Mathematical analysis of a 3D model of cellular electrophysiology

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joint work with

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Elliptic and Parabolic PDEs and Related Topics

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Outline of the talk

1. Introduction:
   background

2. 1D model vs 3D model
   mathematical difficulty

3. Quasi-positivity principle

4. Uniform bounds and global existence

5. Properties of the global attractor

6. The case of infinite cylinder

1. Introduction:

Background

The neuronal axon

神経軸索

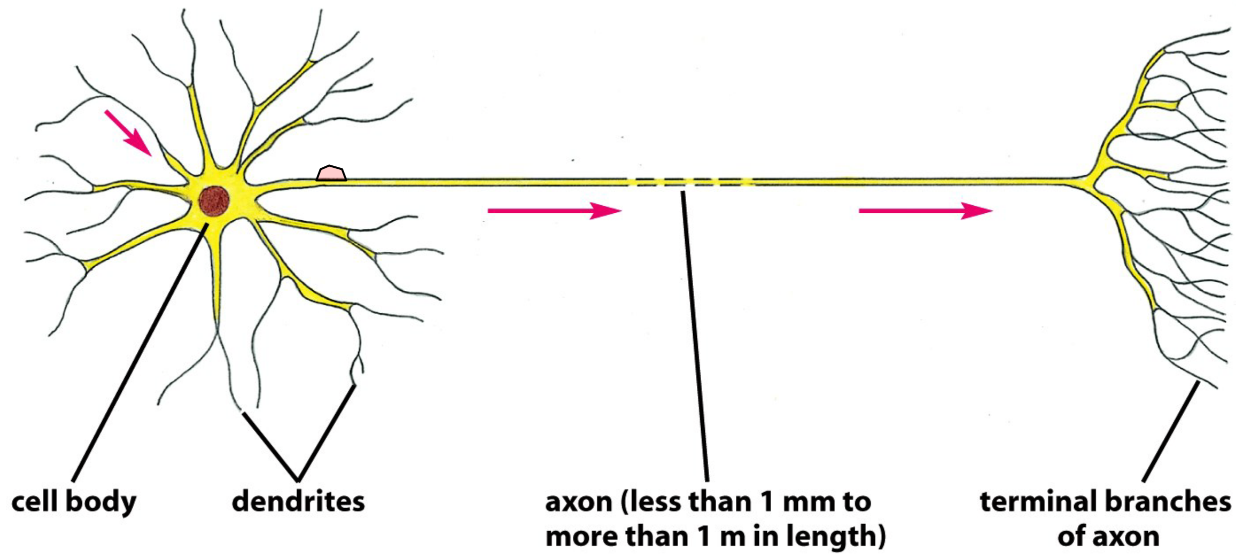


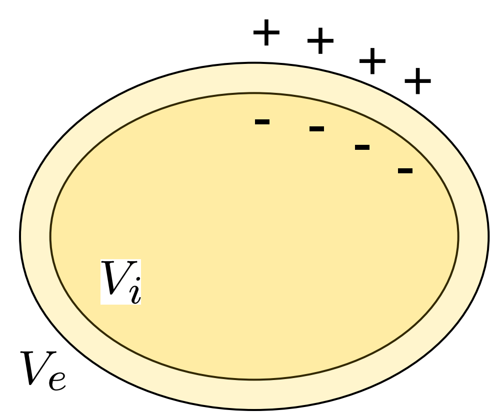
Figure 11-28 Molecular Biology of the Cell 5/e (© Garland Science 2008)

- A neuron has a long thin axon acting as a “wire” along which electrical signals travel.

- Signal = progressive change in the membrane potential.

$$V = V_i - V_e$$

膜電位



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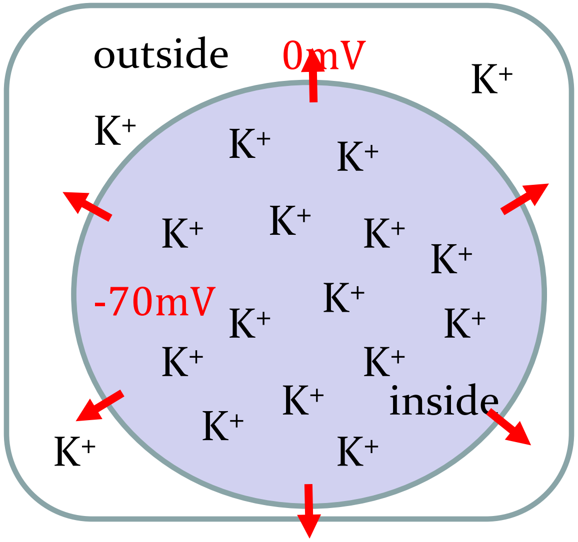
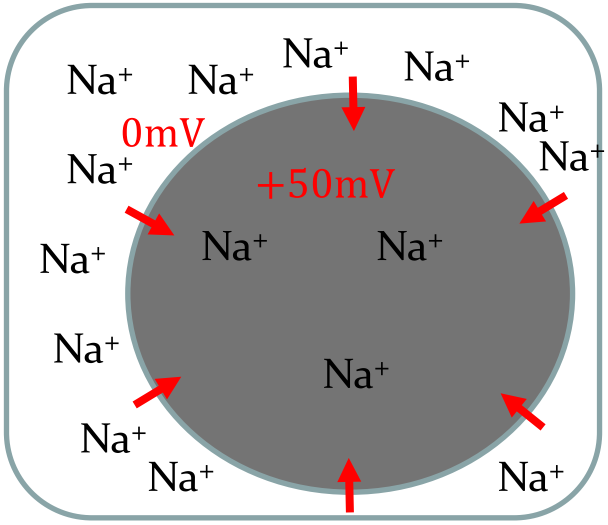
Ion channels and membrane potential

