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Integrate-and-fire Models with Nonlinear Leakage

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Can we express biophysical neuronal models as integrate-and-fire (IF) models with leakage coefficients which are no longer constant, as in the conventional leaky IF model, but functions of membrane potential and other biophysical variables? We illustrate the answer to this question using the FitzHugh–Nagumo (FHN) model as an example. A novel IF type model, the IF-FHN model, which approximates to the FHN model, is obtained. The leakage coefficient derived in the IF-FHN model has nonmonotonic relationship with membrane potential, revealing at least in part the intrinsic mechanisms underlying the FHN models. The IF-FHN model correspondingly exhibits more complex behaviour than the standard IF model. For example, in some parameter regions, the IF-FHN model has a coefficient of variation of the output interspike interval which is independent of the number of inhibitory inputs, being close to unity over the whole range, comparable to the FHN model as we noted previously (Brown *et al*., 1999).

1. INTRODUCTION

Devising methods for approximating biophysical models by abstract models—which preserve the essential complexity of the biophysical mechanism yet are simultaneously concise and transparent—is an important continuing task in computational neuroscience. The advantages are obvious. Biophysical models are usually difficult to understand, and to simulate at a network level, characteristics not shared, for example, by the conventional IF model. Furthermore, a full understanding of the behaviour of biophysical models subjected to random synaptic inputs has so far eluded us [see below for a concrete example in the FitzHugh–Nagumo (FHN) model], although it might not remain 'a formidable task' (page 173 Tuckwell (1988)). A simplified expression might also provide us with a new

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tool to understand the frequently puzzling behaviour of biophysical models, since the response of the conventional leaky IF type model to stochastic input is more comprehensible. Although a rigorous analytical treatment is difficult, various approximations are available [see, for example, Ricciardi and Sato (1990)].

In the present paper we develop a systematic approach to approximating biophysical models by models of the IF type. The two essential components of the leaky IF model are *integration of incoming signals* and *leakage*. Our approach is then to determine terms which reflect these two components for a given biophysical model as exactly as possible. Although many different versions of the IF model have been proposed [see Koch (1999) on page 339, Kistler *et al*. (1997)], our method is novel, opens up new possibilities to mimic biophysical models by simplified models and produces new insights into the complexities of biophysical mechanisms.

As an application of the idea above, we consider the FHN model in the present paper and will report the application to the Morris–Lecar model in a separate paper.

Taking the FHN model, we first extract as exactly as possible the leakage coefficient, a nonlinear function of v, in contrast to the constant leakage coefficient in the conventional IF model. The nonlinear leakage coefficient, taking a V-shape plotted against v, reveals interesting properties of the FHN model. The further the membrane potential is below its threshold, the stronger the leakage is and so the easier the model loses any memory of its recent history. Hence it is difficult to depolarize the cell when the membrane potential is far below the threshold. However, when the membrane potential is near the threshold, the leakage gets smaller, eventually becoming negligible; then incoming depolarizing signals can more easily induce the neuron to fire. In other words, the neuron maintains its memory of recent activation in this range of membrane potential. We also consider the model with reversal potentials. In line with the idea above, we find that the contribution of reversal potentials to the leakage is a term which depends on incoming signals: the stronger the incoming signals, the stronger the leakage.

The coefficient of variation (CV) of the output interspike interval (ISI) of the FHN model is almost independent of the level of inhibitory input, a puzzling feature of the FHN model which we (Brown *et al*., 1999) have reported recently (see below). On the other hand, the so-called 'Central Limit Theorem' phenomenon has been widely reported (Abbott *et al*., 1997; Softky and Koch, 1993): when inhibitory inputs are blocked, the CV of the output interspike interval becomes smaller as the number of (excitatory) inputs increases. Numerical simulations shown in this paper demonstrate that the CV of the output ISI of the IF-FHN is also very flat, similar to the FHN model. Our findings for both the IF-FHN and FHN models thus contradict the 'Central Limit Theorem' prediction. Results in this paper further suggest that the flat CV vs number of inhibitory inputs relationship in both the IF-FHN and FHN models is mainly due to the nature of their nonlinear leakage.

In conclusion, a methodology is presented here which can be applied to any biophysical model: (i) extraction of the leakage coefficient from the model as exactly as possible and then (ii) formation of an IF model with the obtained leakage coefficient. A V-shaped leakage coefficient/membrane potential relationship, at least in the IF-FHN model, contributes largely to the variability of efferent spike trains.

