## To Nick Alikakos On propagation of pulses in axons

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Discussions with Pavel Lushnikov, Mary Pugh, Adam Stinchcombe and Daniel Sigal

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## Axons

It was discovered Luigi Galvani in 1791-1797 and further studied by Alessandro Volta (who developed the earliest-known electric battery to study animal electricity) that signals between the central nervous system and various organs are transmitted by electric impulses (called pulses) propagating along nerve axons



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## Action potential

In 1952, A. Hodgkin and A. Huxley established that the pulses are due to shifting potential differences created by sodium, potassium, and chlorine  $(Na^+, K^+, C^-)$  and other ions moving across the axon membrane



This results in a voltage differ. pulse (action potential) propagating along axon



The separation of charge creates a potential difference of 70 to 90 mV across the only 8-nm-thick cell membrane and the resulting electric field (E = V/d) is huge (on the order of 11 MV/m).

25% of the energy used by cells goes toward creating and maintaining these potentials.

This sodium-potassium pump is an example of active transport, in which cell energy is used to move ions across membranes against diffusion gradients and the Coulomb force.

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## Hodgkin-Huxley system

Hodgkin and Huxley modelled the above process by the system describing the dynamics of the action potential v and the gating rates m, n, h (Nobel Prize, 1963):

$$C_{m}\partial_{t}v = (R/r)\partial_{x}^{2}v - g_{Na}m^{3}h(v - E_{Na}) - \dots$$
  

$$\partial_{t}m = \Theta(T)[\alpha_{m}(v)(1 - m) - \beta_{m}(v)m],$$
  

$$\partial_{t}h = \Theta(T)[\alpha_{h}(v)(1 - h) - \beta_{h}(v)h],$$
  

$$\partial_{t}n = \Theta(T)[\alpha_{n}(v)(1 - n) - \beta_{n}(v)n].$$
(HH)

Here *R* is the axon 'radius', r/2 is the resistance per unit length,  $C_m$  is the membrane capacitance,  $\Theta(T) = 3^{\frac{T-6.3}{10}}$ .

Here an axon is modelled by a straight line without an internal geometric structure.

Since the Hodgkin-Huxley papers, most of the work is done in the 'clumped' case where the diffusion terms are dropped resulting in the system of ODEs.

## FitzHugh-Nagumo system

The FitzHugh-Nagumo system (FHN) modelling the propagation of electric impulses in nerve axons, is a simplified version of the Hodgkin-Huxley system. It is given as

$$\partial_t u_1 = \partial_x^2 u_1 + f(u_1) - u_2, 
\partial_t u_2 = \epsilon(u_1 - \gamma u_2),$$
(FHN)

where  $u_1$  is the electrical potential across the axon membrane, and  $u_2$  combines the  $K^+$  and  $Na^+$  channel activation and inactivation gating rates lumped into a single variable.

Furthermore, the parameters  $\epsilon$  and  $\gamma$  are positive and small and

$$f(u_1) := -u_1(u_1 - \alpha)(u_1 - 1), \quad 0 < \alpha < \frac{1}{2}.$$

 $(u_1 \text{ and } u_2 \text{ are fast and slow variables, respectively.})$ 

Here, an axon is again modelled by a straight line.

## Cylindrical FitzHugh-Nagumo system

To take into account the geometry of the axon, namely, a cylindrical cable-like fibre, with electrical signals propagating on its surface, we model it by a cylindrical surface, S, and extend FHN to S as

$$\partial_t u_1 = \Delta_{\mathcal{S}} u_1 + f(u_1) - u_2, \partial_t u_2 = \epsilon(u_1 - \gamma u_2),$$
(FHN-S)

where  $\Delta_S$  denotes the Laplace-Beltrami operator on S and  $\epsilon$ ,  $\gamma$  and f are the same as above, e.g.

$$f(u_1) := -u_1(u_1 - \alpha)(u_1 - 1), \qquad 0 < \alpha < \frac{1}{2}.$$

We call FHN-S the *cylindrical FitzHugh-Nagumo system*. Taking formally  $S = \mathbb{R}$  in FHN-S gives FHN.

