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DIFFUSION APPROXIMATION OF NEURONAL MODELS REVISITED

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Abstract. Leaky integrate-and-fire neuronal models with reversal potentials have a number of different diffusion approximations, each depending on the form of the amplitudes of the postsynaptic potentials. Probability distributions of the first-passage times of the membrane potential in the original model and its diffusion approximations are numerically compared in order to find which of the approximations is the most suitable one. The properties of the random amplitudes of postsynaptic potentials are discussed. It is shown on a simple example that the quality of the approximation depends directly on them.

1. **Introduction.** Detailed conductance-based Hodgkin-Huxley neuron models ([5]) can reproduce electrophysiological measurements to a high degree of accuracy (for a review, see [1, 6]). Unfortunately, because of their intrinsic complexity, these models are difficult to analyze and are computationally expensive in numerical implementations. For this reason, simple phenomenological spiking neuron models, for example, the integrate-and-fire model with reversal potentials introduced by Tuckwell in [22] are highly popular. This model originates from Stein's model ([21]), for which the synaptic transmission is state-independent and in the current form it reflects the well known fact that the changes in the membrane depolarization due to incoming action potentials are state-dependent (see e.g. [19]). For biological reasoning about this type of models see e.g. [3, 7, 16, 18, 22].

The integrate-and-fire model with reversal potentials has discontinuous trajectories, therefore its mathematical treatment is complicated and the analytical results are exceptionally rare (see [20, 25]). Thus the diffusion approximation scheme has been used by Hanson and Tuckwell in [4]. The diffusion models are somewhat more tractable than the discontinuous process because the discontinuities are smoothed out. The first approach to the diffusion approximation used in neuronal modeling employs analysis of weak and strong convergence of stochastic processes (e.g. [9, 10]). The second one deals with transition probability densities and infinitesimal moments of stochastic processes (e.g. [14, 23]). The diffusion approximation is commonly constructed under the assumption of suitably shrinking the magnitude of the postsynaptic potentials (PSPs) and time intervals between their arrivals (e.g. [9, 10, 12, 23]). When constructing such a sequence, the discontinuous models have

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the first two infinitesimal moments converging to those of the diffusion model and infinitesimal moments of higher orders tending to zero (see e.g. [14, 23]). We show on a simple example that for the integrate-and-fire model with reversal potentials the feature of vanishing infinitesimal moments of higher orders can be accomplished only under violation of some natural physical assumptions about the PSP amplitudes.

One of the features of the diffusion model proposed in [4] is that without an additional boundary condition the membrane potential in the model can fluctuate without limit. Lansky and Lanska proposed in [10] other diffusion variants in which the membrane depolarization is limited without imposing any additional conditions. The aim of this paper is to compare the proposed diffusion models with the original discontinuous model. As the quality of the stochastic neuronal model is rated by its power to reproduce first-passage-time (FPT) distributions comparable with the experimental data, we compare probability distributions of numerically obtained FPTs.

2. Models and methods.

In the modified Stein's neuronal model in which the effect of the reversal potentials is considered, the membrane potential, $U(t)$, given in units of millivolts ([mV]) is described by a one-dimensional stochastic process which can be expressed in the form

$$\begin{aligned} \mathrm{d}U(t) &= -\frac{1}{\tau}\left(U(t)-U_R\right)\mathrm{d}t + \\ &\quad + A_E\left(U_E-U(t)\right)\mathrm{d}N^+(t) + A_I\left(U_I-U(t)\right)\mathrm{d}N^-(t), \quad U(0)=U_0, \end{aligned} \tag{1}$$

where $\tau > 0$ is the membrane time constant ([ms]) reflecting decay of the membrane potential $U(t)$ to the resting (equilibrium) potential U_R of the leakage conductance, U_E (U_I) is the corresponding excitatory (inhibitory) reversal potential, $U_I < U_R < U_E$ ([mV]). Furthermore, $A_E > 0$ and $A_I > 0$ are dimensionless random PSP amplitudes scaling the jump sizes of two mutually independent Poisson processes $N^+(t)$ and $N^-(t)$ with intensities λ_E and λ_I. Model (1) was discussed in detail from a theoretical as well as a neurophysiological point of view (see [22, 25]).

The stochastic differential equation (1) describes the membrane potential of a neuron until it reaches a threshold $S > U_0$. After reaching the threshold the neuron fires and the membrane potential is reset back to U_0 and subsequent inputs may lead to another discharge. The time course of the action potential is disregarded in model (1) and only the firing time is recorded. The interspike interval thus corresponds to the FPT, $T_S > 0$, given by the relationship

$$T_S = \inf\left\{t > 0 : U(t) \geq S\right\}, \tag{2}$$

where T_S is a random variable defined as the time interval from the moment when the process is reset to its initial value to the moment of the first threshold crossing. The independent realizations of T_S are identified with time intervals between action potential generations.

Infinitesimal moments of (1) can be calculated,

$$\begin{aligned} M_1(u) &= \lim_{\Delta t\to 0} \mathsf{E}\left(\Delta U(t)|U(t)=u\right)/(\Delta t) \\ &= -\frac{1}{\tau}\left(u-U_R\right) + \lambda_E \mathsf{E}(A_E)\left(U_E-u\right) + \lambda_I \mathsf{E}(A_I)\left(U_I-u\right) \end{aligned} \tag{3}$$

and

$$\begin{aligned} M_k(u) &= \lim_{\Delta t\to 0} \mathsf{E}\left(\Delta U(t)^k | U(t)=u\right)/(\Delta t) \\ &= \lambda_E \mathsf{E}(A_E^k)\left(U_E-u\right)^k + \lambda_I \mathsf{E}(A_I^k)\left(U_I-u\right)^k, \end{aligned} \tag{4}$$

where $\Delta U(t) = U(t+\Delta t) - U(t)$ and $k = 2, 3, \ldots$.

In order to keep the membrane potential $U(t)$ given by (1) in interval $[U_I, U_E]$ the amplitudes of inhibitory and excitatory potentials A_E and A_I must satisfy,

$$\mathrm{P}\left(A_E \in (0,1)\right) = \mathrm{P}\left(A_I \in (0,1)\right) = 1, \tag{5}$$

however, condition (5) can often not be satisfied due to other requirements imposed on the model (see [10]).