2. THE MODEL

With synaptic inputs, the FHN model is defined by

$$\begin{cases} dv(t) &= -\gamma v(v-\alpha)(v-1)dt - wdt + dI_{\text{syn}}(t) \\ dw(t) &= \delta(v-\beta w)dt \end{cases} \tag{2.1}$$

where $\gamma, \alpha, \delta, \beta$ are all positive parameters. We further assume that an FHN neuron receives synaptic inputs modelled by Poisson processes. More specifically, denote $N_i^E(t)$ as the EPSPs (excitatory postsynaptic potentials) arriving at the ith excitatory synapse and $N_i^I(t)$ as the IPSPs (inhibitory postsynaptic potentials) at the ith inhibitory synapse. Then the total synaptic input $I_{\text{syn}}(t)$ can be written as

$$I_{\text{syn}}(t) = a\sum_{i=1}^{p} N_i^E(t) - b\sum_{i=1}^{q} N_i^I(t)$$

where a and b represent the magnitude of EPSP and IPSP, respectively, p is the number of excitatory synapses and q the number of inhibitory synapses, $N_i^E(N_i^I)$ are Poisson processes with rate $\lambda_E(\lambda_I)$.

We also treat the model subject to inputs with reversal potentials, i.e.,

$$\bar{I}_{\text{syn}}(t) = \bar{a}(V_E - v(t))\sum_{i=1}^{p} N_i^E(t) - \bar{b}(v(t) - V_I)\sum_{i=1}^{q} N_i^I(t)$$

where $\bar{a}(V_E - v_{\text{rest}}), \bar{b}(v_{\text{rest}} - V_I)$ are the magnitudes of a single EPSP and IPSP when $v(t) = v_{\text{rest}}$, V_E, V_I are reversal potentials. One can further relate these quantities to, for example, AMPA, NMDA, GABA_A or GABA_B synaptic inputs.

For simplicity of notation we further confine ourselves to the case of the diffusion approximation of synaptic inputs (Tuckwell, 1988), that is

$$\mu^E dt + \sigma^E dB_t \sim \sum_{i=1}^{p} N_i^E(t)dt$$

with $\mu^E = ap\lambda_E$, $(\sigma^E)^2 = a^2 p\lambda_E$ and B_t is standard Brownian motion. A similar expression holds for inhibitory inputs and we have

$$I_{\text{syn}}(t) = \mu t + \sigma B_t$$

with $\mu = \mu^E - \mu^I, \sigma^2 = (\sigma^E)^2 + (\sigma^I)^2$.

Correlated synaptic inputs are also taken into account, which could be simply defined by

$$\tilde{I}_{\text{syn}}(t) = \mu t + \tilde{\sigma} B_t$$

with

$$\tilde{\sigma}^2 = (\sigma^E)^2 + (\sigma^I)^2 = a^2 p(1 + (p-1)c)\lambda_E + b^2 q(1 + (q-1)c)\lambda_I$$

and c as the correlation coefficient [see Brown and Feng (1999, 2000); Feng and Brown (2000a,b) for details].

3. IF-FHN MODEL

We first define leakage coefficient as precisely as possible in a more general context. Consider a general model,

$$\begin{cases} dv(t) &= f(v, w)dt + dI_{\text{syn}}(t) \\ dw(t) &= g(v, w)dt \end{cases} \tag{3.1}$$

in which v is membrane potential, w is a vector of recovery variables, generally representing activation and inactivation variables for the ion channels in the model. Our aim in achieving an IF reduction is to re-express the model as follows:

$$dv(t) = -L(v, t)(v - v_{\text{rest}})dt + dI_{\text{syn}}(t) \tag{3.2}$$

where v_{rest} is the resting potential, $L(v, t)$, the *generalized leakage coefficient*, is restricted to be a smooth function of v and t. In general, it will be possible to obtain a solution for w in terms of t and integrals of functions of v up to time t, since the differential equations in w are linear in w which can therefore be easily integrated. In the extreme case, for the conventional leaky IF model, the model is extremely simple:

$$dv(t) = -L(v - v_{\text{rest}})dt + dI_{\text{syn}}(t) \tag{3.3}$$

where the leakage coefficient L is a constant, independent of the values of v and w. In general, it will only be possible to express a model in the form of equation (3.2) approximately.

