Dissipation of the excitation wavefronts

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An excitation wave in cardiac tissue will fail to propagate if the transmembrane voltage at its front rises too slow and does not excite the tissue ahead of it. Then the sharp voltage profile of the front will dissipate, and subsequent spread of voltage will be purely diffusive. This mechanism is impossible in FitzHugh-Nagumo type systems. Here a simplified mathematical model for this mechanism is suggested. The model has exact traveling front solutions, and gives conditions for the front dissipation. In particular, a front will dissipate if it is not allowed to propagate faster than a certain nonzero speed. This critical speed depends only on the properties of the fast sodium channels. The inactivation gates of these channels play a crucial role in the front dissipation, even if their dynamics are by an order of magnitude slower than those of the voltage.

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Introduction. Fifty years ago, Hodgkin and Huxley have proposed a mathematical model of the electric action of the giant squid axon [2]. It spawned a large family of models describing other biophysically related phenomena, e.g. excitability of heart muscle. Hodgkin-Huxley (HH) system of equations and its descendants are rather complicated (see (4)), do not admit exact solution, and mostly treated numerically.

FitzHugh [3] and Nagumo et al. [4] suggested a simplified analogue of the Hodgkin and Huxley equations:

$$\begin{aligned} \frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + \epsilon_E \left(E - E^3/3 - v\right), \\ \frac{\partial v}{\partial t} &= \epsilon_v (E + \beta - \gamma v). \end{aligned} \tag{1}$$

where E corresponds to the transmembrane voltage [5] and v represents all other, slow variables. FitzHugh has shown that an appropriate 2-dimensional projection of the "phase portrait" of the point system of the HH model looks "similar" to that of (1), and Nagumo et al. have demonstrated that it describes propagating pulses similar to those in HH. This model is much simpler than the HH-type systems, and allows a great deal of analytical and qualitative study.

Throughout these 40 years, the FitzHugh-Nagumo (FHN) system and its modifications served well as simple but reasonable models of excitation propagation in nerve, heart muscle and other biological excitable media.

In this paper, we discuss a phenomenon in biophysically detailed models, which cannot be adequately reproduced in any FHN-type system. This is *dissipation of the excitation wavefronts*, a specific mechanism of propagation block when the sharp gradient of the transmembrane voltage at the wavefront smears out and spread of voltage becomes diffusive, as the main excitation current gets inactivated. This phenomenon, although seen by physiologists and researchers working with detailed models, has not been identified so far as deserving a special attention and understandable in terms of simplified models. Understanding the mechanisms of propagation blocks in heart tissue is of enormous practical importance, as it is thought to be a major factor of cardiac arrhythmias (see [6] as an example of a recent study).

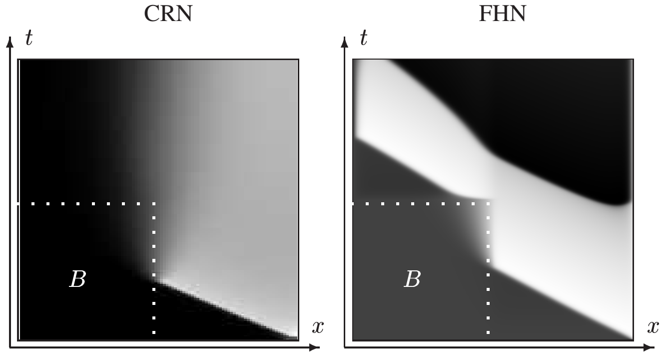
Two different mechanisms of propagation block. A typical scenario of propagation block in heart is that an excitation propagates where the tissue that has not fully recovered after the previous wave, and a recovery wave moves before the new excitation wave. If the recovery wave is slower than the excitation wave, the latter runs into more and more unfavorable condition and may eventually fail to propagate at all. This happens differently in realistic models and in FHN-type caricatures. Fig. 1 illustrates this using an ultimate idealization of the excitability completely but temporarily suppressed in a part of the medium. The illustrations are for two models, the detailed model of human atrial tissue by Courtemanche et al. [7] (CRN) and for the FHN system (1). In the CRN model, when the propagation stops, the wavefronts dissipates. When the conditions for propagation are restored, the excitation wave does not resume, as the sharp increase in the voltage necessary to trigger such wave is not present. Subsequent spread of the voltage is purely diffusive. In the FHN system, the high voltage at the front itself is enough to excite new cells if other conditions are right again; so the excitation front can propagate with arbitrarily slow speed or even stop, without dissipation. When propagation conditions are restored, the excitation wave resumes the propagation, even though the voltage profile in the inexcitable region has been smeared out.