2.1. **Diffusion models.** In diffusion models the membrane potential is described by stochastic diffusion process $V(t)$ given by the stochastic differential equation

$$\mathrm{d}V(t) = \mu\left(V(t)\right)\mathrm{d}t + \sigma\left(V(t)\right)\mathrm{d}W(t), \quad V(0) = V_0, \tag{6}$$

where μ and σ are real-valued functions of their arguments and $W(t)$ is a standard Wiener process. The infinitesimal moments of process (6) are

$$M_1(v) = \mu(v), \quad M_2(v) = \sigma^2(v), \tag{7}$$

and $M_k(v) = 0$ for $k > 2$. The simplest way to obtain the diffusion approximation, $V(t)$, of the discontinuous stochastic model $U(t)$, is to let $V(t)$ have the same first two infinitesimal moments as $U(t)$. In case of a sequence of discontinuous models, $U_n(t)$, the infinitesimal moments should tend to those of the diffusion model. Especially, the infinitesimal moments of order higher than two should tend to zero.

Investigation of infinitesimal moments, $M_k(u)$, of higher orders is greatly improved by the Pawula theorem (see e.g. [17]). Pawula proved that if the infinitesimal moments $M_k(u)$ exists for all k, vanishing of any even order infinitesimal moment implies $M_k(u) = 0$ for $k \geq 3$. It means that whenever the process contains a finite number of nonzero infinitesimal moments, its number is always two (see [14]). Simultaneously it implies that one only needs to find a single nonzero infinitesimal moment of even order greater than two to prove that the model $U(t)$ has infinite number of nonzero infinitesimal moments.

2.1.1. *Diffusion approximation of neuronal models.* The diffusion approximation of neuronal models is commonly constructed under the assumption that the intensities of the Poisson processes $N^+(t)$ and $N^-(t)$ are high, while PSP amplitudes get very small (see e.g. [9, 10, 23]). Therefore, we will work with sequence of models $U_n(t)$ specified by (1) with PSP amplitudes $A_E(n)$, resp. $A_I(n)$, and intensities $\lambda_E(n) > 0$, resp. $\lambda_I(n) > 0$, where $n = 1, 2, \ldots$. We assume

$$\mathsf{E}A_E(n) = a_E(n) \to 0, \quad \mathsf{E}A_E^2(n) = \sigma_E^2(n) \to 0, \tag{8}$$

$$\mathsf{E}A_I(n) = a_I(n) \to 0, \quad \mathsf{E}A_I^2(n) = \sigma_I^2(n) \to 0, \tag{9}$$

and

$$\lambda_E(n) \to \infty, \quad \lambda_I(n) \to \infty, \tag{10}$$

for $n \to \infty$ in such a way that the sequences of the first two infinitesimal moments, $\{M_1(u)\}_n$, resp. $\{M_2(u)\}_n$ converge to those of the diffusion,

$$\{M_1(u)\}_n \to \mu(u), \quad \{M_2(u)\}_n \to \sigma^2(u) > 0, \tag{11}$$

where $|\mu(u)| < \infty$. According to (5), means of PSP amplitudes must satisfy $0 < a_E(n) < 1$ and $0 < a_I(n) < 1$. Furthermore, from the Jensen's inequality,

the second moments must satisfy inequalities $\sigma_E^2(n) \geq a_E^2(n)$ and $\sigma_I^2(n) \geq a_I^2(n)$ for each n.

A sequence of neuronal models, $U_n(t)$, tends to a diffusion model $V(t)$ given by (6) if $\{M_k(u)\}_n \to 0$ for each $k \geq 3$ and $n \to \infty$. Whether this condition is satisfied depends on the probability distribution of the random amplitudes $A_E(n)$ and $A_I(n)$ and will be studied in Section 3.1.

2.1.2. *Specific diffusion models.* The sequence of discontinuous models, $U_n(t)$, specified by (1) and introduced in the previous Section can be modified in order to achieve different diffusion models in its limit by considering various modifications of stochastic PSPs, see [10]. In these models the PSPs commonly vanish when the membrane potential approaches the excitatory or inhibitory reversal potential. In this Section we briefly recall four such modifications and corresponding diffusion models proposed in [4, 10]. The first infinitesimal moment is the same for all of them,

$$\mu(v) = -(v - U_0)/\tau + \lambda_E(n) a_E(n) (U_E - v) + \lambda_I(n) a_I(n) (U_I - v), \tag{12}$$

but they differ in the form of the second infinitesimal moment.

1. In the basic model, the sequence of neuronal models is obtained directly from (1) and has form

$$\begin{aligned} \mathrm{d}U_n(t) &= -\frac{1}{\tau}(U_n(t) - U_R)\,\mathrm{d}t + A_E(n)(U_E - U_n(t))\,\mathrm{d}N_n^+(t) + \\ &\quad + A_I(n)(U_I - U_n(t))\,\mathrm{d}N_n^-(t), \end{aligned} \tag{13}$$

where $A_E(n)$ and $A_I(n)$ are two sequences of random variables describing PSP amplitudes and satisfying (8) and (9). The corresponding diffusion model is specified by the infinitesimal variance

$$\sigma^2(v) = \lambda_E(n)\sigma_E^2(n)(U_E - v)^2 + \lambda_I(n)\sigma_I^2(n)(U_I - v)^2. \tag{14}$$

2. Modification of model (13) was introduced in [10],

$$\begin{aligned} \mathrm{d}U_n(t) = &-\frac{1}{\tau}(U_n(t) - U_R)\,\mathrm{d}t + \\ &+ \left[a_E(n)(U_E - U_n(t)) + A'_{E,n}\sqrt{(U_E - U_n(t))(U_n(t) - U_I)}\right]\mathrm{d}N_n^+(t) + \\ &+ \left[a_I(n)(U_I - U_n(t)) + A'_{I,n}\sqrt{(U_E - U_n(t))(U_n(t) - U_I)}\right]\mathrm{d}N_n^-(t), \end{aligned} \tag{15}$$

where $A'_{E,n} = A_E(n) - a_E(n)$, $A'_{I,n} = A_I(n) - a_I(n)$ and thus $\mathsf{E}A'_{E,n} = \mathsf{E}A'_{I,n} = 0$. The difference between (13) and (15) is that in the latter the PSPs have separated random parts which decrease near both boundaries. The diffusion approximation of model (15) is determined by the infinitesimal variance

$$\sigma^2(v) = \left(\lambda_E(n)\sigma_E^2(n) + \lambda_I(n)\sigma_I^2(n)\right)(U_E - v)(v - U_I). \tag{16}$$