Now we carry out the idea above for the FHN model. First of all we see that the second differential equation of the FHN model can be solved as follows:

$$w(t) = \delta \int_0^t v(s) \exp(-\beta\delta(t - s))ds. \tag{3.4}$$

Substituting equation (3.4) into the first differential equation of the FHN model we obtain

$$dv(t) = -\gamma(v-1)(v-\alpha)vdt - \delta\int_0^t v(s)\exp(-\beta\delta(t-s))ds + dI_{\text{syn}}(t). \quad (3.5)$$

Using our basic idea—to extract the leakage coefficient from the FHN model as exactly as possible, i.e., to rewrite this differential equation in the form of equation (3.2), we rewrite equation (3.5) as:

$$\begin{aligned} dv(t) &= -\left[\gamma(v-1)(v-\alpha) + \delta\textstyle\int_0^t \exp(-\beta\delta(t-s))ds\right]v(t)dt \\ &\quad -\delta\textstyle\int_0^t (v(s)-v(t))\exp(-\beta\delta(t-s))dsdt + dI_{\text{syn}}(t) \\ &= -\left[\gamma(v-1)(v-\alpha) + \tfrac{1}{\beta}(1-\exp(-\beta\delta t))\right]v(t)dt \\ &\quad -\delta\textstyle\int_0^t (v(s)-v(t))\exp(-\beta\delta(t-s))dsdt + dI_{\text{syn}}(t). \end{aligned} \quad (3.6)$$

Note that in the equation above the term

$$\delta\int_0^t (v(s)-v(t))\exp(-\beta\delta(t-s))ds$$

is a higher order term, which we could omit in the first-order approximation. Equation (3.6) becomes

$$dv(t) = -\left[\gamma(v-1)(v-\alpha) + \frac{1}{\beta}(1-\exp(-\beta\delta t))\right]v(t)dt + dI_{\text{syn}}(t). \quad (3.7)$$

Let us define

$$L(v,t) = \gamma(v-1)(v-\alpha) + \frac{1}{\beta}(1-\exp(-\beta\delta t)) \quad (3.8)$$

which gives us the leakage coefficient (approximated to the first order) extracted from the FHN model.

The leakage coefficient $L(v,t)$ is a nonhomogeneous one, depending on time t, but for simplicity we assume that the term $-\exp(-\beta\delta t)$ is small enough to be negligible. Let us now compare the leakage coefficient $L(v,t)$ with that of the conventional leaky IF model, denoted as $L > 0$ (constant).

Figure 1 depicts a typical case of the leakage coefficient extracted from the FHN model. When the membrane potential is between the resting potential $v_{\text{rest}} \sim 0$ and the threshold $v_{\text{thre}} \sim \alpha$ (indicated by right arrow), the leakage coefficient is positive. Hence the system will gradually lose its memory of recent activation. However, $L(v,t)$ is very different from L, which is a constant and is independent of its membrane potentials. $L(v,t)$ is larger when the membrane potential is close

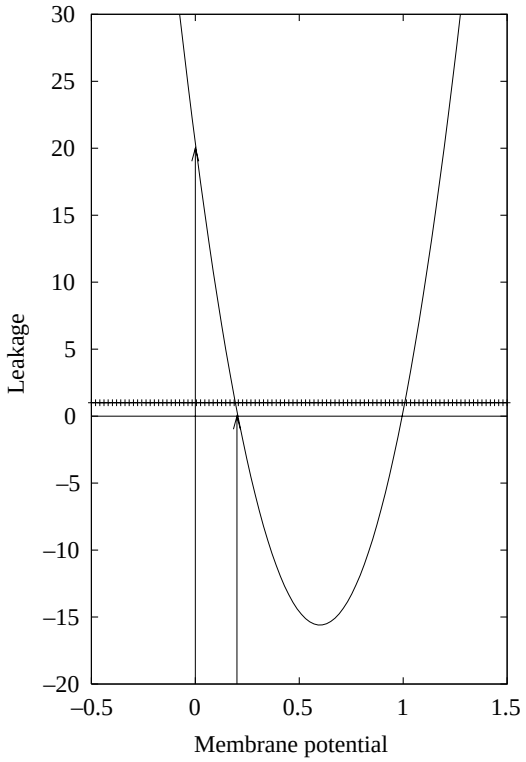

Figure 1. $L(v,t)$ and L vs the membrane potentials. Between the resting potential and the threshold (indicated by arrows), $L(v,t)$ are positive, but the closer the membrane potential to the threshold, the weaker the leakage, in contrast to the conventional IF model. $-$, $L(v,t)$; $+$, L.

to the resting potential, and vanishes when the membrane potential is close to the threshold. In other words, when the membrane potential is near resting potential, the model loses its memory rapidly. Incoming signals accumulate less effectively to increase membrane potential. When membrane potential is near to the threshold, however, the FHN model behaves more like a perfect IF model. The FHN now has a very good 'memory' and in a sense 'waits' just below the threshold. As soon as some positive signals arrive, the neuron fires. Therefore, below the threshold, the IF-FHN behaves as a combination of the *leaky* IF model and the *perfect* IF model.