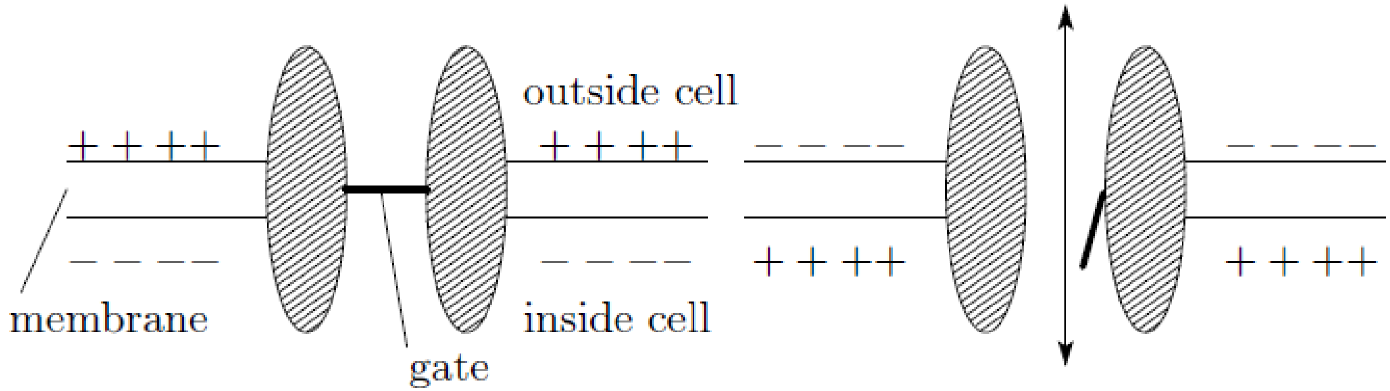




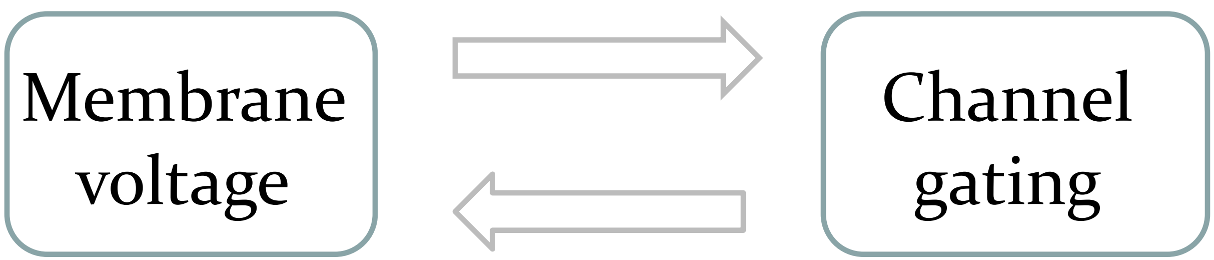
- K channels $\xrightarrow{\text{open}}$ negative membrane potential.
- Na channels $\xrightarrow{\text{open}}$ positive membrane potential.

- One can change the membrane potential by controlling the relative number of (open) Na and K channels.

Opening and closing of channels



- Some channels open or close in response to membrane voltage (channel gating).
- Membrane voltage is controlled by the channel gating.



Propagation of action potential

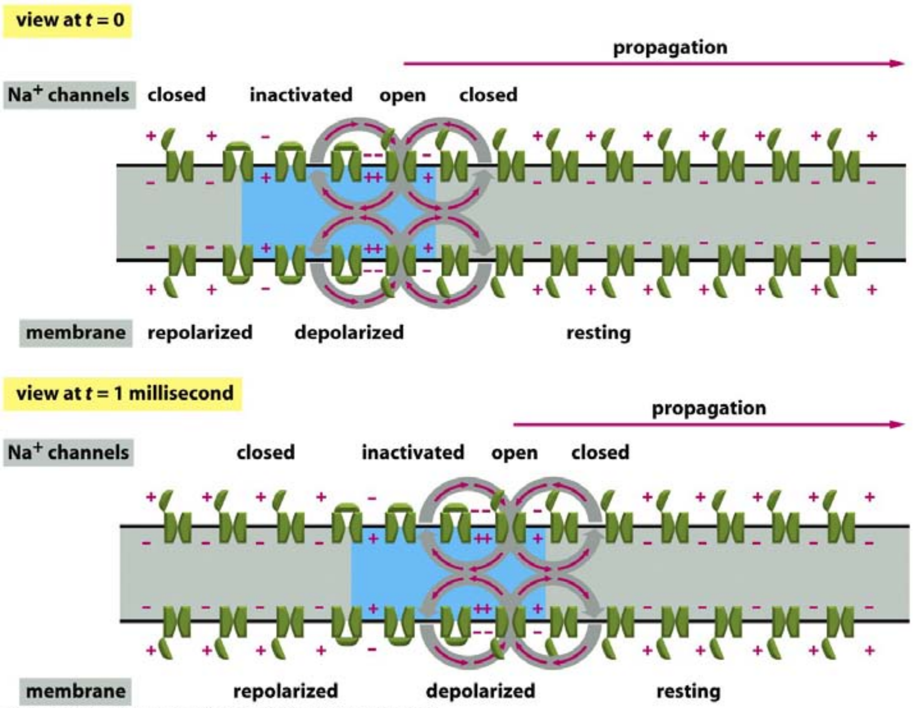


Figure 11-30b Molecular Biology of the Cell 5/e (© Garland Science 2008)

- Na channels open, leading to elevated voltage
- Elevated voltage in a neighboring region leads to Na channel opening.

J.P. Keener & J. Sneyd,

Mathematical Physiology, Springer , 1998.

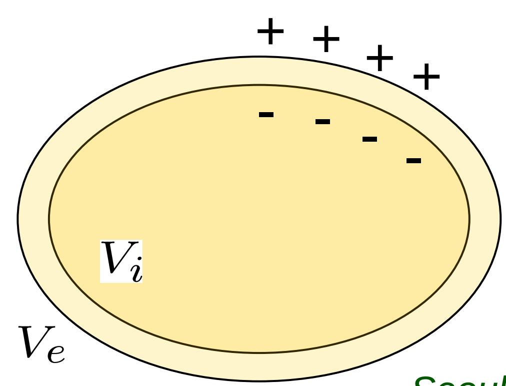
Hodgkin-Huxley model

$$C_\mathrm{m}\frac{\partial V}{\partial t} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} - G_{Na}m^3h(V - V_{Na}) - G_K n^4(V - V_K) - G_L(V - V_L)$$
$$\frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n$$
$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h$$

- Through careful experimentation on squids (squid giant axon), Hodgkin and Huxley derived a set of equations that describe action potential propagation in 1952 (Nobel prize 1963).

Q

What if we take into account the 3D structure of the cell?



