Ignition of waves in excitable systems

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Soft Tissue Modelling 3
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Bezekci, Idris, Simitev, Biktashev, PRE (2015)
Motivation

Excitable systems are widespread in nature

- Nerve electrical excitation;
- Cardiac electrical excitation;
- Other biological signalling waves;
- Phase transitions; Domain wall movement in liquid crystals;
- Combustion and other chemical reaction waves and oscillations:
  - the Briggs–Rauscher reaction
  - the Belousov–Zhabotinsky reaction

Excitability

An excitable system is a non-equilibrium dynamical system that has the capacity to generate and propagate a wave as a result of a sufficiently strong stimulus.
**Mathematical problem**

Classify initial conditions into

- “DECAY” initial conditions that DO NOT lead to the generation of a wave;
- “IGNITION” initial conditions that DO lead to the generation of a wave.

**Mathematical challenge**

This problem is difficult as it is essentially non-stationary, spatially-extended and nonlinear, and does not have any helpful symmetries.

**Outline**

- We propose a practical method of finding the ignition criteria analytically or semi-analytically.
- The method is illustrated on the Nagumo equation - a model with simple explicit solution.
The FitzHugh-Nagumo model

Numerical illustration of ignition in the FitzHugh-Nagumo model.

Model equations
The FHN is the archetypal excitable system

\[ u_t = f(u) - v + u_{xx}, \quad f(u) = u(u - \theta)(1 - u), \]
\[ v_t = \varepsilon(\alpha u - v), \]

where \( \alpha > 0, \theta \in (0, 1/2) \), and \( 0 < \varepsilon \ll 1 \), is a small parameter.

Domain
First quadrant: \((x, t) \in [0, \infty) \times [0, \infty)\).

Boundary conditions: “stimulation by current”
A current injection at \( x = 0 \) of amplitude \( I_s \) and duration \( t_s \)

\[ u_x(0, t) = I_s \Theta(t_s - t). \]

(Equivalent to including a stimulus current \( I_s \Theta(t_s - t)\delta(x) \) in the equations.)

Initial conditions: “stimulation by voltage”
A rectangular perturbation in voltage of amplitude \( u_s \) and length \( x_s \)

\[ u(x, 0) = u_s \Theta(x_s - x), \quad v(x, 0) = 0 \]

where \( \Theta(\cdot) \) is the Heaviside step function.
Numerical experiments (stimulation by voltage)

Fig. Response to slightly below-threshold (a,c) and slightly above-threshold (b,d) amplitudes.

<table>
<thead>
<tr>
<th>$x_S$</th>
<th>$u_S$</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 2.1</td>
<td>0.431929399574766</td>
<td>decay</td>
</tr>
<tr>
<td>(b) 2.1</td>
<td>0.431929399574768</td>
<td>ignition</td>
</tr>
<tr>
<td>(c) 10.</td>
<td>0.191802079312694</td>
<td>decay</td>
</tr>
<tr>
<td>(d) 10.</td>
<td>0.191802079312696</td>
<td>ignition</td>
</tr>
</tbody>
</table>

Observation

The rectangular initial conditions morph into a slow, low-amplitude propagating pulse that becomes unstable and subsequently either decays or evolves into a fast, high-amplitude stable propagating pulse.

Conjecture

The low-amplitude slowly propagating pulse is an unstable equilibrium with a stable manifold that serves as the threshold hypersurface dividing the phase space into decay and initiation domains.
**Nagumo equation**

In the limit of $\varepsilon \to 0$ the FHN problem reduces to the Nagumo problem

$$
\begin{align*}
    u_t &= u_{xx} + u(u - \theta)(1 - u), \quad (x,t) \in [0,\infty) \times [0,\infty), \\
    u(x,0) &= u_s \Theta(x_s - x), \\
    u_x(0,t) &= I_s \Theta(t_s - t).
\end{align*}
$$

**Existence of travelling front solutions**

The Nagumo equation has a travelling front solution,

$$
U = \frac{1}{1 + e^{\xi / \sqrt{2}}}, \quad c = \frac{1 - 2\theta}{\sqrt{2}}, \quad \xi = x - ct.
$$

**Decay and ignition**

For given parameter values $u_s, x_s, I_s$ and $t_s$, the Nagumo problem produces either

- “decay” solution s.t. $\max_x u(x,t) \to 0$, as $t \to \infty$, or
- “initiation” solution s.t. $\max_x |u(x,t) - U(x - ct)| \to 0$ as $t \to \infty$.