3. Another modification restricts excitation to its deterministic part only,

$$\begin{aligned} \mathrm{d}U_n(t) &= -\frac{1}{\tau}(U_n(t) - U_R)\,\mathrm{d}t + a_E(n)(U_E - U_n(t))\,\mathrm{d}N_n^+(t) + \\ &\quad + A_I(n)(U_I - U_n(t))\,\mathrm{d}N_n^-(t), \end{aligned} \tag{17}$$

where all parameters are the same as in (13). In the same way as in the previous cases we derive the diffusion approximation with second infinitesimal moment

$$\sigma^2(v) = \lambda_I(n)\sigma_I^2(n)\left(v - U_I\right)^2. \tag{18}$$

4. The last model we show is a combination of (15) and (17),

$$\begin{aligned} \mathrm{d}U_n(t) &= -\frac{1}{\tau}\left(U_n(t) - U_R\right)\mathrm{d}t + a_E(n)\left(U_E - U_n(t)\right)\mathrm{d}N_n^+(t) \\ &\quad + \left[a_I(n)\left(U_I - U_n(t)\right) + A'_{I,n}\sqrt{\left(U_n(t) - U_I\right)}\right]\mathrm{d}N_n^-(t). \end{aligned} \tag{19}$$

In this model the excitation is again restricted to its deterministic part and the random part of inhibition decreases near the inhibitory reversal potential. The corresponding diffusion model (6) is specified by

$$\sigma^2(v) = \lambda_I(n)\sigma_I^2(n)\left(v - U_I\right) \tag{20}$$

and commonly known as the Feller model.

3. Results.

3.1. PSP amplitudes.

It was shown that in the case of Stein's model with state independent PSPs the corresponding sequence of discontinuous models tends to an Ornstein-Uhlenbeck process even for deterministic PSPs, see e.g. [9, 15, 23]. In the integrate-and-fire model with reversal potentials (1) the situation is more complex and random PSP amplitudes are essential (see [10]). We show that in this case the sequence $U_n(t)$ specified by (1) may not tend to diffusion (6) in terms of infinitesimal moments of orders higher than two. We investigate properties of $A_E(n)$ only, extension to $A_I(n)$ is analogous. From now on we assume that $a_E(n) = O(1/n^s)$, $\sigma_E^2(n) = O(1/n^s)$ and $\lambda_E(n) = O(n^s)$ such that (11) is satisfied and $s > 0$ to ensure convergence of the first two moments of $A_E(n)$ to zero.

The simplest and natural way how to introduce noise in excitatory PSPs is to assume that $A_E(n)$ follows a Gaussian probability distribution,

$$A_E(n) \sim \mathsf{N}\left(a_E(n), \sigma_E^2(n) - a_E^2(n)\right), \tag{21}$$

where the choice of coefficients ensures that $A_E(n)$ satisfy requirements (8). If we construct $A_I(n)$ analogously it can be easily verified that sequence of infinitesimal moments $\{M_k(u)\}_n$ specified by (4) tends to zero with increasing n for each $k \geq 3$ and therefore convergence to diffusion (6) is confirmed, see Appendix A. However, it holds

$$\mathrm{P}\left(A_E(n) \leq 0\right) = \Phi\left(-\frac{a_E(n)}{\sqrt{\sigma_E^2(n) - a_E^2(n)}}\right) \longrightarrow \frac{1}{2} \tag{22}$$

for $n \to \infty$, where $\Phi(.)$ is the cumulative distribution function of the standardized Gaussian distribution. It means that for n large the random variable $A_E(n)$, which should be strictly positive from a physical point of view, takes negative values with probability approaching $1/2$.

By taking probability distributions of PSP amplitudes defined on the positive real axis, for example Beta or Gamma, and satisfying requirements (8) and (9), the infinitesimal moments $\{M_k(u)\}_n$ do not tend to zero with increasing n for each $k \geq 3$, see Appendix A. To verify the existence of a positive probability distribution

that allows convergence of sequence $U_n(t)$ to a diffusion process we focus on a simple discrete probability distribution. Let us assume that

$$\mathsf{P}\left(A_E(n) = a_E(n) + \varepsilon_1(n)\right) = p(n), \quad \mathsf{P}\left(A_E(n) = a_E(n) - \varepsilon_2(n)\right) = r(n), \tag{23}$$

where $p(n) \geq 0$ and $r(n) \geq 0$ are probabilities that $A_E(n)$ take one of the two possible values, $p(n) + r(n) = 1$, $\varepsilon_1(n) > 0$ and $\varepsilon_2(n) > 0$. Imposing condition (8) on the amplitudes $A_E(n)$ defined by (23) we obtain

$$\varepsilon_1(n) = \sqrt{\frac{1-p(n)}{p(n)}\left(\sigma_E^2(n) - a_E^2(n)\right)}, \tag{24}$$

$$\varepsilon_2(n) = \sqrt{\frac{p(n)}{1-p(n)}\left(\sigma_E^2(n) - a_E^2(n)\right)}. \tag{25}$$

It can be seen that the properties of $A_E(n)$ are fully determined by the properties of probability $p(n)$. To achieve positive values of $A_E(n)$ we must assume $\varepsilon_2(n) \leq a_E(n)$ which implies

$$p(n) \leq \frac{a_E^2(n)}{\sigma_E^2(n)} = O\left(\frac{1}{n^s}\right). \tag{26}$$

Simultaneously, to keep $A_E(n) \leq 1$ it must hold $\varepsilon_1(n) \leq 1 - a_E(n)$, which implies

$$p(n) \geq \frac{a_E^2(n) - \sigma_E^2(n)}{2a_E(n) - \sigma_E^2(n) - 1} = O\left(\frac{1}{n^s}\right). \tag{27}$$

Thus, if we are able to construct a sequence of probabilities $p(n)$ between boundaries (26) and (27) then amplitudes $A_E(n)$ satisfy (5). It can be seen that for such sequence it holds $p(n) = O(1/n^s)$.

