with the above explained consequences on the reversible first-order reaction.

Finally, we computed the Kullback-Leibler (K-L) distance [28] K-L(M) of each stochastic model M from the data generated through the ligand-receptor kinetics by applying the following formula:

$$\text{K}-\text{L}(\text{M}) = \int Pr\left(\hat{n}_b(t)\right)|\text{M})\log\left[Pr\left(\hat{n}_b(t)\right)|\text{M})\right]dt \tag{41}$$

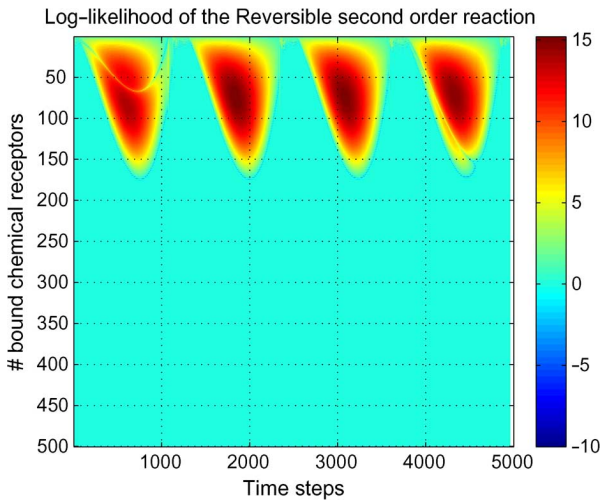

Fig. 20. The reversible second-order reaction log-likelihood for the second set of simulations.

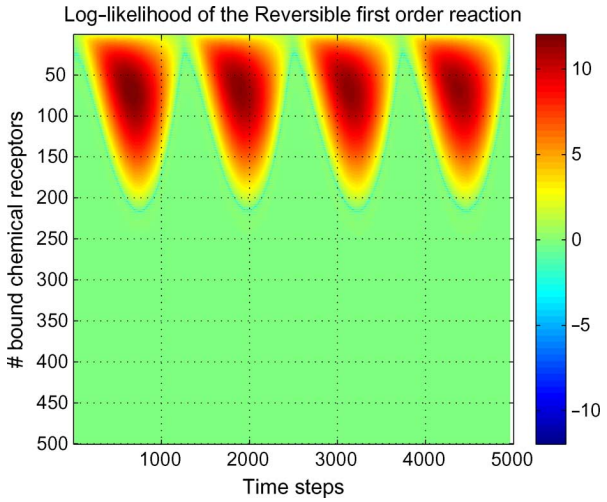

Fig. 21. The reversible first-order reaction log-likelihood for the second set of simulations.

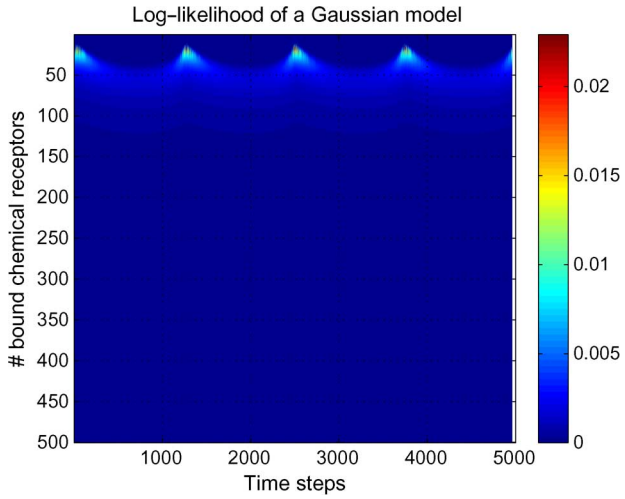

Fig. 22. The log-likelihood of a Gaussian model for the second set of simulations.

where $\hat{n}_b(t)$ is the result of the simulation using the model of the ligand-receptor kinetics. The results in terms of K-L distance are shown in Table I, where values closer to 1 indicate a better matching between the data and the stochastic model. As expected, the values for the stochastic chemical kinetics models are closer to 1 with respect to the values for the Gaussian model. Moreover, the difference in the K-L distance values between the reversible second-order and the reversible first-order reaction models increases for the second set of simulations, where the assumption for the validity of the reversible first-order reaction is no longer valid.

TABLE I
KULLBACK-LEIBLER DISTANCE

	First Simulation Set	Second Simulation Set
Rev. First Order	-64.4435	-64.9863
Rev. Second Order	-65.1680	-66.4959
Gaussian	-89.8191	-115.7583

VII. CONCLUSIONS

In this paper, we analyzed the source of the reception noise due to the ligand-receptor binding at the receiver in a diffusion-based Molecular Communication (MC) system. Contributions from the literature to the noise analysis for diffusion-based MC are mainly based on the results of simulations and do not provide closed-form solutions to the modeling of the noise sources. The reference MC architecture for this paper is described in [18], where the diffusion-based MC is modeled in terms of transmission, propagation and reception of particles and the information encoding is realized through the modulation of the concentration of molecules in the space. The choice of this architecture is motivated by results from the literature related to the information-theoretical analysis of various diffusion-based MC systems.