The FHN wave will not resume propagating only if the block lasts longer than the action potential, so the back of the wave reaches the block site. In contrast, the CRN wave looses the ability to propagate within milliseconds, long before the end of the action potential.

Excitation fronts in FHN-type systems do not dissipate. If $\epsilon_v \ll \epsilon_E$, system (1) belongs to a class of systems

$$\begin{aligned} \frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + f(E, v), \\ \frac{\partial v}{\partial t} &= \epsilon g(E, v), \qquad 0 < \epsilon \ll 1, \end{aligned} \tag{2}$$

($v \in \mathbb{R}^m$, $m \geq 1$), for which the asymptotic theory developed in 1970-1980s (see e.g. [9–12]) can be applied. In a relevant region of v, function $f(E, v)$ is assumed to have three simple roots in E, $E_-(v)$ (recovery) $< E_*(v)$ (threshold) $< E_+(v)$ (excitation), where recovery and excitation are



$$g_{Na} = \begin{cases} 0, & (x,t) \in B, \\ \text{standard otherwise [8].} \end{cases} \qquad \epsilon_E = \begin{cases} 0, & (x,t) \in B, \\ 3, & \text{otherwise.} \end{cases}$$

FIG. 1: Temporary local block of the excitation front: the excitability of the medium is suppressed for $(x,t) \in B = (0,x_b) \times (0,t_b)$, where x_b and t_b are the middles of the space and time intervals (shown by the white dots). Here and below, solutions are represented by shades of gray: black is the smallest value of E and white is the largest value of E within the solution. In CRN model: time range 80 ms, space range 50 s.u. [5], all the kinetic parameters are as in [7]. In FHN model: time range 50, space range 50, $\beta = 0.75$, $\gamma = 0.5$, $\epsilon_v = 0.03$.

stable, $\frac{\partial f}{\partial E}(E_\pm(v),v) < 0$, and the threshold is unstable, $\frac{\partial f}{\partial E}(E_*(v),v) > 0$. Propagation of fronts and backs of excitation waves in the limit $\epsilon \to +0$ is described by trigger waves in the first of the equations (2) with $v = \text{const}$ between $E_-(v)$ and $E_+(v)$ with a speed which is a function of v, $c = c(v)$. The sign of $c(v)$ coincides with the sign of $\int_{E_-(v)}^{E_+(v)} f(E,v)\,\mathrm{d}E$ and thus may change as v changes, i.e. a wavefront may stop and reverse to become a waveback. The motion of the wavefront/waveback on the large scale is described by an ODE

$$\frac{\mathrm{d}X}{\mathrm{d}t} = -c(v(X,t)) = -C(X,t). \tag{3}$$

In any case, as long as the excitability stays, the sharp structure of the front is preserved, i.e. it does not dissipate.

Constructing the simplified model of the excitation front. The realistic models descendants of Hodgkin-Huxley model are all fairly similar in the part that interests us; for definiteness, we refer to the original model [2],

$$\begin{aligned} \frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + g_{Na}(E_{Na} - E)m^3 h \\ &\qquad + g_K(E_K - E)n^4 + g_l(E_l - E), \\ \frac{\partial m}{\partial t} &= (\overline{m}(E) - m)/\tau_m(E), \\ \frac{\partial h}{\partial t} &= (\overline{h}(E) - h)/\tau_h(E), \\ \frac{\partial n}{\partial t} &= (\overline{n}(E) - n)/\tau_n(E), \end{aligned} \tag{4}$$

where E is the transmembrane voltage [5], $g_{Na,K,l}$ are maximal integral specific conductivities per membrane capacitance of Na, K and "leakage" currents respectively, $E_{Na,K,l}$ are corresponding reversal potentials, m, h and n are probability densities of the channel gates being open, $\overline{m}, \overline{h}, \overline{n}$ are their instant equilibrium values, and $\tau_{m,h,n}$ corresponding time scales.

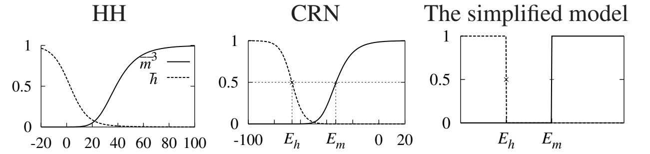


FIG. 2: Dependence of $\overline{m}^3(V)$ and $\overline{h}(V)$ for the Hodgkin-Huxley (HH) (4) [2] and Courtemanche et al. (CRN) [7] detailed models and for the proposed simplified model (5).