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2. 1D and 3D models

mathematical difficulty

Hodgkin-Huxley model

$$C_m \frac{\partial V}{\partial t} = \frac{a}{2R} \boxed{\frac{\partial^2 V}{\partial x^2}} - G_{Na} m^3 h (V - V_{Na}) - G_K n^4 (V - V_K) - G_L (V - V_L)$$

$$\frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V) m$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V) n$$

$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V) h$$

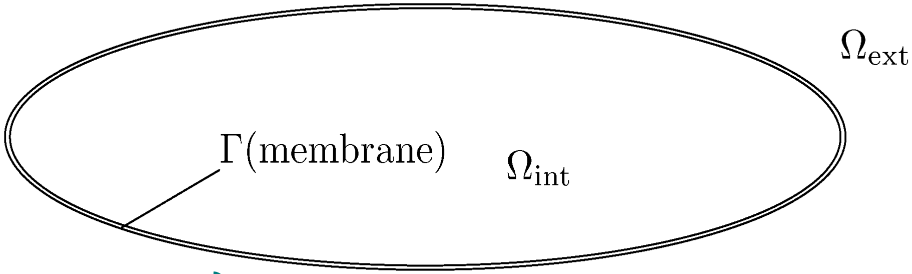
FitzHugh-Nagumo model

$$\begin{cases} \dfrac{\partial u}{\partial t} = \boxed{\dfrac{\partial^2 u}{\partial x^2}} + f(u) - \gamma v \\ \dfrac{\partial v}{\partial t} = \alpha u - \beta v \end{cases}$$

1D cable model

3D model

v = membrane potential



$$\begin{cases} \Delta v_i = 0 \quad \text{in } \Omega_i \\ \Delta v_e = 0 \quad \text{in } \Omega_e \\ \dfrac{\partial v_i}{\partial \mathbf{n}} = \sigma \dfrac{\partial v_e}{\partial \mathbf{n}}, \quad v \equiv v_i - v_e \quad \text{on } \Gamma \\ v_e(x) \to 0 \quad \text{as } |x| \to \infty \\ \dfrac{\partial v}{\partial t} - f(v,w) = -\dfrac{\partial v_i}{\partial \mathbf{n}} \quad \text{on } \Gamma \\ \dfrac{\partial w}{\partial t} = g(v,w) \quad \text{on } \Gamma. \end{cases}$$

To determine v_i, v_e from v.

To determine the evolution of v, w.

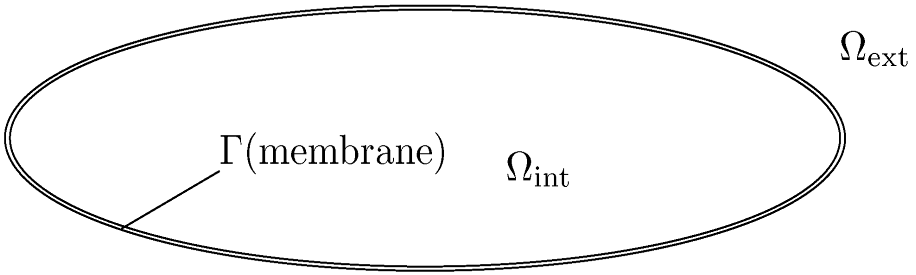
⇩

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$

$$\Lambda : v \mapsto \frac{\partial v_i}{\partial \mathbf{n}}$$

Equation on Γ

The operator Λ



Assume $\sigma = 1$

$$(\Lambda u)(x) = \int_{\Gamma} K(x,y)u(y)dS_y$$

$$K(x,y) = \frac{1}{4\pi|x-y|^3}\Big(-\mathbf{n}_x\cdot\mathbf{n}_y + 3(\mathbf{n}_x\cdot\hat{\mathbf{r}})(\mathbf{n}_y\cdot\hat{\mathbf{r}})\Big), \quad \hat{\mathbf{r}} = \frac{x-y}{|x-y|}.$$

pseudo-differential operator (non-local operator)

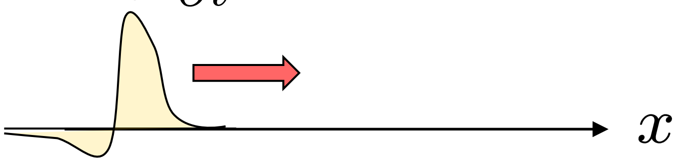
$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$

pseudo-differential equation on **Γ**

Hodgkin-Huxley, FitzHugh-Nagumo

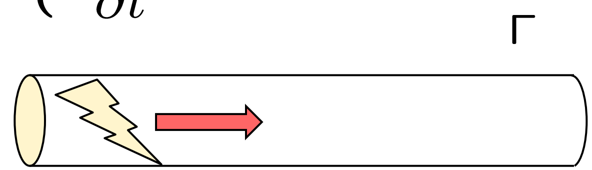
1D Cable model

$$\begin{cases} \dfrac{\partial v}{\partial t} = \dfrac{\partial^2 v}{\partial x^2} + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



3D Cable model

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



GOAL

1. To prove well-posedness of the 3D model (existence local in time, uniqueness).
2. To prove uniform bounds and global existence.
3. Asymptotic smoothing
4. Small diameter limit. (3D $\Rightarrow$ 1D ?)

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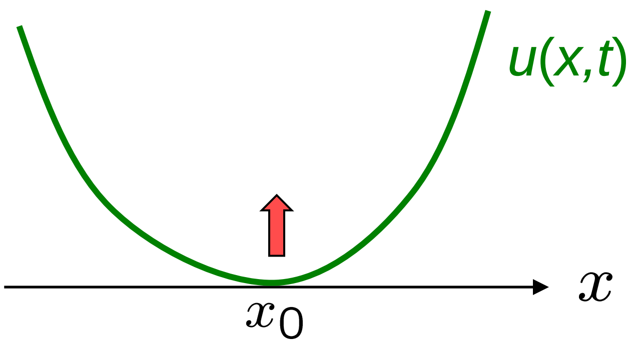
Reason for difficulty in the 3D model

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + f(v,w)$$

maximum principle

positivity preservation



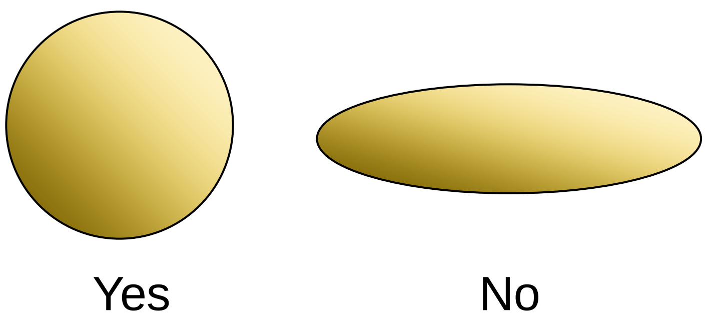
$$u \geq 0,\ \ u(x_0) = 0 \ \ \Rightarrow \ \ u''(x_0) \geq 0$$

$$\frac{\partial v}{\partial t} = -\Lambda v + f(v,w)$$

No maximum principle
(in general)

positivity not
necessarily preserved

except when Γ is
close to a sphere



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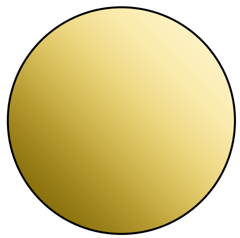
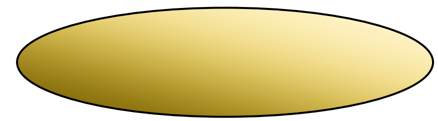
Effect of the shape of Γ