To study the relationship between properties of $A_E(n)$ and the possibility to approximate the discontinuous model by the diffusion model we assume only positivity of PSP amplitudes. The sequence of probabilities $p(n)$ must therefore satisfy (26) only and thus $p(n) = O(1/n^d)$, where $d \geq s$, and $r(n) = 1 - p(n) = O(1)$. Then, the asymptotic properties of the fourth moment of $A_E(n)$ can be calculated,

$$\mathsf{E}A_E^4(n) = O\left(n^{d-2s}\right), \tag{28}$$

see Appendix B. Inserting (28) into the definition of the sequence of the fourth infinitesimal moments $\{M_4(u)\}_n$ specified by (4) with $k = 4$, and under the assumption of equal probability distributions for both excitatory and inhibitory PSP amplitudes, we obtain

$$\{M_4(u)\}_n = O(n^{d-s}), \tag{29}$$

see Appendix B. The fourth infinitesimal moments (29) are not zero and it can be seen that they cannot tend to zero with increasing n as $d \geq s$. Due to the Pawula theorem (see Section 2.1) the sequence of discontinuous models $U_n(t)$ specified by (1) has infinite number of infinitesimal moments of orders higher than two which do not converge to zero with increasing n. It means that the sequence $U_n(t)$ never converges to diffusion model (6) when its PSP amplitudes are strictly positive.

However, if we allow $0 < d < s$, the fourth infinitesimal moments (29) tend to zero with increasing n and due to Pawula all infinitesimal moments of orders higher than two tend to zero in the sequence of discontinuous models. This implies that $U_n(t)$ specified by (1) tend to diffusion model (6) but the probability of $A_E(n)$ being negative is approaching one,

$$\mathsf{P}\left(A_E(n) < 0\right) \longrightarrow 1 \tag{30}$$

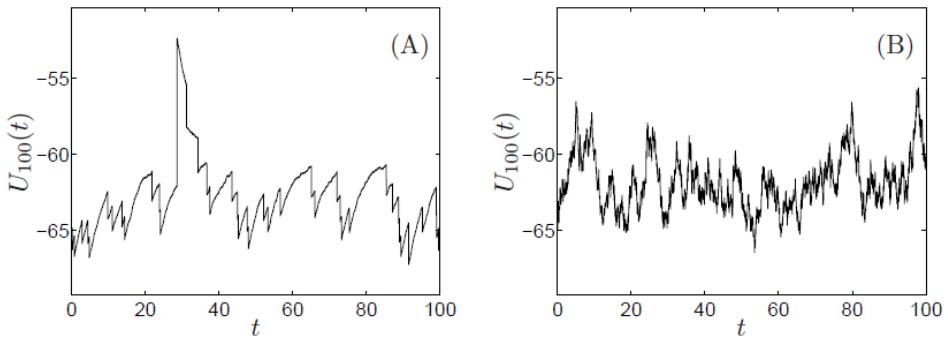

FIGURE 1. Sample paths of the integrate-and-fire model (13) with all parameters specified in Section 3.2, $\lambda_E = 8\tau^{-1}$, $\lambda_I = 4\tau^{-1}$, and with random PSP amplitudes (A) strictly positive, (B) allowing negative realizations. The probability distribution of amplitudes is given by (23) and specified by (37), resp. (38).

for $n \to \infty$, see Appendix C. This result gives us a hint of how to construct PSP amplitudes ensuring that the sequence of discontinuous models $U_n(t)$ is tending to diffusion model (6) with the probability of its amplitudes being negative tending to zero with increasing n. To achieve that we just set $r(n) = O(1/n^c)$ where $0 < c < s$ and $p(n) = 1 - r(n) = O(1)$. It can be then verified that

$$\mathsf{P}\left(A_E(n) < 0\right) \longrightarrow 0 \tag{31}$$

for $n \to \infty$. Similarly to the previous case it can be calculated that $\mathsf{E}A_E(n)^4 = O(n^{c-2s})$ and $\{M_4(u)\}_n = O(n^{c-s})$. As we have set $0 < c < s$, the fourth infinitesimal moments tend to zero with increasing n and, according to Pawula, the sequence $U_n(t)$ tends to diffusion model (6). Nevertheless, in this case negative realizations of PSP amplitudes appear for n finite which implies that the discontinuous model fluctuates across reversal potentials when close to them. If we take $d = 0$, resp. $c = 0$ in the previous cases, the infinitesimal moments of orders higher than two always tend to zero in the discontinuous model. However, the probability of $A_E(n)$ being negative remains constant and positive and therefore we do not take this case into account.

Two sample paths of $U_n(t)$ given by (13) for $n = 100$ are plotted in Figure 1. Parameters of the models are exactly the same in both cases and taken from Section 3.2. The only difference is in the form of the probability distribution of PSP amplitudes.

3.2. **Numerical results.** In this Section we illustrate how the properties of random PSP amplitudes studied in the previous Section influence the rate of convergence of the discontinuous models to their diffusion counterparts and investigate computationally if any of the diffusion models presented in Section 2.1 is more suitable to approximate the discontinuous model (1). The quality of a diffusion model is rated by its power to produce FPT distributions comparable with experimental data for parameters from a physically acceptable range and we compare the probability distributions of FPTs directly. For this purpose we employ the integrated square error

(ISE),

$$ISE(F_U, F_V) = \int_{\mathbb{R}} \left(F_U(x) - F_V(x)\right)^2 \mathrm{d}x, \tag{32}$$

where $F_U(x)$, resp. $F_V(x)$ are empirical cumulative distribution functions calculated from numerically obtained FPTs.