Once the membrane potential is above the threshold, now $L(v,t)$ acts as an amplifier of incoming signals, rather than as a leakage. It will increase membrane potential until it arrives at its maximum value, designated as v_{thre} in this paper, and then $L(v,t)$ becomes positive again.

Now we are in the position to define the following dynamics as the IF model with nonlinear leakage (IF-FHN):

$$\begin{cases} dv_t &= -L(v,t)v\,dt + dI_{\text{syn}}(t) \\ v_0 &= v_{\text{rest}}. \end{cases} \tag{3.9}$$

For a prefixed *threshold* v_{thre}, once v crosses it from below, v is then reset to v_{rest}. Unlike the conventional IF model, for the IF-FHN we could choose a value inside $(\alpha, 1]$ as its threshold without essentially affecting its behaviour since once v is above the threshold, it will rapidly reach $v = 1$ (see Fig. 3 and Section 6 for further explanation).

For the model with reversal potential inputs, by a similar argument, we have

$$d\bar{v}_t = -\left[\gamma(\bar{v}_t - 1)(\bar{v}_t - \alpha) + \frac{1}{\beta}(1 - \exp(-\beta\delta t)) + \mu + \sigma\xi_t\right]\bar{v}_t dt + \bar{\mu}dt + \bar{\sigma}\,dB_t \tag{3.10}$$

where

$$\mu = \bar{a}\,p\lambda_E - \bar{b}q\lambda_I, \qquad \sigma = \sqrt{\bar{a}^2 p\lambda_E + \bar{b}^2 q\lambda_I}$$
$$\bar{\mu} = \bar{a}V_E\,p\lambda_E - \bar{b}V_I q\lambda_I, \qquad \bar{\sigma} = \sqrt{(\bar{a}V_E)^2 p\lambda^E + (\bar{b}V_I)^2 q\lambda_I}$$

and $\xi_t dt = dB_t$. Hence now the leakage coefficient $\bar{L}(v, t)$ is given by

$$\bar{L}(v, t) = \gamma(v - 1)(v - \alpha) + \frac{1}{\beta}(1 - \exp(-\beta\delta t)) + \mu + \sigma\xi_t$$

depending not only on the membrane potential, but also on inputs. The stronger the inputs are, the stronger the leakage is.

4. Deterministic Inputs

In this section we consider the IF-FHN model with deterministic inputs, i.e., equations (3.9) and (3.10) with $\sigma = 0$ ($\bar{\sigma} = 0$). It is known that the FHN model exhibits type II behaviour (Koch, 1999). Hence it is a natural question to ask whether the IF-FHN inherits the property.

However a close check tells us that the IF-FHN is a type I model. Commencing from small $\mu > 0$, the IF-FHN has two fixed point attractors, one near the resting potential and the other near v_{thre}. When μ increases, the attractor near the resting potential disappears and the only attractor is the one near v_{thre}. This happens if and only if

$$\mu_0 = \gamma[(v_m - \alpha)(v_m - 1) + 1/\beta]v_m$$

where v_m is the only local minimum of the function $\gamma[(v - \alpha)(v - 1) + 1/\beta]v$. As soon as $\mu > \mu_0$, v_t converges to the attractor near v_{thre}. Let

$$T = \inf\{t : v_t \geq v_{\text{thre}}\}$$

the ISI, we see that

$$\lim_{\mu \to \mu_0 +} T = \infty.$$

Furthermore, we want to emphasize here that while type I and type II is a useful way to distinguish deterministic dynamics, application of the definition to stochastic dynamics (a neuronal model subjected to random synaptic inputs) is inappropriate. Randomness tends to smear everything out: the discontinuity in the $f - I$ curve no longer exists. Therefore to predict stochastic model behaviour in terms of type I and type II dynamics is inappropriate, as we reported early [see Brown *et al*. (1999) and reference therein] and demonstrate here again.