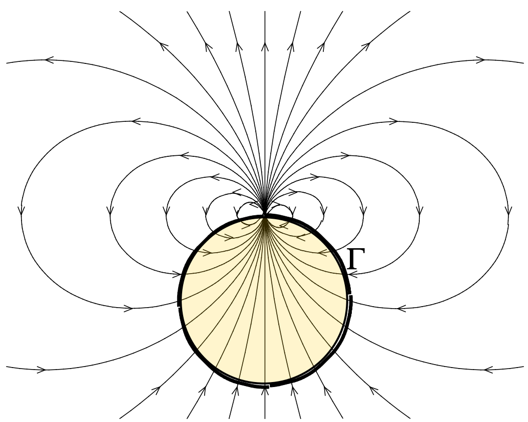
$$\frac{\partial v}{\partial t} = -\Lambda v + f(v, w)$$



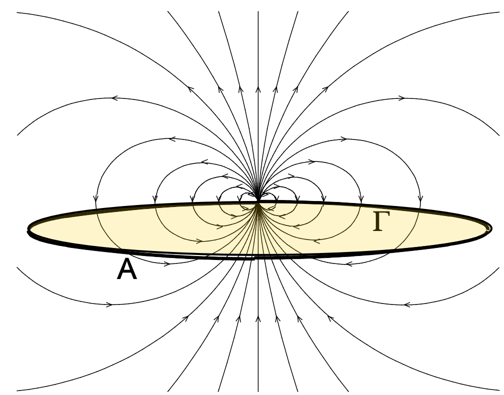
Λ positive operator



Λ not positive



The lines of electric force of each dipole on Γ intersect Γ only once.



The lines of electric force of some dipole intersects Γ more than once.

Classical method of "invariant rectangle"

Based on the maximum principle

FitzHugh-Nagumo

$$\begin{cases} \dfrac{\partial v}{\partial t} = \dfrac{\partial^2 v}{\partial x^2} + f(v) - \gamma w \\ \dfrac{\partial w}{\partial t} = \alpha v - \beta w \end{cases}$$

Solution confined in the rectangle

⇩

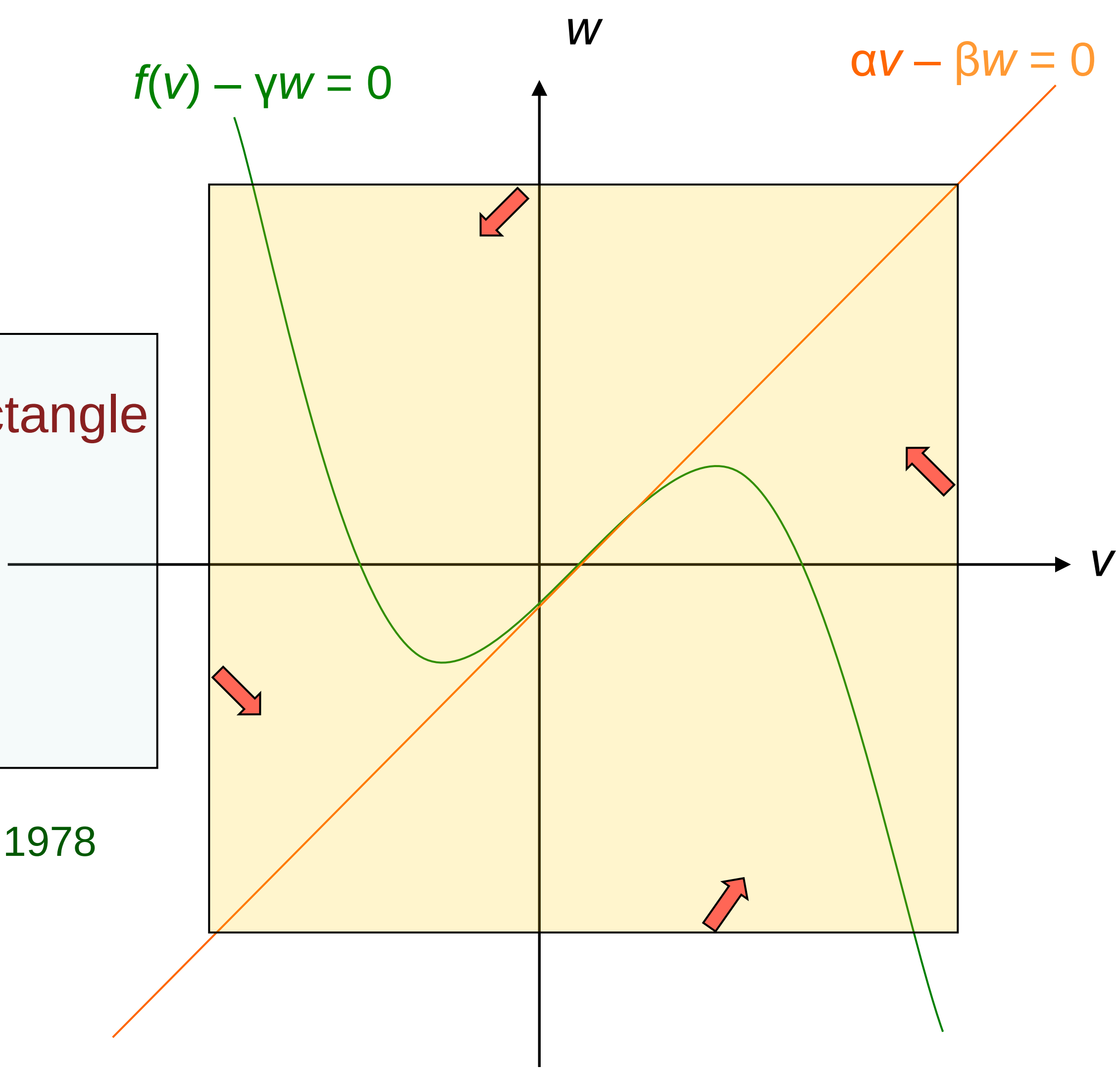
Uniform bound

⇩

Global existence

Mimura 1976 Rauch-Smoller 1978

This argument does not work for the 3D model !