Combination of parameter values used in previous studies on model (1) performed in [8, 13, 22, 25] have been applied here. We set $U_E = 35\text{mV}$, $U_I = -75\text{mV}$ and $U_R = -65\text{mV}$, the initial value of all processes is set to $U(0) = U_0 = V(0) = -65\text{mV}$ and the threshold is set to $S = -55\text{mV}$. The parameter of spontaneous decay was chosen to be $\tau = 5.8\text{ms}$. We set

$$a_E(n) = a_E/n, \quad a_I(n) = a_I/n, \tag{33}$$

where $a_E = 0.02$ and $a_I = 0.2$ which ensures that the means of the PSP amplitudes are equal at the resting level. The second moments of PSP amplitudes are

$$\sigma_E^2(n) = \sigma_E^2/n, \quad \sigma_I^2(n) = \sigma_I^2/n, \tag{34}$$

where $\sigma_E^2 \geq a_E^2$ and $\sigma_I^2 \geq a_I^2$ are constants. Intensities of the input processes satisfy

$$\lambda_E(n) = \lambda_E n, \quad \lambda_I(n) = \lambda_I n, \tag{35}$$

where $\lambda_E > 0$ and $\lambda_I > 0$ are constants taken in units of τ^{-1} provided that their sum does not exceed $20\tau^{-1}$ in any case. Selected dependency on n implies that the first two infinitesimal moments of the models shown in Section 2.1.2 are independent of n.

For sake of comparison we require the second infinitesimal moment to be the same at the resting level for all diffusion models described in Section 2 and for fixed combination of intensities λ_E and λ_I. Thus we consider parameters σ_E^2 and σ_I^2 in the form

$$\sigma_E^2 = wa_E^2, \quad \sigma_I^2 = wa_I^2, \tag{36}$$

where $w \geq 1$ must be satisfied due to Jensen's inequality. Parameter w is calculated separately for each diffusion model and values λ_E and λ_I to achieve the same second infinitesimal moment at the resting level such that $w \geq 1$ is always satisfied. For example, if $\lambda_E = 8\tau^{-1}$ and $\lambda_I = 4\tau^{-1}$ we set $w = 3.625$, $w = 1.0662$, $w = 10.875$ and $w = 108.75$ in the sequence of models (13), (15), (17) and (19) in order to achieve $M_2(U_0) = 30$ for all of them.

The probability distribution of amplitudes $A_E(n)$ and $A_I(n)$ is always the same and given by (23). For $A_E(n)$ probabilities $p(n)$, resp. $r(n)$ are taken to achieve

i) strictly positive realizations of the amplitudes,

$$p(n) = \frac{a_E^2}{n\sigma_E^2 + 1}, \quad r(n) = 1 - p(n), \tag{37}$$

ii) sequence of neuronal models tending to diffusion (6) with probability of amplitudes being negative tending to zero with increasing n,

$$r(n) = \frac{1}{3\sqrt[3]{n}}, \quad p(n) = 1 - r(n), \tag{38}$$

and $\varepsilon_1(n)$ and $\varepsilon_2(n)$ are specified by (24) and (25) to ensure that $A_E(n)$ satisfy (8). For $A_I(n)$ the probability distribution is constructed similarly. Finally, if we work with the discontinuous model (1) its PSP amplitudes and intensities equal those of model (13) for $n = 1$ under the same conditions.

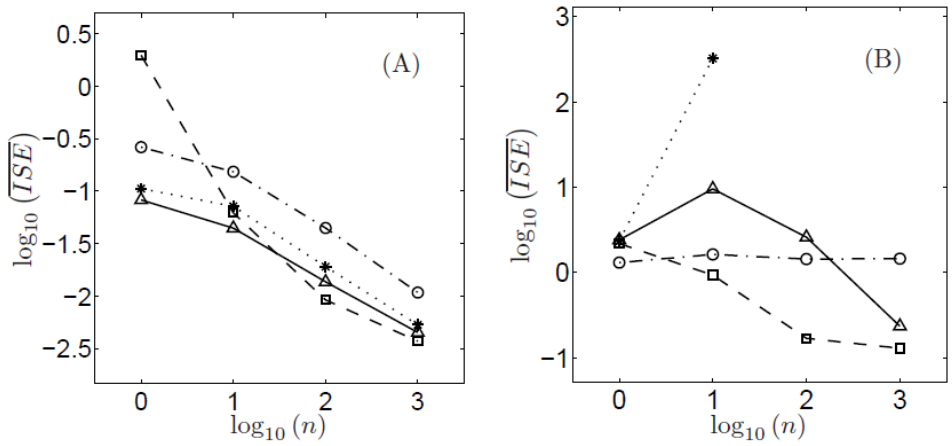

FIGURE 2. Average ISE between FPT cumulative distribution function estimated from simulated discontinuous model (13) (solid, △), (15) (dashed, □), (17) (dash-dotted, ○) and (19) (dotted,⋆), and corresponding diffusion model. Intensities of input processes are fixed and taken to be $\lambda_E = 8/\tau \approx 1.3793\text{ms}^{-1}$ and $\lambda_I = 4/\tau \approx 0.6897\text{ms}^{-1}$. Parameter w in (36) is taken to achieve $M_2(U_0) = 30$ for each model and PSP amplitudes (A) allow negative realizations, (B) are strictly positive.

All the models are numerically simulated in the mathematical software Matlab. For simulation of diffusion models we use standard method described, for example, in [24] with time step $\Delta t = 10^{-4}$ ms. Empirical cumulative distribution functions $F_U(x)$, resp. $F_V(x)$, are calculated from 1000 numerically obtained FPTs. Integral (32) is then calculated numerically. This procedure is $N = 200$ times repeated and an average, $\overline{ISE}$, and sample standard deviation, SD, are calculated. The FPT distributions are also compared via Kolmogorov-Smirnov test for equality of one-dimensional cumulative distribution functions in Section 3.2.2. In this case, method *kstest2* implemented in Matlab is employed.

3.2.1. *Rate of convergence.* In this Section we illustrate how properties of random PSP amplitudes studied in Section 3.1 influence rate of convergence of the sequence of discontinuous models $U_n(t)$ to the corresponding diffusion model, both presented in Section 2.1.2. We compare empirical FPT cumulative distribution functions via ISE with increasing n. In Figure 2 A are shown errors between distributions when negative realizations of PSP amplitudes are allowed in the discontinuous models. Decreasing tendency of errors with increasing n can be seen for each sequence. In Figure 2 B are plotted ISEs between empirical FPT cumulative distribution functions in the case when PSP amplitudes are strictly positive and n is increasing. Despite some of the models exhibit decreasing tendency of errors with increasing n, it can be seen that the errors are still significantly larger in contrast to the case when negative realizations of PSP amplitudes are allowed. Discontinuous models (19) do not even reach the threshold for $n > 10$ and therefore the errors are not shown.