On the front of an excitation wave, E grows rapidly, due to the large magnitude of the Na current and/or the intercellular current described by the diffusion term. Elsewhere, evolution of E is influenced also by the smaller currents. To describe the front separately from other phases of the wave, we consider a limit $g_{Na} \to +\infty$, in which all ionic currents other than Na are disregarded. Thus, only m and h which are responsible for the Na current remain, while variable n, as well as many other variables in more complicated models, become irrelevant.

Values of $\tau_m(E)$ at the front are very small compared to other characteristic time scales of the problem. Thus m is always close to its quasi-stationary value $\overline{m}(E)$. The differential equation for m is therefore eliminated.

Thus we get a system of two equations,

$$\begin{aligned} \frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + I_{Na}(E)\overline{m}^3(E)h, \\ \frac{\partial h}{\partial t} &= \frac{1}{\tau_h(E)}\left(\overline{h}(E) - h\right), \end{aligned} \tag{5}$$

where $I_{Na}(E) = g_{Na}(E_{Na} - E)$. This system is intended to describe the propagation of the excitation front (the fast process) only, leaving all other processes, such as action potential and recovery (the slow processes), out of the scope. Compared to the FHN model, this system plays the same role as the first equation in (2), but here we do not assume h to be much slower than E, thus two fast equations in place of one.

So far we exploited small parameters available in the model, and (5) can be expected to be in a reasonable quantitative agreement with the full system. Further simplifications are based on qualitative considerations, and do not claim to produce quantitative results. We note that $\overline{m}(E)$ and $\overline{h}(E)$ are step-like functions, taking values either close to 0 or close to 1 (see fig. 2). Thus we replace them with

$$\overline{m}(E) = \theta(E - E_m) = \overline{m}^3(E), \qquad \overline{h}(E) = \theta(E_h - E),$$

were $\theta(a)$ is the Heaviside step function.

Further, we replace $\tau_h(E)$ and $I_{Na}(E)$ by constants as their dependence on E is not essential here. So, growth of E stops when h or m close down, not when E reaches E_{Na}, and the maximal voltage in a front is usually significantly lower than E_{Na} (e.g. in CRN, by more than 60mV).

After appropriate nondimensionalization, by choosing the scale of E so that $E_h = 0$, $E_m = 1$ and scale of t so that

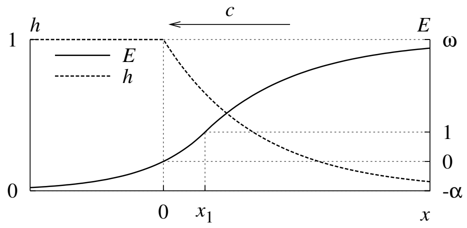


FIG. 3: A propagating front solution (8,9) to (7) ($\tau = 8$, $\alpha = 1$, $c \approx 0.444$).

$I_{Na} = 1$ [5], we finally obtain the system

$$\begin{aligned} \frac{\partial E}{\partial t} &= \frac{\partial^2 E}{\partial x^2} + \theta(E-1)h, \\ \frac{\partial h}{\partial t} &= \frac{1}{\tau}\left(\theta(-E) - h\right), \end{aligned} \qquad (6)$$

depending on one dimensionless parameter, τ.

Spatially homogeneous equilibria here are not isolated, but form two continua, $(E, h) \in (-\infty, 0)\times\{1\}\cup(0,+\infty)\times\{0\}$. This is due to the idealizations that ionic currents other than Na only produce slow dynamics and therefore disregarded in considering fronts, and that Na gates work as perfect switches. This means that E will remain constant (in reality, slowly vary) at any value as long as the Na channels are closed.

The traveling front solutions. A front propagating leftwards with speed c satisfies

$$cE' = E'' + \theta(E-1)h, \qquad ch' = \frac{1}{\tau}\left(\theta(-E) - h\right) \quad (7)$$

with auxiliary conditions:

$$\begin{aligned} &E(-\infty) = -\alpha < 0; \quad E(+\infty) = \omega > 1; \\ &h(-\infty) = 1; \quad h(+\infty) = 0. \end{aligned}$$

We choose the phase of the front so that $E(0) = 0$, denote $x_1 > 0$ the point where $E(x_1) = 1$, and require that $E(x) \in C^1$ and $h(x) \in C^0$, which implies obvious internal boundary conditions at $x = 0$ and $x = x_1$.