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3. Quasi-positivity principle

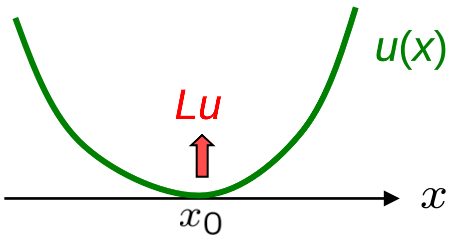
擬正値性原理

Quasi-positivity　擬正値性

K: compact set,　$L: C(K) \to \mathbf{R}$ densely defined,　domain $\mathcal{D}(L)$

Def. 1 (positivity)

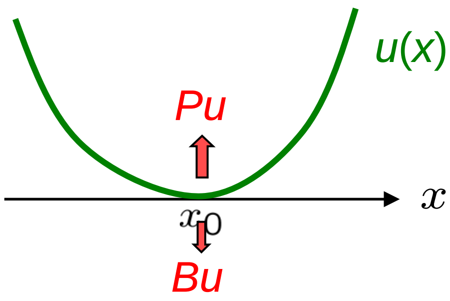
$^\forall u \in \mathcal{D}(L)$, $u \geq 0$, $u(x_0) = 0$　　$(Lu)(x_0) \geq 0$



The semigroup e^{tL} preserves positivity.

$$\frac{du}{dt} = Lu,\ u(0) = u_0 \geq 0 \ \Rightarrow\ u(t) := e^{tL}u_0 \geq 0.$$

Def. 2 (quasi-positivity)



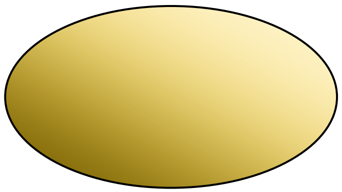
$L = P - B$,　$^\exists P$: positive, $^\exists B$: bounded

$$\beta(L) := \inf \|B\|_{C(K)}$$

"non-positivity index"

$$L: \text{ positive } \Leftrightarrow \beta(L) = 0$$

Estimate of the non-positivity index $\beta(-\Lambda)$ （非正值指数）



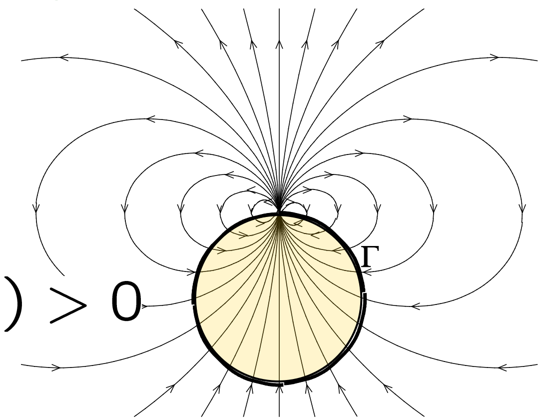
ellipsoid

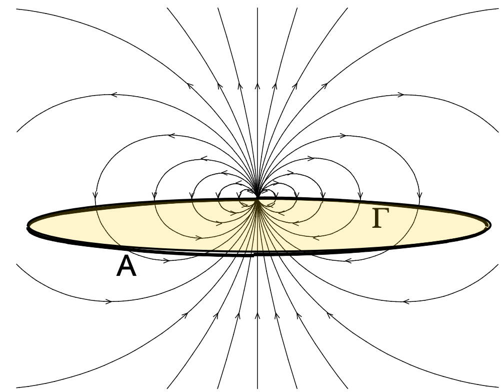
$$\beta(-\Lambda) = 0 \iff \frac{r_{\max}}{r_{\min}} \le \sqrt{2} + \sqrt{3}$$

Λ positive

torus

$$\beta(-\Lambda) > 0$$





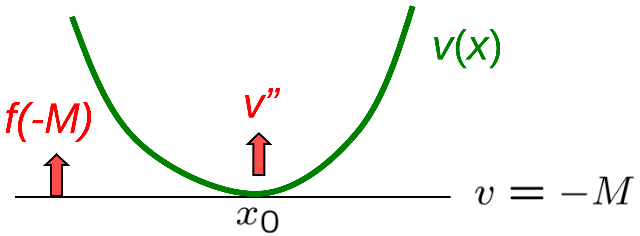
In general, $\beta(-a\Lambda) = a^{-1}\,\beta(-\Lambda) \quad (a > 0)$

The bigger the size of the cell, the smaller the non-positivity index.

Proposition. $-\Lambda$ is quasi-positive on $C(\Gamma)$.

1D model

$$\begin{cases} \dfrac{\partial v}{\partial t} = \dfrac{\partial^2 v}{\partial x^2} + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



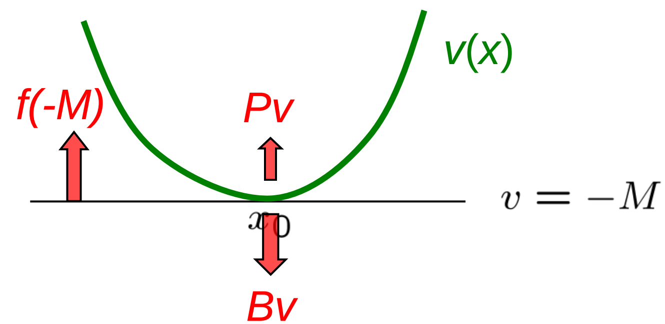
$$f(-M) \geq 0 \;\Rightarrow\; v \geq -M$$

⇩

uniform bound

3D model

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



$$f(-M) \geq \beta(\Lambda)\|v\| \;\Rightarrow\; v \geq -M$$

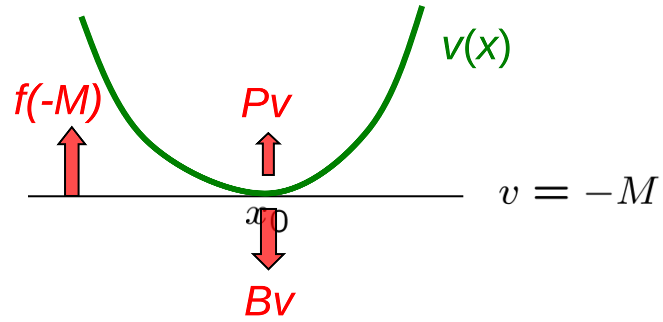
⇩

uniform bound

4. Uniform bounds and global existence

3D model

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



$$f(-M) \geq \beta(\Lambda)\|v\| \;\Rightarrow\; v \geq -M$$

⇩

uniform bound

3D FitzHugh-Nagumo

$$\begin{cases} \dfrac{\partial u}{\partial t} = -\Lambda u + f(u) - \gamma v \\ \dfrac{\partial v}{\partial t} = \alpha u - \beta v \end{cases}$$

⇨ The above argument gives uniform bound of the solution.

$$f(s)/s \to -\infty \quad (s \to \pm\infty)$$

f is superliner in the negative direction

Hodgkin-Huxley

$$C_{\mathrm{m}}\frac{\partial V}{\partial t} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} - G_{Na}m^3h(V - V_{Na}) - G_K n^4(V - V_K) - G_L(V - V_L)$$

$$\frac{\partial m}{\partial t} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h$$

The kinetics not superliner but Lipschitz

Standard a priori estimates	⇨	uniform bounds
Standard a priori estimates + Quasi-positivity	⇨	cell-size independent uniform bounds