3.2.2. *Comparison of diffusion models.* In this Section we compare the discontinuous model (1) with the diffusion models described in Section 2.1.2 in order to identify the most suitable approximation of (1) in terms of FPTs. The average

ISEs between the empirical FPT cumulative distribution functions with the corresponding standard deviations are shown in Table 1 (negative realizations of PSP amplitudes are allowed) and Table 2 (PSP amplitudes are strictly positive). In the first Table it can be seen that the best results (smallest average error) are commonly obtained for diffusion models specified by (14) followed by the model specified by (16). However, intervals $\overline{ISE} \pm SD$ often overlap for a given combination of the input intensities, which holds for diffusion models specified by (14) and (16) and also for the diffusion specified by (20) which commonly provides error between FPT distributions close to the actual minimum. On the other hand, the diffusion model specified by (18) seems not to be suitable for approximation of the discontinuous model (1) having, with a few exceptions, always worse results than the others. If we require strictly positive realizations of PSP amplitudes then results shown in Table 2 identify the most suitable diffusion model similarly but with errors significantly larger than those obtained under assumption of allowed negative realizations of PSP amplitudes.

In addition, we compared empirical cumulative distribution functions calculated from 200 simulated FPTs via two-sided Kolmogorov-Smirnov test on significance level $\alpha = 0.05$. Percentage of success (hypothesis is not rejected) in 1000 tests is shown in Table 3. In this Table, the simulations were performed allowing negative realizations of PSP amplitudes in model (1). The results are in relative agreement with those based on ISE and presented in Table 1. The best results (highest percentage of success) are again achieved for diffusion models specified by (14) followed by the diffusion specified by (16). The diffusion model specified by (18) has again the worst results. If strictly positive PSP amplitudes are required then the hypotheses are almost always rejected, with a few exceptions when intensities of excitatory postsynaptic potentials are high, and therefore the Table is not shown.

4. **Discussion.** Requirements (5) and (8) - (11) are imposed on the PSP amplitudes in papers devoted to the diffusion approximation of the discontinuous model (1), see e.g. [8, 10]. These requirements are physically acceptable and can be easily satisfied by taking, for example, the Beta probability distribution and therefore they are formally correct. However, we have shown that the convergence of the discontinuous models to the diffusion is not possible if all these requirements are taken into account simultaneously. Condition (5) must be violated and negative values of PSP amplitudes must be taken into account in order to achieve the diffusion approximation of the discontinuous model (1). This behavior is not just asymptotic as we have seen in Section 3.2.2 and therefore the choice of probability distribution of PSP amplitudes always influences the possibility to approximate model (1). In this paper the simplest possible discrete probability distribution is considered, nevertheless, the author believes that the diffusion approximation cannot be achieved even for more complex discrete or continuous probability distributions defined on the positive real axis. However, rigorous verification and further study on this topic are needed.

Another aim of this work was to identify the most suitable diffusion approximation of the discontinuous model (1) from a FPT point of view. Similar comparisons were already performed on both Stein's model and the integrate-and-fire model with reversal potentials (1) (see [2, 8, 11, 13, 22, 25]). Parameters used and discussed in these papers were employed here. In contrast to these papers, not only the first two FPT moments but entire cumulative distribution functions were compared.

TABLE 1. Mean, $\overline{ISE}$, and sample standard deviation, SD, of errors between FPT distribution functions of the discontinuous model (1) and the diffusion model (6) specified by second infinitesimal moments (14), (16), (18) and (20). The errors are calculated for various intensities of excitation and inhibition which are given in units of τ^{-1}. Negative realizations of PSP amplitudes are allowed. Minimal values in each row are indicated.

		Diffusion (14)	Diffusion (16)	Diffusion (18)	Diffusion (20)
λ_I	λ_E	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$
2	2	1.13 (0.29)	**0.64 (0.20)**	1.51 (0.30)	0.79 (0.22)
	4	**0.27 (0.09)**	**0.27 (0.09)**	0.62 (0.13)	0.32 (0.10)
	6	**0.12 (0.05)**	0.17 (0.06)	0.35 (0.09)	0.19 (0.05)
	8	**0.07 (0.03)**	0.12 (0.04)	0.23 (0.05)	0.13 (0.04)
	10	**0.05 (0.02)**	0.08 (0.03)	0.16 (0.04)	0.09 (0.03)
	12	**0.03 (0.02)**	0.05 (0.02)	0.10 (0.02)	0.06 (0.02)
	14	**0.02 (0.01)**	0.04 (0.01)	0.08 (0.02)	0.05 (0.02)
	16	**0.02 (0.01)**	0.03 (0.01)	0.06 (0.01)	0.04 (0.01)
	18	**0.02 (0.01)**	0.03 (0.01)	0.05 (0.01)	0.03 (0.01)
4	4	0.44 (0.12)	**0.25 (0.09)**	0.39 (0.12)	0.27 (0.10)
	6	0.20 (0.06)	**0.14 (0.05)**	0.25 (0.08)	0.17 (0.06)
	8	**0.10 (0.04)**	**0.10 (0.03)**	0.17 (0.05)	**0.10 (0.04)**
	10	**0.06 (0.03)**	0.07 (0.03)	0.13 (0.03)	0.08 (0.03)
	12	**0.04 (0.02)**	0.05 (0.02)	0.09 (0.03)	0.06 (0.02)
	14	**0.03 (0.01)**	0.04 (0.01)	0.08 (0.02)	0.05 (0.02)
	16	**0.03 (0.01)**	0.04 (0.01)	0.07 (0.02)	0.05 (0.01)
6	6	0.27 (0.08)	**0.14 (0.06)**	0.18 (0.06)	0.16 (0.06)
	8	0.16 (0.05)	**0.10 (0.04)**	0.15 (0.05)	0.11 (0.04)
	10	0.09 (0.03)	**0.07 (0.03)**	0.12 (0.04)	0.08 (0.03)
	12	**0.06 (0.03)**	**0.06 (0.02)**	0.09 (0.03)	**0.06 (0.02)**
	14	0.05 (0.02)	**0.04 (0.02)**	0.08 (0.02)	0.05 (0.02)
8	8	0.19 (0.05)	**0.09 (0.04)**	0.12 (0.05)	0.10 (0.04)
	10	0.14 (0.04)	**0.08 (0.04)**	0.11 (0.04)	**0.08 (0.03)**
	12	0.08 (0.03)	**0.06 (0.03)**	0.09 (0.03)	0.07 (0.03)
10	10	0.15 (0.04)	**0.07 (0.03)**	0.08 (0.03)	0.08 (0.03)