## Radial (1D) pulses

A *pulse* is a solution to FHN which is a function of a single variable, z = x - ct, c > 0, vanishing at infinity (trav. wave). If  $0 < \alpha < \frac{1}{2}$ ,  $0 < \gamma < m(\alpha)$ , and  $\epsilon > 0$  is sufficiently small, then FHN has two different pulse solutions: the *fast* pulse with speed

$$c_f(\epsilon) = rac{\sqrt{2}}{2}(1-2lpha) + o(\epsilon),$$



Fig. 7. Comparison of the pulse shapes derived from Hodgkin–Huxley and FitzHugh–Nagumo equations. Pulse solution of the Hodgkin–Huxley Eq. (3) (red curve) with solution of the FitzHugh–Nagumo Eq. (4) (black curve) for T =18.5 °C. In both cases, the pulse speed is 1873 cm/sec and the pulse maximum is 90.6 mV.

Phillipson and Schuster, A comparative study of the Hodgkin-Huxley and Fitzhugh-Nagumo models of neuron pulse propagation. *Intl J Bifurcation Chaos*, (2005).

and a *slow* pulse with speed  $c_s(\epsilon) = O(\sqrt{\epsilon})$ . The fast pulse is stable (in 1D), while the slow pulse is unstable.

### Pulses

Consider FHN-S on the straight cylinder,  $S_R := \mathbb{R} \times RS^1$ , of a constant radius R centered about the x-axis in  $\mathbb{R}^3$ , parametrized as

$$\mathcal{S}_{R} = \left\{ (x, R \cos \theta, R \sin \theta) \in \mathbb{R}^{3} \mid x \in \mathbb{R}, \, \theta \in [0, 2\pi) \right\} \,,$$
 (1)

with the Riemannian area element is  $R d\theta dx$ .

Clearly, FHN-S on  $S = S_R$  is invariant under translations. If  $u(x, \theta, t)$  is a solution, then so are its translates

$$u_h(x, \theta, t) := u(x - h, \theta, t), \quad h \in \mathbb{R}.$$

Each pulse  $\Phi$  on  $S = \mathbb{R}$  defines a smooth axisymmetric traveling wave solution of FHN-S on  $S_R$ :

$$u(x,\theta,t)=\Phi(x-ct).$$

It is a consequence of translation invariance that all translates  $\Phi_h$ of  $\Phi$  are pulses of the same speed c.

## Manifold of pulses (with A. B. and A. T.)

The translates,  $\Phi_h(x) := \Phi(x - h)$ , of the pulse  $\Phi(x)$  form a one-dimensional manifold of pulses

$$\mathcal{M} := \{ \Phi_h \mid h \in \mathbb{R} \} \,. \tag{2}$$

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Let  $H^{k,m}$  be anisotropic Sobolev space on S with the norm  $\|\cdot\|_{k,m}$  and let dist $(v, \mathcal{M}) := \inf_{h} \|v - \Phi_{h}\|_{2,1}$  = distance of v from  $\mathcal{M}$ .

Our first result shows that for a *straight cylinder* there is a tubular neighborhood  $\mathcal{W} = \{w \in H^{2,1} \mid \text{dist}(w, \mathcal{M}) < \eta\}$  of  $\mathcal{M}$  for which

$$\mathsf{dist}(u(t),\mathcal{M}) \leq C_1 e^{-\nu t} \, \mathsf{dist}(u_0,\mathcal{M}) \tag{Stab-Cyl}$$

for all solutions, u(t), with initial values,  $u_0$ , in W.

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As  $t \to \infty$ , each solution converges to a particular traveling pulse

$$\Phi(x-ct-h_*).$$

## Near-pulse solutions (with A. B. and A. T.)

Consider FHN-S on a cylinder  $S_{\rho}$  of variable radius, i.e.  $S_{\rho}$  is defined as a graph over the straight cylinder  $\mathbb{R} \times S^1$  (*warped cyl.*):

$$\mathcal{S}_{
ho} := ig\{(x,
ho(x,\omega))\in \mathbb{R}^3: x\in \mathbb{R}, \ \omega\in \mathcal{S}^1ig\}.$$

When  $\rho$  is non-constant, FHN-S is not expected to have pulse solutions. However, there are near-pulse solutions:

#### Theorem (Near-pulse solutions, warped cylinder)

There are a constant  $\delta_* > 0$  and a tubular neighborhood  $\mathcal{W}$  of  $\mathcal{M}$  s.t. if  $\delta := R^{-1} \| \rho - R \|_{C^2} \leq \delta_*$ , then  $\forall u_0 \in \mathcal{W}$ ,  $\exists$  the unique mild solution u(t) with i.e.  $u_0$  and u(t) satisfies

$$\mathsf{dist}(u(t),\mathcal{M}) \leq M e^{-\xi t} \, \mathsf{dist}(u_0,\mathcal{M}) + M'\delta\,, \tag{3}$$

where, recall,  $\mathcal{M}$  is the manifold of pulses  $\mathcal{M} := \{\Phi_h \mid h \in \mathbb{R}\}.$ 