Modified invariant rectangle method

3D FitzHugh-Nagumo

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v) - \gamma w \\ \dfrac{\partial w}{\partial t} = \alpha v - \beta w \end{cases}$$

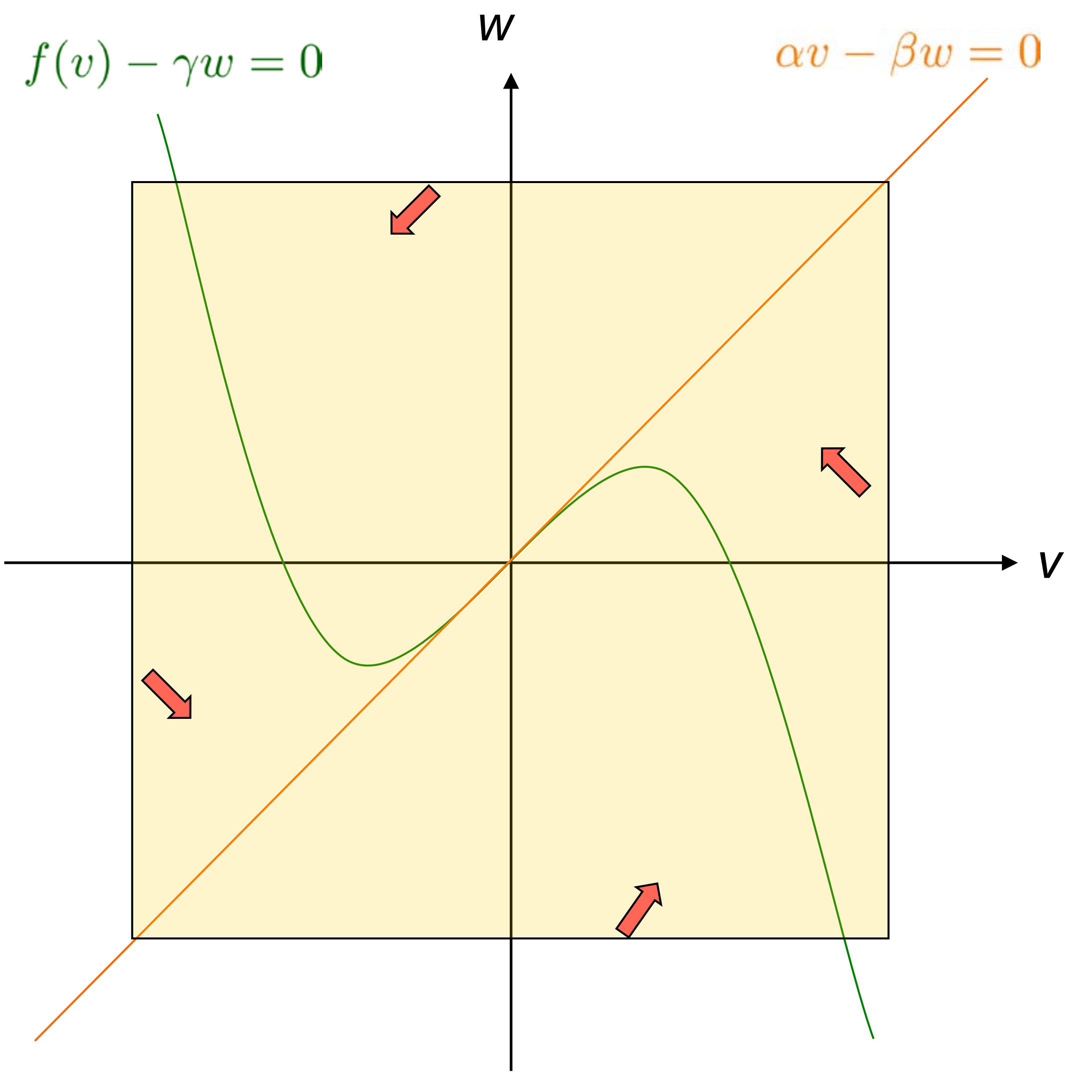
The vector field points inward "strongly enough" along the boundary of the rectangle

⇩

Boundedness of the solution

⇩

Time-global existence



5. Asymptotic smoothing effect and the global attractor

3D model

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$

Note: Λ has a smoothing effect.

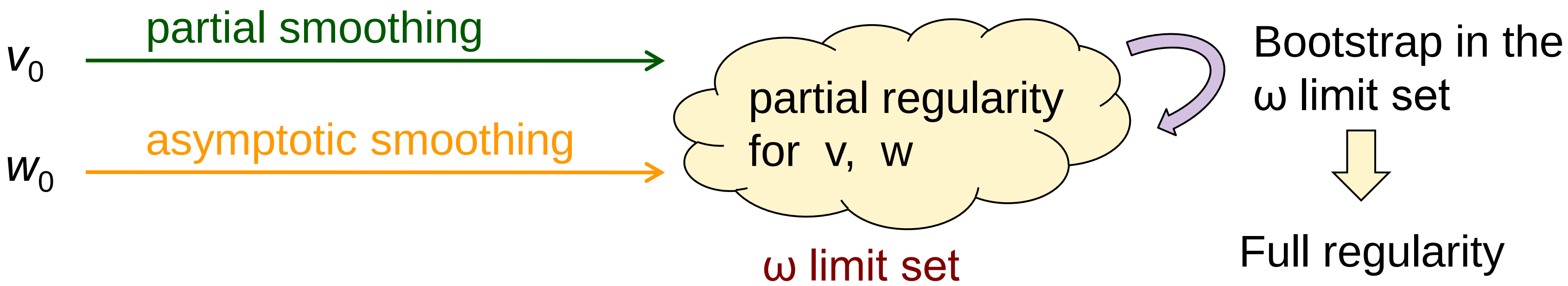
But there is no immediate smoothing for *w*.

Therefore the smoothing effect for *v* is also limited.

Nonetheless, we have:

$g_w < 0$ ⟹ Asymptotic smoothing for both *v* and *w*.

Consequently, for both HH and FHN systems, the global attractor consists of C^∞ functions.