5. NUMERICAL RESULTS

We use the following set of parameters in simulations (Brown *et al*., 1999):

$$\gamma = 100, \qquad \alpha = 0.2, \qquad \delta = 0.25, \qquad \beta = 2.5, \qquad a = b = 0.05,$$

$\lambda_I = \lambda_E = 100$Hz, $v_{\text{thre}} = 1$, $v_{\text{rest}} = 0$ and $c = 0$ in this section.

We first compare the IF-FHN model with the FHN model with deterministic inputs. In Fig. 2 numerical simulations are shown for $\mu = 2, 3, 4, 10$ (superthreshold stimuli). It is easily seen that the IF-FHN model gives an excellent fit before the membrane reaches v_{thre}, when input is strong enough ($\mu = 3, 4, 10$). When the input is weak ($\mu = 2$) and when the membrane potential is below the threshold, the fit is still quite good. A clear discrepancy is then observed when the membrane is above the threshold. Note that for obtaining higher order accuracy of approximation, we could expand the term $v(s) - v(t)$ in equation (3.6) to higher orders. However, as we emphasized at the beginning, the main purpose of the present paper is to introduce a new generation of IF models which could help us to understand intrinsic mechanisms of biophysical models and qualitatively match their behaviour, rather than to follow them in detail. We do not therefore pursue the further expansion of the FHN model. It is also worth emphasizing that we are usually interested in the behaviour of the model below the firing threshold. The exact form of the spike is for some purposes not very important.

Now we turn to stochastic input cases. The FHN model has been widely studied in the literature for many purposes, ranging from network to single neuron behaviour. Figure 3 shows a simulation for the IF-FHN model with random inputs with a reset mechanism.

Another issue which has been widely discussed in the literature during the past few years is how to generate spike trains with a high CV(ISI), greater than 0.5. For this purpose, many different mechanisms have been proposed. We have shown in previous publications that for the conventional IF model, there is a range of parameters in which the model could produce efferent spike trains with a high CV, if independent Poisson process inputs are considered. If the inputs are correlated, then within plausible physiology parameters regions of the model, a high CV(ISI) spike train is generated, independent of the number of inhibitory inputs q (Feng and Brown, 1998, 1999, 2000a). Nevertheless, broadly speaking, for the IF model, when only excitatory inputs are presented, then CV(ISI) is small.

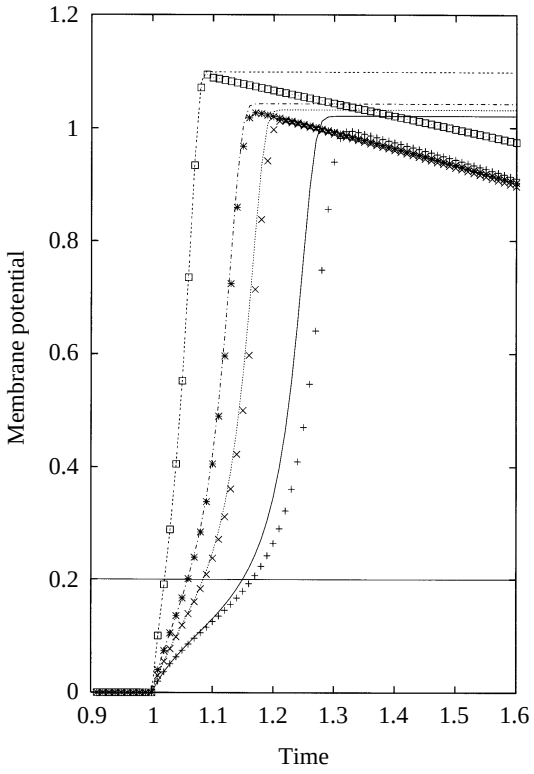

Figure 2. A comparison between the IF-FHN (without resetting) and the FHN model when they are subjected to deterministic inputs. It is easily seen that the IF-FHN approximate the FHN reasonably well when the input μ is large. The input starts when time equals 1. $\mu = 2$: $-$, IF; $+$, FHN. $\mu = 3$: ----, IF ; $\times$, FHN. $\mu = 4$: –·–; IF; *, FHN. $\mu = 10$: ----, IF ; $\boxdot$, FHN.

We have observed that for some biophysical models this phenomenon totally disappears, CV(ISI) is almost independent of whether inhibitory inputs are blocked or not (Brown *et al.*, 1999). What is the behaviour of the IF-FHN? In Fig. 4 we see that CV(ISI) is quite high and is not sensitive to the number of inhibitory inputs, similar to what we have observed for the FHN model itself (Brown *et al.*, 1999). However, in Brown *et al.* (1999) we were not able to elucidate the mechanism which ensures the occurrence of the phenomenon. Based upon the numerical results of the IF-FHN model, we conclude that the nonlinear leakage coefficient contributes to the flat CV which is a typical feature of some biophysical models and which is not captured by conventional IF models.