# Dimensional reduction (with G. K. and K. T.)

Consider FHN-S with  $\rho \in C^2$ , bounded (and radially symmetric) with  $\|\partial_x \rho\|_{L^{\infty}} < \infty$ . Let  $\overline{f}(x) := \frac{1}{2\pi} \int_0^{2\pi} f(x, \theta) d\theta$ . We compare FHN-S with

$$\partial_t w_1 = \Delta_{\rho}^{\rm rad} w_1 + f(w_1) - w_2,$$

$$\partial_t w_2 = \epsilon (w_1 - \gamma w_2),$$
(4)

where  $\Delta_{\rho}^{\text{rad}} = \frac{1}{\sqrt{g}} \partial_x \frac{\bar{\rho}^2}{\sqrt{g}} \partial_x$ ,  $\sqrt{g} = \bar{\rho} \sqrt{1 + \bar{\rho}_x^2}$ . We have:

Theorem (1D effective approximation)

There exist  $r_*$  and  $\delta_*$  s.t., for any  $0 < \rho \leq r_*$ , the strong solution  $\mathbf{u}(t)$  of FHN-S in  $H^{1,0}$ , with an i.c.  $\mathbf{u}_0$  obeying  $\|\mathbf{u}_0 - \bar{\mathbf{u}}_0\|_{1,0} \leq \delta_*$ , and a strong sol.  $\mathbf{w}$  to (4) in  $H^{1,0}_{rad}$ , with  $\delta := \|\bar{\mathbf{u}}_0 - \mathbf{w}_0\|_{1,0} \ll 1$ , satisfy

$$\|\mathbf{u}(t) - \mathbf{w}(t)\|_{1,0} \leq e^{-\kappa t} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} + 2C\,\delta,$$
 (5)

for some C > 0 independent of  $\epsilon$  and the existence time interval and  $\kappa \propto \frac{\gamma}{2} \epsilon$ . 1st step: Spontaneous symmetrization [KTS]

Recall  $\overline{f}(x) := \frac{1}{2\pi} \int_0^{2\pi} f(x, \theta) d\theta$ . In the first step, we prove

Theorem (Radial collapse theorem (RCT)) Under the conditions of the previous theorem, any strong solution  $\mathbf{u}(t)$  to FHN-S in H<sup>1,0</sup> satisfies the estimate

$$\|\mathbf{u}(t) - \bar{\mathbf{u}}(t)\|_{1,0} \leq C e^{-\lambda t} \|\mathbf{u}_0 - \bar{\mathbf{u}}_0\|_{1,0},$$
 (6)

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where  $\lambda := \frac{\gamma}{2} \epsilon$  and C > 0 is a const. independent of  $\epsilon$  and the existence time interval.

This result shows that the signal intensity is close to its sectional average which is measured in experiments.

# Idea of proof of RCT, general approach

Let  $\mathcal{M}$  be a manifold of radial functions from  $H^{1,0}$ . Look for a solution near  $\mathcal{M}$  as a point  $\chi \in \mathcal{M}$  plus a transversal fluctuation:

$$\mathbf{u} = \chi + \mathbf{v}, \qquad \chi \in \mathcal{M}, \qquad \mathbf{v} \perp \mathcal{M}. \tag{7}$$

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Plugging (7) into FHN-S and projecting onto  $T_{\chi}\mathcal{M}$  and  $T_{\chi}^{\perp}\mathcal{M}$ 

$$\implies \partial_t \chi = f(\chi, \nu) \quad \text{and} \quad \partial_t \nu = L \nu + N(\nu, \chi).$$

Here L is the linearization of FHN-S about the approximate solution  $\chi$  and  $N(v, \chi)$  is the nonlinear part.