Furthermore, random PSP amplitudes are used in order to achieve equal second infinitesimal moment at the resting level for all diffusion models via modification of variability of PSP amplitudes. Different values of second infinitesimal moments at the resting level were applied for each combination of intensities λ_E and λ_I. One would wish to achieve the same value of second infinitesimal moment for all the intensities, however, in this case the variability of PSP amplitudes is often extremely large if compared with the mean. Using these settings, the most suitable diffusion model for approximation of the integrate-and-fire model with reversal potentials (1) was not clearly identified. The best results were in general obtained for models specified by second infinitesimal moments (14) and (16), however, the differences were relatively small between all diffusion models except the one specified by (18) and we cannot distinguish whether the differences were not caused by statistical errors only. The results can also be influenced, for example, by the fact that the inhibitory reversal potential is set closer to threshold.

TABLE 2. Mean, $\overline{ISE}$, and sample standard deviation, SD, of errors between FPT distribution functions obtained from the discontinuous model (1) and the diffusion model (6) specified by second infinitesimal moments (14), (16), (18) and (20). The errors are calculated for various intensities of excitation and inhibition which are given in units of τ^{-1}. PSP amplitudes are strictly positive. Minimal values in each row are indicated.

		Diffusion (14)	Diffusion (16)	Diffusion (18)	Diffusion (20)
λ_I	λ_E	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$	$\overline{ISE}(SD)$
2	2	908.97 (30.77)	906.98 (35.10)	911.74 (34.52)	**906.33 (30.79)**
	4	24.52 (1.33)	**24.37 (1.40)**	26.30 (1.34)	24.76 (1.44)
	6	**2.66 (0.24)**	2.83 (0.25)	3.46 (0.28)	2.92 (0.28)
	8	**0.58 (0.08)**	0.70 (0.09)	0.95 (0.09)	0.72 (0.10)
	10	**0.19 (0.04)**	0.26 (0.04)	0.38 (0.06)	0.28 (0.05)
	12	**0.08 (0.02)**	0.12 (0.03)	0.20 (0.03)	0.13 (0.03)
	14	**0.04 (0.01)**	0.07 (0.02)	0.12 (0.02)	0.07 (0.02)
	16	**0.02 (0.01)**	0.04 (0.01)	0.07 (0.01)	0.04 (0.01)
	18	**0.02 (0.01)**	0.03 (0.01)	0.05 (0.01)	0.03 (0.01)
4	4	103.89 (4.22)	**101.99 (4.12)**	103.48 (4.01)	102.58 (4.49)
	6	12.46 (0.76)	**12.03 (0.75)**	12.73 (0.71)	12.23 (0.73)
	8	2.90 (0.24)	**2.86 (0.22)**	3.20 (0.26)	2.93 (0.21)
	10	**0.99 (0.11)**	1.02 (0.11)	1.19 (0.12)	1.03 (0.12)
	12	**0.43 (0.06)**	0.46 (0.06)	0.57 (0.07)	0.48 (0.06)
	14	**0.21 (0.04)**	0.24 (0.03)	0.32 (0.04)	0.26 (0.04)
	16	**0.12 (0.02)**	0.15 (0.03)	0.20 (0.03)	0.15 (0.03)
6	6	34.95 (1.78)	33.95 (1.57)	34.14 (1.74)	**33.94 (1.56)**
	8	8.19 (0.45)	**7.81 (0.49)**	8.15 (0.50)	7.85 (0.50)
	10	2.77 (0.22)	**2.63 (0.22)**	2.81 (0.22)	2.66 (0.20)
	12	1.18 (0.11)	**1.11 (0.11)**	1.27 (0.12)	1.15 (0.12)
	14	**0.57 (0.07)**	**0.57 (0.07)**	0.67 (0.07)	0.59 (0.06)
8	8	18.30 (0.86)	**17.51 (0.96)**	17.62 (0.88)	17.61 (0.81)
	10	6.11 (0.37)	**5.72 (0.39)**	5.83 (0.35)	5.76 (0.38)
	12	2.51 (0.20)	**2.35 (0.19)**	2.48 (0.21)	2.40 (0.19)
10	10	11.76 (0.63)	11.07 (0.64)	**11.06 (0.60)**	11.13 (0.60)

Appendix A.

1. If $A_E(n)$ follow the Gaussian distribution then the fourth moment satisfies
$$\mathsf{E}A_E^4(n) = 3\sigma_E^4(n) - 2a_E^4(n) = O(n^{-2s}), \tag{39}$$
where $s > 0$. If $A_I(n)$ follow the same distribution as $A_E(n)$ then inserting them into (4) for $k = 4$ implies that $\{M_4(u)\}_n = O(n^{-s})$. According to the Pawula theorem (see Section 2.1) this result means that all infinitesimal moments of $U_n(t)$ of orders higher than two tend to zero with increasing n and therefore the sequence $U_n(t)$ tends to the diffusion (6).
2. The Beta probability distribution was proposed for PSP amplitudes e.g. in [8] as the distribution satisfies condition (5). In this case, the fourth moment has the form
$$\mathsf{E}A_E^4(n) = \prod_{i=0}^{4} \frac{\alpha + i}{\alpha + \beta + i}, \tag{40}$$

TABLE 3. Percentage of non-rejected null hypotheses in 1000 two-sided Kolmogorov-Smirnov tests on significance level $\alpha = 0.05$. Each test is based on two samples of 200 simulated FPTs of the discontinuous model (1) with PSP amplitudes allowing negative realizations, and the diffusion model (6) specified by second infinitesimal moments (14), (16), (18) and (20). The intensities of excitation and inhibition given are in units of τ^{-1}. Maximum values each in row are indicated.