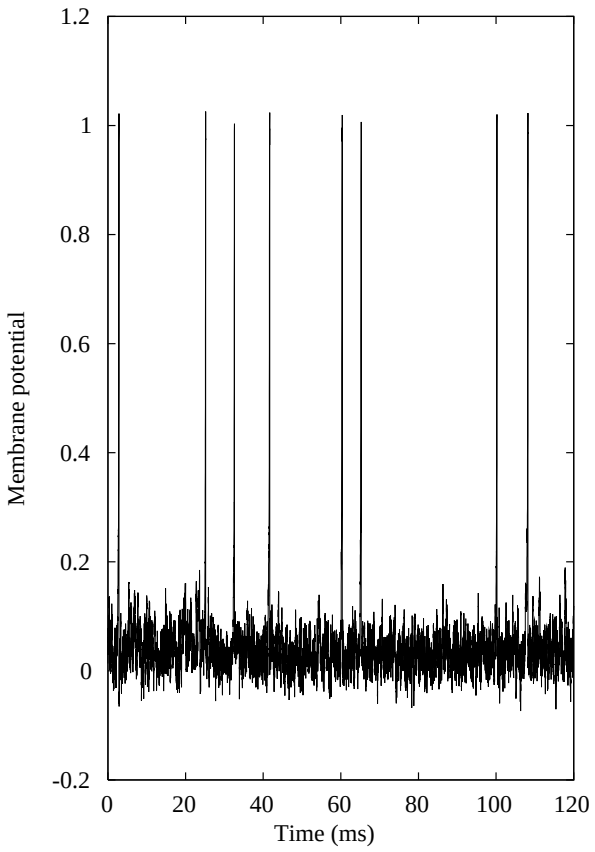

Figure 3. The behaviour of the IF-FHN with random inputs. When the membrane potential reaches 1, it is then reset to 0.

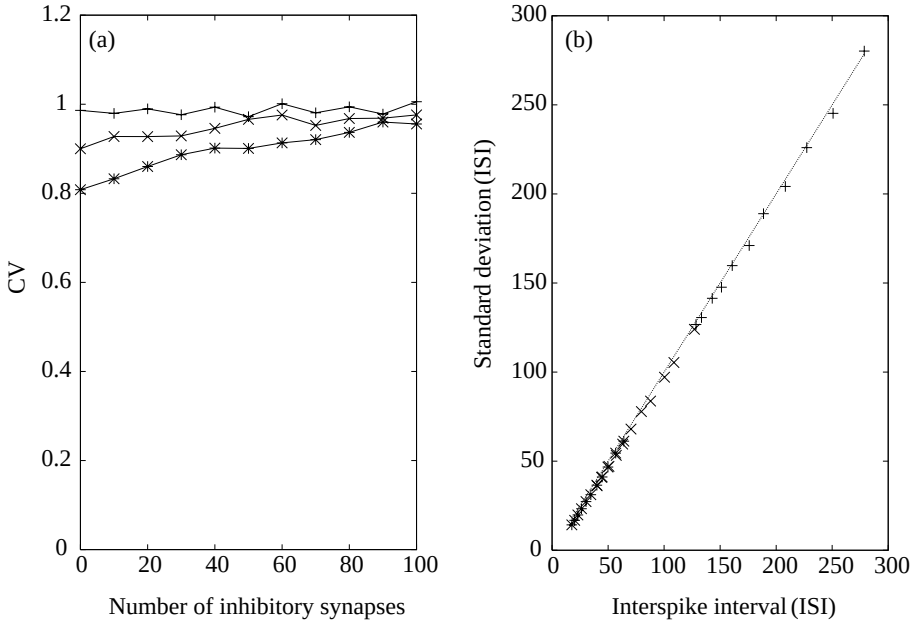

Figure 4. (a) CV vs q and (b) standard deviation of ISIs vs mean ISIs of the IF-FHN model. With respect to varying q, CV (calculated after adding a refractory period of 3.2 ms) is quite flat. +, $p = 80$; -*-, $p = 90$; --*--, $p = 100$. Note that in (b) the standard deviation almost equals the mean ISI. +, $p = 80$; ×, $p = 90$; *, $p = 100$; ----, $y = x$. 10 000 spikes were generated to calculated the mean and standard deviation.