To estimate the fluctuation  $v(t) \equiv \mathbf{u}(t) - \chi(t)$ , we use spectral gap estimates for the non self-adjoint operator-matrix L and differ. ineq. for quadratic functionals to obtain

$$\|v(t)\|_{1,0} \leq C e^{-\lambda t} \|v_0\|_{1,0}.$$

### Proving effective approx. thm.: Guided stability argum. By the radial collapse theorem (RCT), we have the estimate

$$\|\mathbf{u}(t) - \bar{\mathbf{u}}(t)\|_{1,0} \leq C e^{-\lambda t} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0},$$
 (8)

where  $\lambda := \frac{\gamma}{2} \epsilon$ , provided  $\mathbf{w}_0$  is s.t.  $\|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} \le \|\mathbf{u}_0 - \bar{\mathbf{u}}_0\|_{1,0}$ . Next, similarly to RCT, we prove the effective approx. estimate

$$\|\bar{\mathbf{u}}(t) - \mathbf{w}(t)\|_{1,0} \leq C e^{\mu t} \delta, \qquad (9)$$

where  $\delta := \| \bar{\mathbf{u}}_0 - \mathbf{w}_0 \|_{1,0}$ . Choose  $\tau$  so that  $C \ e^{-\lambda \tau} = 1/2$ .



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### Proving effective approx. thm.: Guided stability argum. By the radial collapse theorem, we have the estimate

$$\|\mathbf{u}(t) - \bar{\mathbf{u}}(t)\|_{1,0} \leq C' e^{-\lambda t} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0},$$
 (10)

where  $\lambda := \frac{\gamma}{2} \epsilon$ , provided  $\mathbf{w}_0$  is s.t.  $\|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} \le \|\mathbf{u}_0 - \bar{\mathbf{u}}_0\|_{1,0}$ . Next, similarly to the radial collapse theorem, we prove

$$\|\bar{\mathbf{u}}(t) - \mathbf{w}(t)\|_{1,0} \leq C'' e^{\mu t} \delta,$$
 (11)

where  $\delta := \|\mathbf{\bar{u}}_0 - \mathbf{w}_0\|_{1,0}$ . Choose  $\tau$  so that  $C' e^{-\lambda \tau} = 1/2$ .

Let  $C := C'' e^{\mu \tau}$ . Then, estimates (10) and (11) yield

$$\|\mathbf{u}(\tau) - \mathbf{w}(\tau)\|_{1,0} \leq 2^{-1} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} + C \delta.$$
 (12)

Iterating (12), using the semi-group property of the flow, yields

$$\|\mathbf{u}(k\tau) - \mathbf{w}(k\tau)\|_{1,0} \leq 2^{-k} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} + 2C \delta.$$

Interpolating this, we obtain

$$\|\mathbf{u}(t) - \mathbf{w}(t)\|_{1,0} \leq e^{-\kappa t} \|\mathbf{u}_0 - \mathbf{w}_0\|_{1,0} + 2C\delta.$$
(13)

## Summary

We discussed

- An extension of the FitzHugh-Nagumo system (FHN) to warped cylindrical surfaces
- Existence and stability of pulse-like solutions on surfaces of warped cylinders ([BST]: nearly radial pulses surrounded by small fluctuations propagate along the cylindrical axis, as in the case with real axons)
- Approximation of solutions of the 2D surface system by solutions of an effective 1D system ([KTS]: any strong solution u(t) of FHN-S can be approximated by a strong solution w(t) of an effective system in 1D)

### Previous works

There is a huge computational literature on the classical 1D FHN system, see Cebrián-Lacasa et al, Six decades of the FitzHugh–Nagumo model, Phys Rep 1096 (2024). (323 references and counting)

There is also a rich mathematical literature for this system, see KTS, J. Nonlin. Scie. 2025 for a review and references.

For higher dimensions, Tsujikawa, Nagai, Mimura, Kobayashi and Ikeda considered the FHN in  $\mathbb{R}^n = \mathbb{R}^{n-1} \times \mathbb{R}$  with periodic conditions in  $\mathbb{R}^{n-1}$  and proved stability of fast pulse solutions propagating along the axis  $\mathbb{R} = (\mathbb{R}^{n-1})^{\perp}$ .

Similar equations on compact surfaces in R<sup>3</sup> appear in cellular electrophysiology, with existence theory developed in Franzone, Savare, Amar, Andreucci, Bisegna, Gianni, Veneroni, Matano, Mori and others.

## Open problems

- Extension of the result above to a wider class of warped cylinders.
- Derivation of dynamical equations for the pulse centre.
- Adiabatic approximation and the derivation of FHN.
- Dynamic geometry coupled to the electric potential  $u_1$ .
- Stochastic FHN (internal and external noise, random geometry, random firing).
- Derivation of the FHN system (heuristic and microscopic).
- Relation to quantum noise! (Comput. Structural Biotech. J. 30 (2025))

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- Hodgkin-Huxley system



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#### Thank-you for your attention