λ_I	λ_E	Diffusion (14)	Diffusion (16)	Diffusion (18)	Diffusion (20)
2	2	12.33 %	**39.11 %**	3.89 %	26.33 %
	4	**43.00 %**	41.44 %	5.44 %	35.00 %
	6	**54.89 %**	38.00 %	5.33 %	31.44 %
	8	**54.33 %**	32.00 %	3.11 %	25.00 %
	10	**57.44 %**	31.67 %	4.11 %	26.11 %
	12	**61.11 %**	36.56 %	6.00 %	30.11 %
	14	**61.22 %**	33.67 %	4.33 %	26.56 %
	16	**57.33 %**	27.89 %	3.56 %	24.67 %
	18	**58.00 %**	24.56 %	3.44 %	24.67 %
4	4	21.22 %	**46.33 %**	19.67 %	41.56 %
	6	34.33 %	**48.22 %**	18.67 %	43.11 %
	8	51.00 %	**54.22 %**	21.56 %	46.56 %
	10	**57.00 %**	52.78 %	18.22 %	47.56 %
	12	**61.11 %**	54.89 %	18.89 %	45.44 %
	14	**61.56 %**	46.78 %	14.11 %	44.56 %
	16	**53.00 %**	32.22 %	7.22 %	30.00 %
6	6	25.67 %	**52.56 %**	30.22 %	45.67 %
	8	34.44 %	**51.44 %**	22.22 %	48.89 %
	10	44.22 %	**52.67 %**	23.11 %	50.56 %
	12	**54.44 %**	53.78 %	25.00 %	48.00 %
	14	**56.89 %**	54.56 %	22.56 %	48.00 %
8	8	26.78 %	**57.89 %**	31.56 %	50.67 %
	10	29.33 %	47.33 %	27.44 %	**48.11 %**
	12	43.11 %	**54.67 %**	28.33 %	51.22 %
10	10	31.67 %	**57.56 %**	39.44 %	53.33 %

where

$$\alpha = \frac{a_E(n)(a_E(n) - \sigma_E^2(n))}{\sigma_E^2(n) - a_E^2(n)}, \quad \beta = \frac{(a_E(n) - \sigma_E^2(n))(1 - a_E(n))}{\sigma_E^2(n) - a_E^2(n)}, \tag{41}$$

which gives

$$\mathsf{E}A_E^4(n) = O\left(\frac{1}{n^s}\right). \tag{42}$$

If the inhibitory PSP amplitudes $A_I(n)$ have the same probability distribution as $A_E(n)$, the fourth infinitesimal moments (4) with $k = 4$ satisfy $\{M_4(u)\}_n = O(1)$ and always remain non-zero.

3. If we require only positivity of PSP amplitudes, the Gamma probability distribution can be a good example. In this case, the fourth moment is

$$\mathsf{E}A_E^4(n) = k^4\theta^4 + 6k^3\theta^4 + 11k^2\theta^4 + 6k\theta^4, \tag{43}$$

where

$$k = \frac{a_E^2(n)}{\sigma_E^2(n) - a_E^2(n)}, \quad \theta = \frac{\sigma_E^2(n) - a_E^2(n)}{a_E(n)}, \tag{44}$$

which gives

$$\mathsf{E}A_E^4(n) = O\left(\frac{1}{n^s}\right). \tag{45}$$

It means that under assumption of the same probability distribution of inhibitory and excitatory PSP amplitudes the fourth infinitesimal moments (4) for $k = 4$ satisfy $\{M_4(u)\}_n = O(1)$ and always remain non-zero.

Appendix B. The fourth moment of $A_E(n)$ satisfies

$$\mathsf{E}A_E^4(n) = p(n)\left(a_E(n) + \varepsilon_1(n)\right)^4 + r(n)\left(a_E(n) - \varepsilon_2(n)\right)^4, \tag{46}$$

where $p(n) + r(n) = 1$. It holds that $p(n) = O(1/n^d)$ where $d \geq s$ and $r(n) = O(1)$. It can be calculated that $\varepsilon_1(n) = O(\sqrt{n^{d-s}})$ and $\varepsilon_2(n) = O(\sqrt{n^{-d-s}})$. We obtain $a_E(n) - \varepsilon_2(n) = O(1/n^s)$ and $a_E(n) + \varepsilon_1(n) = O(\varepsilon_1(n)) = O(\sqrt{n^{d-s}})$. As $p(n)\varepsilon_1^4(n)$ has the highest order in the sum of expanded fourth power then assuming $p(n)$ simple we obtain

$$\mathsf{E}A_E^4(n) = O\left(p(n)\left(a_E(n) + \varepsilon_1(n)\right)^4 + O(1/n^{4s})\right) = O(p(n)\varepsilon_1(n)^4) = O\left(n^{d-2s}\right). \tag{47}$$

Now, if we assume $A_I(n)$ having the same distribution as $A_E(n)$, we get due to equation $\lambda_E(n) = O(\lambda_I(n)) = O(n^s)$ that

$$\{M_4(u)\}_n = \lambda_E(n)\mathsf{E}A_E^4(n)(U_E - u)^4 + \lambda_I(n)\mathsf{E}A_I^4(n)(u - U_I)^4 = O(n^{d-s}), \tag{48}$$

and as $d \geq s$ the fourth infinitesimal moment will never tend to zero.

Appendix C. The probability distribution of $A_E(n)$ is given by (23) and $p(n) = O(1/n^d)$ where $0 < d < s$. It means that there exists $n_0 > 0$ such that for each $n > n_0$ the inequality (26) does not hold. Thus $a_E(n) - \varepsilon_2(n) < 0$ for $n > n_0$ and as $p(n) \to 0$, we obtain

$$\mathsf{P}\left(A_E(n) < 0\right) = \mathsf{P}\left(A_E(n) = a_E/n - \varepsilon_2(n)\right) = r(n) = 1 - p(n) \longrightarrow 1 \tag{49}$$

for $n \to \infty$.

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