The ligand-receptor binding is modeled in this paper by following two different approaches, namely, through the ligand-receptor kinetics and through the stochastic chemical kinetics. The goal of this analysis is to provide both mathematical expressions for the noise source simulation and closed-form solutions for the noise stochastic modeling at the receiver, as we provided in [17] for the noise sources at the transmitter and in the diffusion channel. The ligand-receptor kinetics stems from the classical chemical kinetics, which is the discipline that studies how the time evolution of chemical reactions can be described in terms of mathematical models. The stochastic chemical kinetics provides us with the tools to derive a closed-form solution for modeling the reception noise. The results of the ligand-receptor kinetics analysis are summarized through a block scheme which expands the reception process of the end-to-end physical model from [18]. The stochastic chemical kinetics analysis results in a twofold characterization in terms of random processes, namely, the reversible second-order reaction and the reversible first-order reaction chemical master equations, and in the analytical expression of the variance of the noise on the output signal from the reception process.

Simulations are shown to prove that the analytical formulation of the reception noise in terms of stochastic chemical kinetics is compliant with the reception noise behavior resulting from the simulations of the ligand-receptor kinetics model.

The analysis of the reception noise provided in this paper and the results in terms of mathematical modeling will serve to expand the knowledge on diffusion-based MC system and to support further investigation on its performance in terms of capacity and throughput. This paper provides an initial study on the reception noise source stemming from the ligand-receptor binding theory and we envision that further study will be conducted on the basis of these results.

APPENDIX A
PARTICLE BINDING AND RELEASE RATES

The rate k_+ of particle binding is defined in chemical kinetics [31] as follows:

$$k_+ = ZF_C(E_a) \tag{42}$$

where Z is the average collision frequency, E_a is the activation energy of the ligand-receptor binding and $F_C(E_a)$ is the fraction of collisions having a higher energy than the activation energy. The average collision frequency Z quantifies how frequently a collision occurs between a particle and an unbound receptor and it is expressed as follows:

$$Z = \langle N_p \rangle \langle N_R - n_b \rangle \pi (r_p + r_R)^2 \langle \bar{v}_p \rangle \tag{43}$$

where $c_R(t)$ is the concentration of particles at the receiver, $\langle N_p \rangle$ is the average number of particles inside the receptor space, $\langle N_R - n_b \rangle$ is the average number of unbound chemical receptors, r_p and r_R are the radius of a particle and a receptor in the system, respectively, and $\langle \bar{v}_p \rangle$ is the average velocity of the particles. The fraction $F_C(E_a)$ of collisions having a higher energy than the activation energy is expressed through the Boltzmann distribution [32] as

$$F_C(E_a) = e^{-\frac{E_a}{k_B T}} \tag{44}$$

where E_a is the activation energy, T is the absolute temperature of the system, and k_B is the Boltzmann constant. The average collision frequency Z depends on the average velocity $\langle \bar{v}_p \rangle$ of the particles subject to the Brownian motion and it is known from the kinetic theory [32] to have the following expression:

$$\langle \bar{v}_p \rangle = \sqrt{\frac{8 k_B T}{\pi m_p}} \tag{45}$$

where k_B is the Boltzmann constant, T is the absolute temperature of the system and m_p is the mass of a particle.

The rate k_- of particle release is defined in transition state theory [33] as follows:

$$k_- = \frac{k_B T}{h} \left(1 - e^{-\frac{h\nu}{k_B T}}\right) e^{-\frac{E^\theta}{RT}} \tag{46}$$

where k_B is the Boltzmann constant, T is the absolute temperature of the system, h is the Planck constant, ν is the vibrational frequency of the bond, E^θ is the unbinding energy at absolute zero, and R is the universal gas constant.

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Massimiliano Pierobon (S'09–M'09) received the M.S. degree in telecommunication engineering from the Politecnico di Milano, Italy, in 2005.

During 2006, he was a researcher with the R&D Department of Siemens Carrier Networks, Milan, Italy. From January 2007 to July 2009, he was a graduate Research Assistant at the Politecnico di Milano. From November 2008 until July 2009, he was a Visiting Researcher at the BWN Lab of the School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, where he joined as a Ph.D. student in August 2009. His research interests are in molecular communication for nanoscale networks.

Ian F. Akyildiz (F'96) received the B.S., M.S., and Ph.D. degrees in computer engineering from the University of Erlangen-Nürnberg, Germany, in 1978, 1981, and 1984, respectively.

Currently, he is the Ken Byers Chair Professor with the School of Electrical and Computer Engineering, Georgia Institute of Technology (Georgia Tech), Atlanta, the Director of Broadband Wireless Networking Laboratory, and Chair of the Telecommunication Group at Georgia Tech. In June 2008, he became an honorary professor with the School of Electrical Engineering, Universitat Politècnica de Catalunya (UPC), Barcelona, Spain. He is also the Director of the newly founded NaNoNetworking Center in Catalunya (N3Cat). Since March 2009, he has also been an Honorary Professor with the University of Pretoria, South Africa. His research interests are in nanonetworks, cognitive radio networks and wireless sensor networks.

Dr. Akyildiz is the Editor-in-Chief of the *Computer Networks (Elsevier) Journal*, and the founding Editor-in-Chief of the *Ad Hoc Networks (Elsevier) Journal*, the *Physical Communication (Elsevier) Journal*, and the *Nano Communication Networks (Elsevier) Journal*. He serves on the advisory boards of several research centers, journals, conferences, and publication companies. He is an ACM Fellow (1997). He received numerous awards from the IEEE and ACM.