This problem has a family of solutions depending on one parameter, the pre-front voltage α:

$$\begin{aligned} E(x) &= \begin{cases} -\alpha + \alpha\exp(cx) & (x \le x_1), \\ \omega - \dfrac{\tau^2 c^2}{1+\tau c^2}\exp\left(-\dfrac{x}{\tau c}\right) & (x \ge x_1), \end{cases} \\ h(x) &= \begin{cases} 1 & (x \le 0), \\ \exp\left(-\dfrac{x}{\tau c}\right) & (x \ge 0), \end{cases} \end{aligned} \qquad (8)$$

where $\omega = 1 + \tau c^2(\alpha + 1)$, $x_1 = \frac{1}{c}\ln\left(\frac{1+\alpha}{\alpha}\right)$ and c is an implicit function of τ and α,

$$\tau c^2 \ln\left(\frac{(1+\alpha)(1+\tau c^2)}{\tau}\right) + \ln\left(\frac{\alpha+1}{\alpha}\right) = 0. \quad (9)$$

Note that here the post-front voltage ω depends on τ; this is different from the FHN-type systems where it only depends on the right-hand sides of the equation for E.

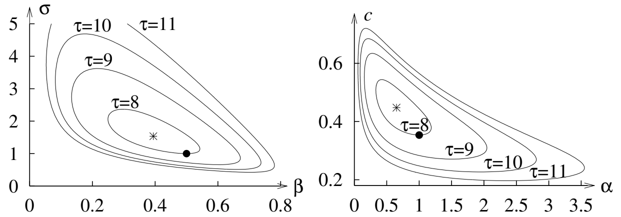


FIG. 4: Pre-front voltage vs front speed for a selection of values of τ (labels on the curves), in (β, σ) coordinates, and in the original (α, c) coordinates. •: exact solution $\beta = 0.5$, $\sigma = 1$, $\tau = 8$. $*$: the minimum of τ: $\beta_* \approx 0.394$, $\sigma_* \approx 1.537$, $\tau_* \approx 7.67$.

Properties of the speed equation. Equation (9) is equivalent to the equation of level curves $\ln\tau = g(\beta, \sigma)$ of the function $g(\beta, \sigma) \equiv \ln(1+\sigma) - \ln(1-\beta) - \sigma^{-1}\ln\beta$, where $\sigma = \tau c^2$, $\beta = \alpha/(\alpha+1)$, $(\beta, \sigma) \in S = (0,1)\times(0,+\infty)$. It can be seen that (i) For every fixed β, $\partial g/\partial\sigma$ changes sign once as σ runs through $(0, +\infty)$. (ii) $g(\beta, \sigma)$ has a local minimum $\sigma_* \approx 1.53659\ldots$, $\beta_* \approx 0.39423\ldots$, $g_* \approx 2.0378\ldots$, which is its only critical point in S. (iii) Function $g(\beta, \sigma)$ has the following lower bounds

$$\begin{aligned} &g(\beta,\sigma) > \ln\left[\ln(1/\beta)\right], \quad g(\beta,\sigma) > \ln(1/(1-\beta)), \\ &g(\beta,\sigma) > \ln(1/\sigma), \quad g(\beta,\sigma) > \ln\sigma, \quad \forall(\beta,\sigma) \in S. \end{aligned}$$

Using [13], we deduce from here that for every $C > g_*$, the set $g(\beta, \sigma) = C$ is a simple closed curve, crossing each line $\beta = \mathrm{const}$ at most twice, and (β_*, σ_*) is a global minimum in S. A selection of level curves is presented on fig. 4.

Thus, for every $\tau > \tau_* = e^{g_*} \approx 7.6740\ldots$, there exists a range of pre-front voltages $0 < \alpha_{\min}(\tau) < \alpha < \alpha_{\max}(\tau) < +\infty$, for each of which there are two propagating front solutions (8) with different speeds, and all propagation speeds possible at various pre-front voltages, span an interval $0 < c_{\min}(\tau) \le c \le c_{\max}(\tau) < +\infty$. Explicit estimates of critical parameters can be obtained in the limit of large τ, e.g.

$$c_{\min} = e^{1/2}\tau^{-1} + 1.25e^{3/2}\tau^{-2} + O(\tau^{-3}). \quad (10)$$

Existence of a minimal propagation speed implies that the excitation front can not be stopped or reversed, and is therefore crucial for the phenomenon of front dissipation.

Some numerical results. For every admissible pair of τ and α, except the marginal values of α, equation (9) gives two values of the speed c. Numerical experiment suggests that the faster fronts are stable, and the slower fronts are unstable and either dissipate or develop into the faster solutions (see fig. 5). This conjecture requires a further investigation.