6. Application of Large Deviation Theory

From the data shown in Fig. 4 we might envisage that Kramer's formula can predict the model behaviour, which has been successfully applied to estimate the firing rate in certain circumstances (Chow and White, 1996). Kramer's formula (a special case of the large deviation theory, see Albeverio *et al*. (1995) and references therein for details Risken (1989)) reads

$$\langle \bar{T} \rangle \sim \frac{2\pi}{\sqrt{H''(v_{\min})|H''(v_{\max})|}} \exp(2(H_{\max} - H_{\min})/\sigma^2) \tag{6.1}$$

where $\bar{T}$ is the first exit time from a potential well, and $H_{\max}$, $H_{\min}$ are the local maximum and local minimum of the potential well (see below).

Furthermore, $\bar{T}$ is exponentially distributed, as the plot of standard deviation vs ISIs of Fig. 4 shows. If this is the case then we might conclude that the flat CV is simply due to perturbations of a deterministic system, a simple, classic and clear picture. Denote

$$\bar{H}(v) = \int_0^v uL(u, \infty)du = \gamma\left(\frac{1}{4}v^4 - (\alpha + 1)\frac{1}{3}v^3 + \frac{1}{2}\alpha v^2\right) + \frac{1}{2\beta}v^2.$$

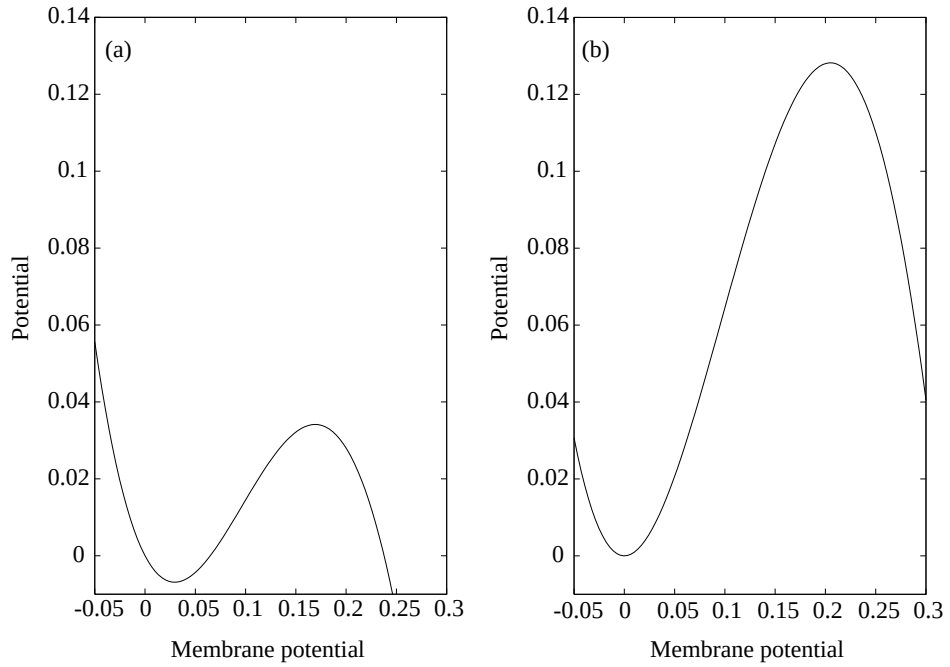

Figure 5. The potential of the IF-FHN model ($p = 100$) defined by equation (6.2) with parameters as in previous section and (a) $q = 0$, (b) $q = p$.

For the IF-FHN model we could write the potential H of the system in terms of two terms

$$H(v) = \bar{H} + \mu v \tag{6.2}$$

and therefore

$$H_{\max} - H_{\min} = \bar{H}(v_{\max}) - \bar{H}(v_{\min}) + \mu(v_{\max} - v_{\min})$$

where $v_{\max}$ and $v_{\min}$ are the value at which H attains the local maximum and minimum (see Fig. 5). As we mentioned before for the IF-FHN model, its behaviour does not substantially change if we set the threshold as a value inside $[v_{\max}, 1]$.

Figure 6 shows an application of Kramer's formula to the IF-FHN model with correlated inputs. When the input is uncorrelated, $c = 0$, Kramer's formula gives a rough estimate, with an obvious discrepancy between numerical results and theoretical estimate. Nevertheless when a small correlation is added ($c \geq 0.005$), i.e., the IF-FHN model receives a more random input, Kramer's formula gives an excellent estimate. As one might expect, the mean ISI and standard deviation exhibit a linear relationship.