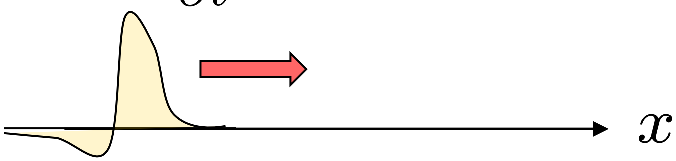


6. Equations on an infinite cylinder

Equations on an infinite cylinder

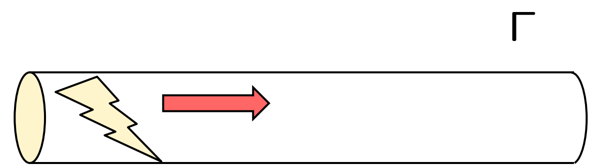
1D Cable model

$$\begin{cases} \dfrac{\partial v}{\partial t} = \dfrac{\partial^2 v}{\partial x^2} + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



3D Cable model

$$\begin{cases} \dfrac{\partial v}{\partial t} = -\Lambda v + f(v,w) \\ \dfrac{\partial w}{\partial t} = g(v,w) \end{cases}$$



GOAL

1. To prove well-posedness of the 3D model.
2. To prove uniform bounds and global existence.
3. Existence and stability of traveling waves.
4. Small diameter limit. (3D ⟹ 1D ?)

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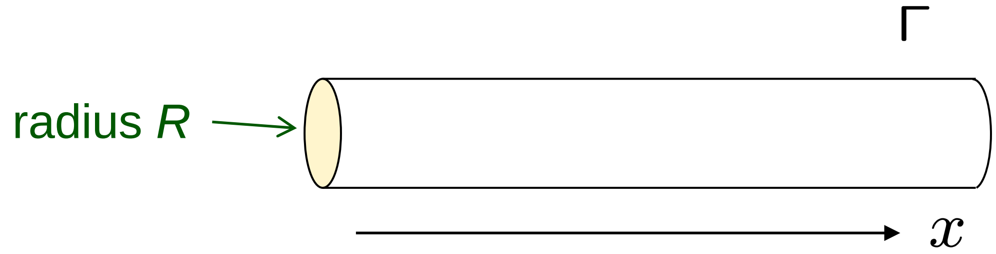
Well-posendess



Idea

1. To show that the principal part of $\dfrac{\partial v}{\partial t} = -\Lambda v$ generates an analytic semigroup on a suitable function space.

2. For that purpose we use coordinates $(x,\,\theta)$ and Fourier decomposition

$$v(x,\theta,t) = \sum_{n=0}^{\infty} v_n(x,t)\, e^{in\theta} \qquad \frac{\partial v_n}{\partial t} = -\Lambda_n v_n \quad (n = 0, 1, 2, \ldots)$$

3. In order to study Λ_n, we use Fourier transform in x .

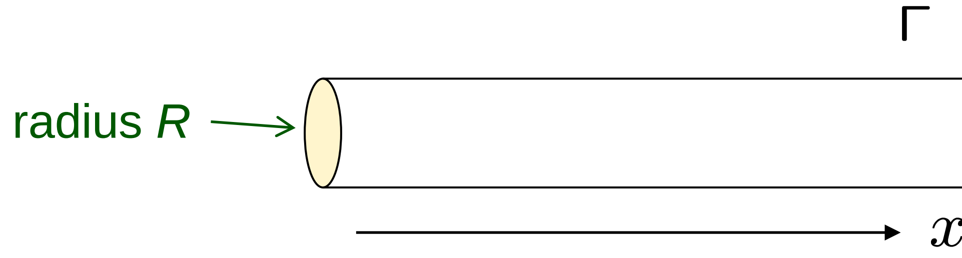
$$\Lambda_n v(x) = \frac{1}{R^2}\,\mathcal{F}^{-1} M_n(R|\xi|) \mathcal{F}\, v(x)$$

Estimate by modified Bessel functions

$$e^{-t\Lambda_n} v = \mathcal{F}^{-1} \exp\big(-t\, R^{-2} M_n(R|\xi|)\big) \mathcal{F}\, v$$

Comparison with Laplacian

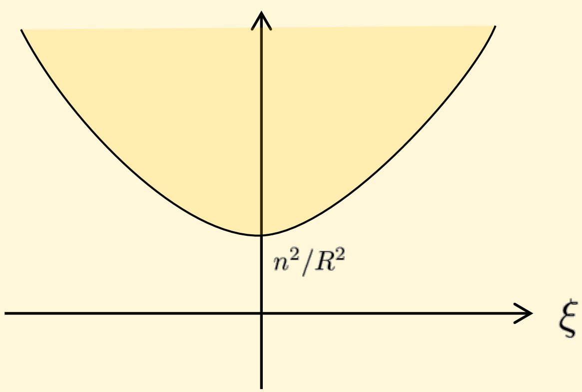
$$\Delta = \partial_x^2 + R^{-2}\partial_\theta^2$$



Fourier decomposition in θ $\quad v(x,\theta,t) = \sum_{n=0}^{\infty} v_n(x,t)\, e^{in\theta}$

$$\frac{\partial v_n}{\partial t} = \Delta_n v_n := (\partial_x^2 - R^{-2}n^2)v_n$$

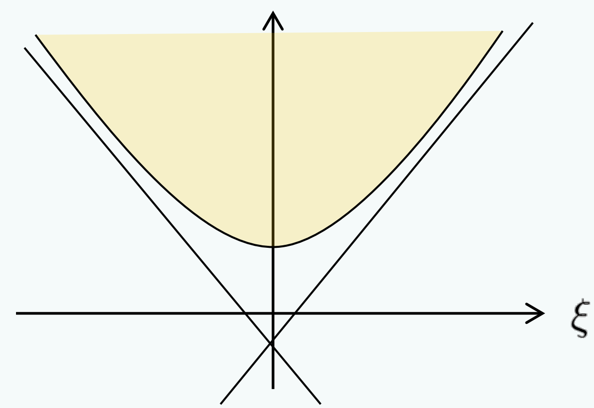
$$-\Delta_n v(x) = \mathcal{F}^{-1}\left(|\xi|^2 + \frac{n^2}{R^2}\right)\mathcal{F}\, v(x)$$



All Δ_n satisfy comparison principle

$$\frac{\partial v_n}{\partial t} = -\Lambda_n v_n$$

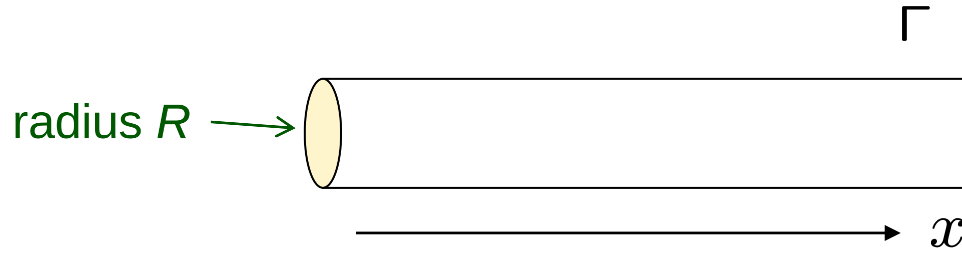
$$\Lambda_n v(x) = \mathcal{F}^{-1}\left(R^{-2}M_n(R|\xi|)\right)\mathcal{F}\, v(x)$$