**Critical ignition curves**

Find a condition that for given $u_s, x_s, I_s$ and $t_s$ predicts if the “decay” or the “ignition” outcome will take place.

- Strength-duration curve – the curve in the $(t_s,I_s)$ plane, at $u_s = 0$, separating the two outcomes.
- Strength-extent curve – the curve in the $(x_s,u_s)$ plane, at $I_s = 0$, separating the two outcomes.
The critical nucleus of the Nagumo equation

The critical nucleus

The stationary Nagumo problem, $u''_* + f(u_*) = 0$, has a non-trivial standing wave solution

$$u_*(x) = 3\theta \sqrt{2} \left[ (1 + \theta) \sqrt{2} + \cosh(x \sqrt{2}) \sqrt{2 - 5\theta + \theta^2} \right]^{-1}.$$ 

Stability of the critical nucleus

The critical nucleus $u_*(x)$ is a saddle equilibrium point with only one unstable direction.

Proof.

- Linearise the Nagumo equation near $u_*(x)$,
  $$v_t = \mathcal{L}v = \left[ \partial_x^2 + f'(u_*(x)) \right]v, \text{ where } v(x,t) = u(x,t) - u_*(x) \ll 1 \text{ is a small perturbation.}$$

- Stability of $u_*$ is determined by the spectrum of $\mathcal{L}$, $\mathcal{L}\phi_j = \lambda_j \phi_j$

- $\mathcal{L}$ is a Sturm-Liouville operator so all of its eigenvalues $\lambda_j$ are real.

- Order eigenvalues in descending order $\lambda_1 > \lambda_2 > \lambda_3 > \ldots$, then by Sturm’s oscillation theorem, the eigenfunction $\phi_j$ has precisely $j - 1$ zeros.

- Notice that $u'_*(x)$ is an eigenfunction corresponding to eigenvalue 0, since $\mathcal{L} \partial_x u_* = 0$.

- The critical nucleus $u_*(x)$ is an even function and has a single maximum at $x = 0$, so $u'_*(x)$ has exactly one zero, and therefore we have $u'_*(x) \propto \phi_2$ with $\lambda_2 = 0$.

- So there is exactly one positive eigenvalue, $\lambda_1 > 0$ which implies that $u_*$ is unstable.
The critical nucleus $u_*$ has a stable manifold with codimension one and which thus partitions the phase space to two regions (decay and ignition).

A one-parametric family of rectangular initial conditions, (say fixed $x_S > 0$ and parameter $u_S$), will cross the stable manifold once, say at $u_S = u_s^*(x_S)$. For $u_S < u_s^*(x_S)$, we have decay, and for $u_S > u_s^*(x_S)$ initiation. This defines the strength-extent curve $u_S = u_s^*(x_S)$.

The role of the stable manifold as the threshold surface is an empirically observable fact – it means that the critical nucleus will be observed as a transient for any initial conditions sufficiently close to the threshold.

**Fig.** Sketch of a stable manifold of the critical nucleus of the Nagumo equation.
The strength-extent curve is the critical curve in the case of stimulation by voltage \( u_s \neq 0, I_s = 0 \)

- The solution of the linearized problem is
  
  \[ v(x,t) = u - u_\ast = \sum_{j=1}^{\infty} a_j e^{\lambda_j t} \phi_j(x), \]

  with coefficients given by
  
  \[ a_j = \int_{-\infty}^{\infty} \phi_j(x) \left( u(x,0) - u_\ast(x) \right) dx. \]

- \( a_2 = 0 \), since eigenfunction \( \phi_2(x) = u'_\ast(x) \) is odd, while \( u_\ast(x) \) and \( u(x,0) \) are even. \( \sum_{j=3}^{\infty} a_j e^{\lambda_j t} \phi_j(x) \to 0 \) as \( t \to \infty \) since \( \lambda_j \leq \lambda_3 < 0 \) for \( j \geq 3 \).

- Hence \( u(x,t) \to u_\ast(x) \) if and only if \( a_1 = 0 \). This gives the equation of the stable space
  
  \[ a_1 = \int_{0}^{\infty} \phi_1(x) \left( u_s \Theta(x - x_s) - u_\ast(x) \right) dx = 0. \]

- This is a finite equation for \( x_s, u_s \), which provides the desired analytical definition of the strength-extent curve.
The strength-duration curve is the critical curve in the case of ... 