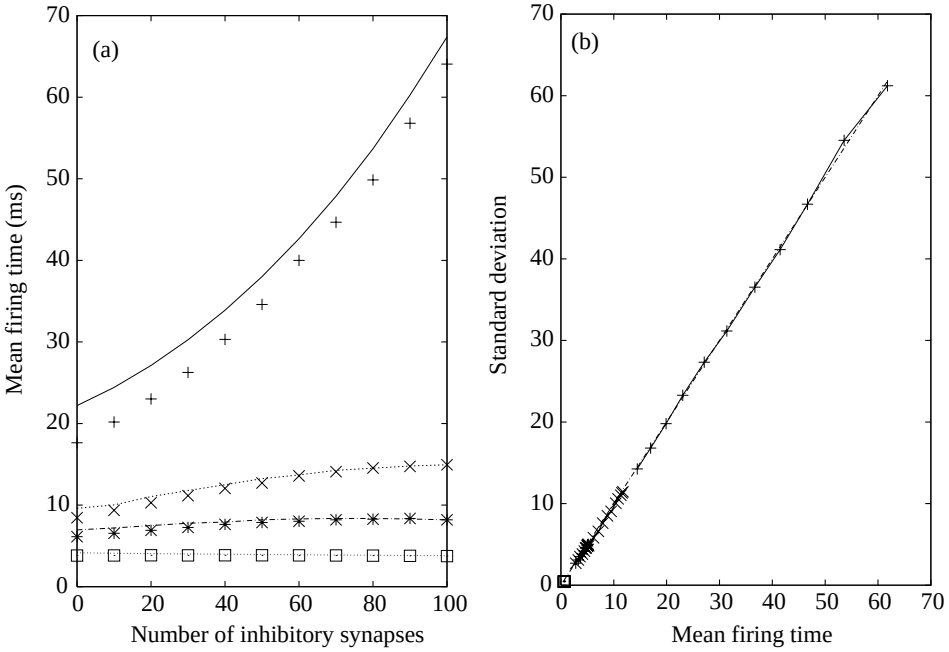

Figure 6. A comparison between Kramer's formula and numerical simulations with parameters as specified in the context, $p = 100$. (a) —, $c = 0.00$, Kramer; +, $c = 0.00$, simulation; ----, $c = 0.005$, Kramer; ×, $c = 0.005$, simulation; –.–.–, $c = 0.01$, Kramer; *, $c = 0.01$, simulation; ----, $c = 0.10$, Kramer; □, $c = 0.10$, simulation. (b) +, $c = 0.00$; -*-, $c = 0.005$; --*--, $c = 0.01$; ----□----, $c = 0.10$, -.-.-, $y = x$.

7. DISCUSSION

We answer the following questions in the present paper: what is the leakage coefficient for a given biophysical model? Can we extract it as exactly as possible from the biophysical model and therefore obtain an IF model with the same leakage coefficient? We find that the leakage coefficient extracted from the FHN takes the form of a V-shape. The IF-FHN is defined with the leakage coefficient. The approach presented here introduces a new generation of IF models with the feature that their nonlinear leakage coefficients are extracted from and therefore mimic the original biophysical models.

The IF-FHN model generates efferent spike trains with a high CV. From the results presented in the paper we conclude that the V-shape leakage coefficient contributes largely to the variability of efferent spike trains.

As we have pointed out above, in recent years interest has grown in mechanisms which allow neurons to generate spikes with a high CV(ISI). Different arguments have been put forward. Although it turns out that both the IF model and some biophysical models are capable of generating spike trains with a high CV, how and why biophysical models behave so differently from the IF model is still mysterious. In the present paper we reveal a key mechanism: a nonlinear leakage coefficient

having a V-shaped relationship with membrane potential ensures a neuron generates spike trains with a high CV.

Finally, we want to emphasize that now the time is ripe to replace the classic IF model with a constant leakage coefficient by a new generation of IF models with a nonconstant leakage coefficient as introduced here. Because of the wide usage of the IF model, we hope that the models presented here will contribute significantly to computational neuroscience. The computational complexity of the IF-FHN is very similar to the conventional IF model, but the former captures some interesting and essential features of the FHN model. It is possible to obtain an analytical formula for the mean first exit time, rather than an approximation as we developed here by using the large deviation theory.

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