Only $-\Lambda_0$ satisfies comparison principle

Comparison with Laplacian

$$\Delta = \partial_x^2 + R^{-2}\partial_\theta^2$$



Fourier decompostion in θ

$$v(x,\theta,t) = \sum_{n=0}^{\infty} v_n(x,t)\, e^{in\theta}$$

$$\frac{\partial v_n}{\partial t} = \Delta_n v_n := (\partial_x^2 - R^{-2}n^2)v_n$$

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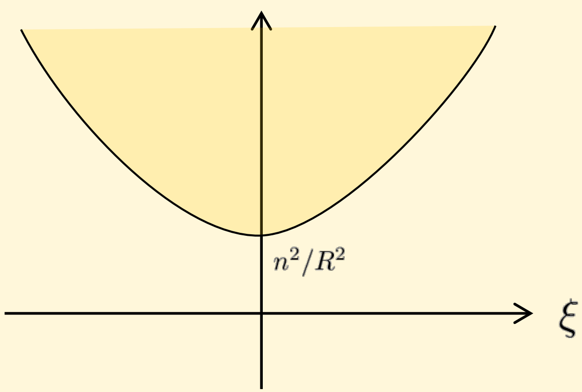
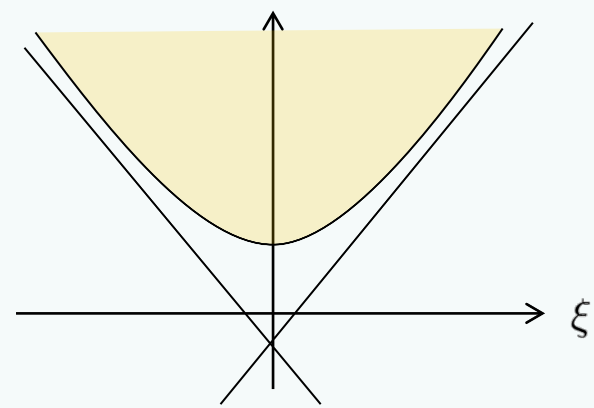


$$\frac{\partial v_n}{\partial t} = -\Lambda_n v_n$$

$$\Lambda_n v(x) = \mathcal{F}^{-1}\left(R^{-2}M_n(R|\xi|)\right)\mathcal{F}\, v(x)$$

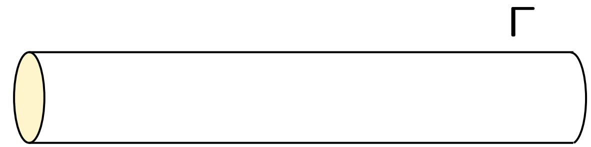


$$-\Lambda_0 \to \Delta_0 \quad (R \to 0)$$

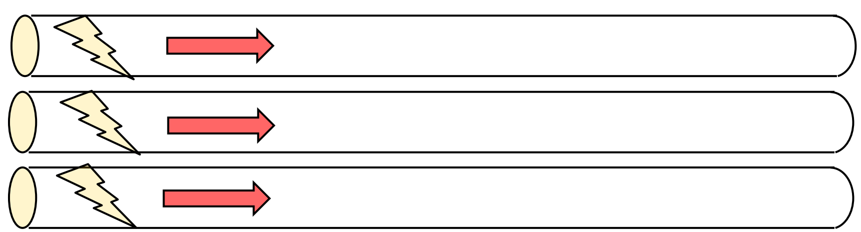
Convergence to 1D model

Problems yet to be solved

dynamics on the cylinder



- Traveling waves in 3D Allen-Cahn eq. (stability analysis)
- Traveling waves in 3D FitzHugh-Nagumo (existence and stability)
- Study the effect of geometry (of the cross-section) on the behavior of TWs (the existence, speed, etc).
- Study the case of many parallel cylinders: What kind of mutual interactions occur? (Ephaptic coupling.)

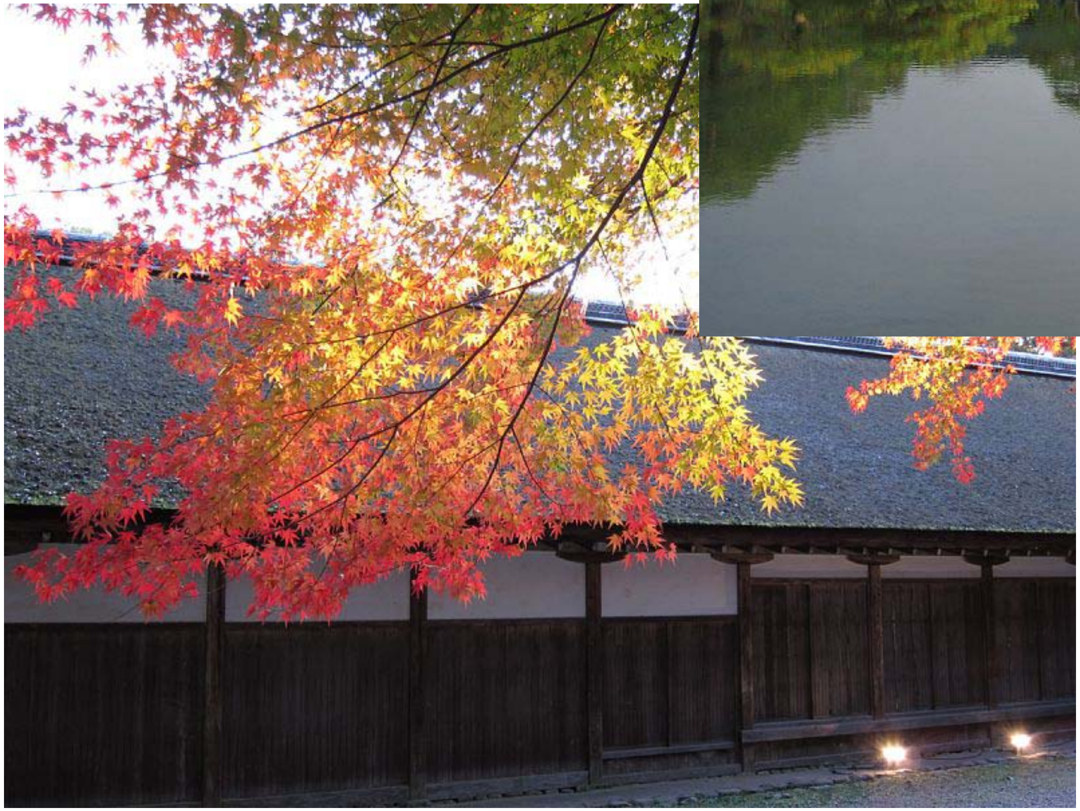


Thank you!

감사합니다.

Seoul, 2012

Thank you!



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