**stimulation by current** $u_s = 0, I_s \neq 0$

- The solution of the linearized problem is

$$v(x,t) = u - u_\ast = \sum_{j=1}^{\infty} A_j(t) \phi_j(x).$$

with coefficients defined by

$$A_j(0) = \int_{-\infty}^{\infty} \phi_j(x) \left( u(x,0) - u_\ast(x) \right) \, dx,$$

$$\frac{dA_j}{dt} = \lambda_j A_j + 2I_s \Theta(t_s - t) \phi_j(0),$$

upon projection and upon substitution in the problem, respectively.

- Similarly to the strength-extent case the critical condition is $A_1(+\infty) = 0$, or the strength-duration curve is given by

$$A_1(0) + 2I_s \phi_1(0) \int_{0}^{\infty} e^{-\lambda_1 t} \Theta(t_s - t) \, dt = 0.$$
**Quadratic kinetics, \( f(u) = u(u - \theta) \)**

- Consider the case \( \theta \ll 1 \), then \( u_* = O(\theta) \) so \( u \leq \theta \) and hence we can approximate
  \[
  f(u) \approx u(u - \theta)
  \]

- Then the critical nucleus is
  \[
  u_* \approx \frac{3}{2} \theta \sech^2 \left( x \sqrt{\theta}/2 \right).
  \]

- The only positive eigen-pair is
  \[
  \lambda_1 = \frac{5}{4} \theta, \quad \phi_1(x) = \sech^3 \left( x \sqrt{\theta}/2 \right).
  \]

- Explicit equation for the strength-extent curve
  \[
  u_s = \frac{9}{8} \theta \left[ \frac{2}{\pi} \tanh \left( \frac{x_s \sqrt{\theta}}{2} \right) \sech \left( \frac{x_s \sqrt{\theta}}{2} \right) + \frac{4}{\pi} \arctan \left( e^{x_s \sqrt{\theta}/2} \right) - 1 \right]^{-1}.
  \]

- Explicit equation for the strength-duration curve
  \[
  I_s = I_{rh} \left[ 1 - e^{-t_s/\tau} \right]^{-1}, \quad I_{rh} = \phi_1(0) \left[ \lambda_1 \int_0^\infty \phi_1(x) u_*(x) \, dx \right]^{-1} = \frac{45}{64} \pi \theta^{3/2}, \quad \tau = \frac{1}{\lambda_1} = \frac{4}{5\theta}.
  \]

This is a classical empirical result known as the Lapicque-Blair-Hill equation

(Lapicque, 1907; Blair, 1932; Hill, 1936).
Comparison with numerical simulations

Fig. Comparison of the analytical results with numerical simulations at $\theta = 0.1$.
(a) Strength-extent curves for stimulation by voltage with rectangular stimuli.
(b) Strength-duration curves for stimulation by current with rectangular stimuli.

Red solid lines: analytical approximations for quadratic kinetics.
Blue stars (“cub“): numerical results for cubic kinetics.
Magenta diamonds (“quad“): numerical results for quadratic kinetics.
Summary

- Outlined a semi-analytical approach to establishing conditions of ignition of propagating waves in excitable and bistable systems.
  
  - The approach is based on linearization of the stable manifold of a certain critical solution about its linear tangent stable space.
  
  - Previously any such criteria were obtained experimentally or numerically and any analytical expression was constructed by parameter fitting.

- Obtained explicit analytical expressions for the ignition criteria in a specific simple example.
  
  - The expression for the strength-duration curve is coincides precisely with a classical form (the Lapicque-Blair-Hill formula) used for over 100 years for analytical fitting of empirical data.
  
  - The expression for the strength-extent curve is new.

Reference

Extensions of the method

Generalizations

- Generalized to a wider class of excitable systems:
  - multicomponent reaction-diffusion systems;
  - systems with non-self-adjoint linearized operators;
  - systems with moving critical solutions (critical fronts and critical pulses).

- Generalized to higher-order approximation of the stable manifold:
  - a quadratic approximation (resulting in a significant increase in accuracy).

- Applied to more physiologically realistic models:
  - the Beeler-Reuter ventricular myocite model.

Reference