Fig. 6 shows results of computations of (6) with a temporary local excitability block as in fig. 1. As the only parameter in the model is τ and front propagation is possible if $\tau > \tau_* \approx 7.674$, the block was simulated by a decrease of τ below this threshold. The front dissipated as soon as it reached the blocked region. When excitability in that region was restored, the front did not resume but continued to spread diffusively. So, the new model behaves similar to the detailed equations and different from the FHN model.

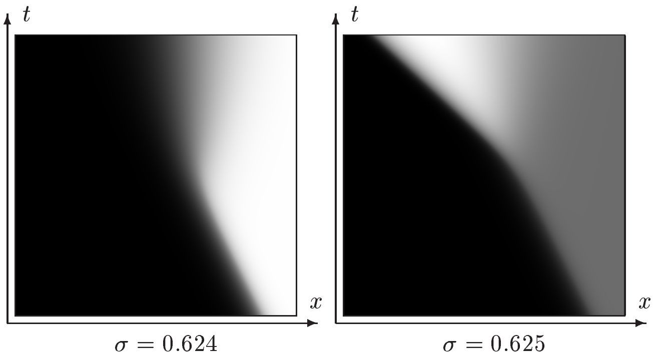
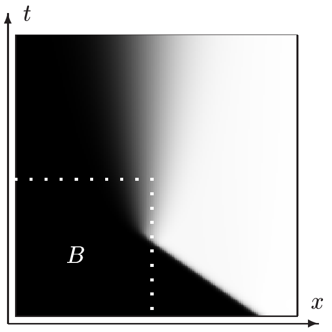


FIG. 5: Solutions of (6) with initial conditions (8), for $\tau = 10$, $\alpha = 1$ and σ close to the low speed solution of (9). Space range is 100, time range is 200. Depending on minute details, the slow front either dissipates or develops into the faster front, corresponding to $\sigma \approx 2.955$.



$$\tau = \begin{cases} 7 < \tau_*, & (x,t) \in B, \\ 8 > \tau_*, & \text{otherwise.} \end{cases}$$

FIG. 6: Temporary local block (B, white dots) of the excitation front in the simplified model (6), as in fig. 1. Front propagation did not resume after the excitability has been restored. Initial conditions (8) with $\tau = 8$, $\alpha = 1$, $c = 0.444$. Time range 1000, space range 300.

Conclusions. Fronts of excitation waves in realistic models of cardiac tissues cannot be stopped or reversed. If they are not allowed to propagate, they dissipate. This makes them different from the FHN-type caricatures, where fronts can slow down and persist until the waveback catches up, or reverse and turn into the wavebacks. Local propagation blocks lead to breaks in the excitation waves and are essential in fibrillation. An established belief, based on intuition gained in FHN-type models and exemplified by [6], is that a wavebreak happens when the waveback catches up with the wavefront and "the length of the excitation wave becomes zero". In the mechanism described here, based on realistic models, the wavelength is irrelevant and whether or not the wave breaks is decided exclusively by events in its front.

The proposed simplified model (6) captures the main features of realistic models responsible for the propagation and dissipation of the excitation fronts. Briefly, the main qualitative predictions are: (i) Front parameters, including propagation speed, are determined by the pre-front voltage. (ii) The range of pre-front voltages at which propagation is possible, is bounded from above and from below. (iii) The range of possible propagations speeds is bounded from above and from below. The boundedness of possible propagation speeds from below implies that the excitation front can not be stopped or reversed, and is therefore crucial for the front dissipation.

Model (6) provides exact analytic solution for the front shape (8) and speed (9), wherefrom explicit conditions of front dissipation can be obtained, e.g. (10). For an accurate quantitative description, a less simplified model (5) can be used instead [14]. The traveling front solutions may then need to be studied numerically, with a possible exception of qualitative questions like boundedness of the speed spectrum. These models can serve as the fast subsystems in an asymptotic theory of the cardiac excitation waves, which is yet to be developed and to replace, in applications to cardiology, the asymptotic theory of FHN-type systems [9–12].

The key process responsible for dissipation of the front is the closure of the slow Na gate h. Thus any asymptotic or simplified model intended to describe front propagation at slow speed or its failure, must take the dynamics of h into account, alongside with the those of the transmembrane voltage E. Our results show that this is necessary even if the ratio of characteristic time scales of E and h is rather high, say around 8.

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[14] Equation (5) does not have pre-front ($h = 1$) and post-front ($h = 0$) steady state solutions, so to describe fronts it needs a slight modification by taking into account that $\overline{m}(E)$ is very small below some E, and $\overline{h}(E)$ is very small above some E and replacing them by zero in those regions.