Numerical Stability Analysis of PTW Solutions in Excitable RD Systems

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Joint work
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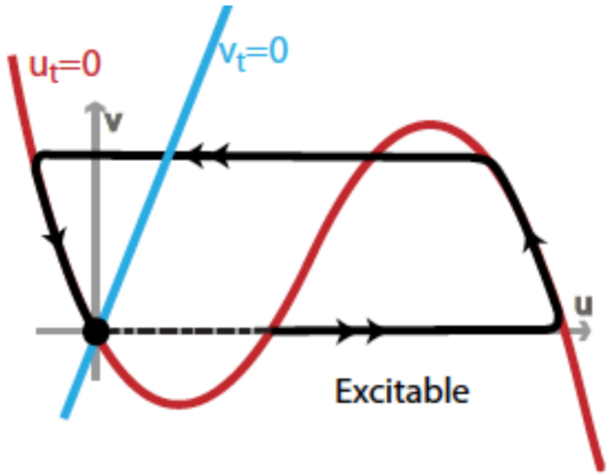
反応拡散現象にみられる境界層とその周辺の数理
November 28, 2014

Outline

- Background and Motivation
  (Some basics about heart and heart cells contraction)
- Existing mathematical models for cardiac electrical activities
- Existence and stability of PTWs for FHN model
- Existence and stability of PTWs for a proposed model
- Eckhaus and Hopf type instability
- Spiral wave instability in 2D
- Summary

Excitable media

- The system which has **one stable rest state** (monostable) with small perturbations is called excited system.

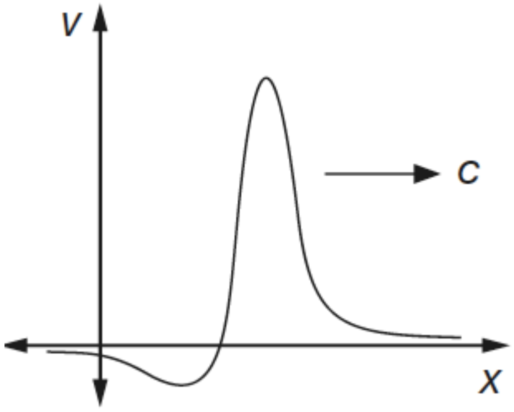


- Examples:

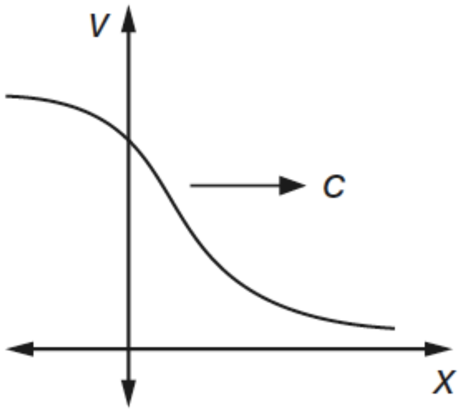
1. The axon of a nerve cell or neuron
2. The Belousov-Zhabotinsky (BZ) reaction
3. The predator-prey models of population dynamics
4. Cardiac cell etc.

Common Patterns in Excitable media

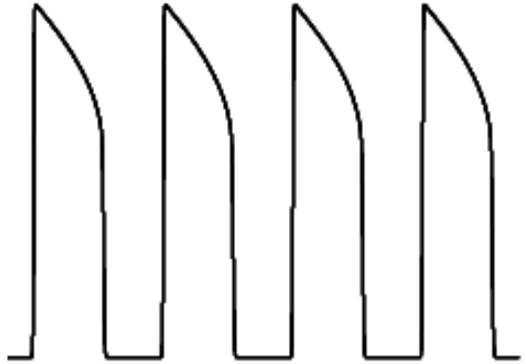
1D:



Traveling Pulse



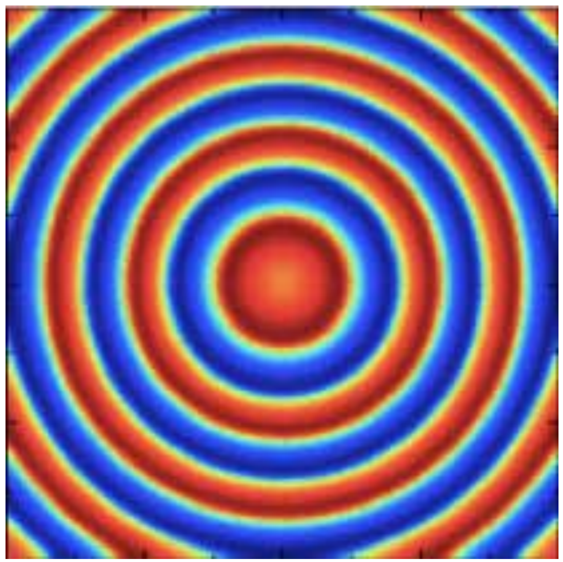
Traveling Front



Periodic Traveling Wave

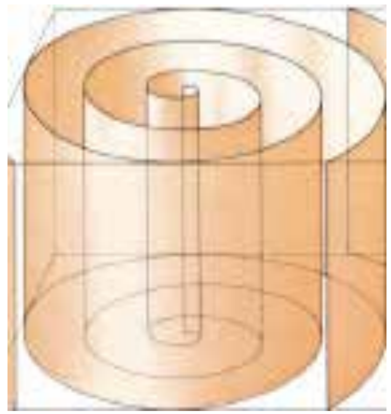
2D:

Rotating Spiral
Single wave front



Target Pattern
More than one wave front

3D:



Scroll Wave

Winfree(1974)

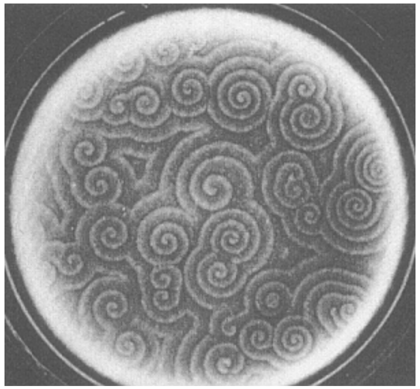
Spiral Patterns in Nature

1. Spiral Patterns in nature

http://en.wikipedia.org
/wiki/Logarithmic_spiral

http://www.messersmith.name/
wordpress/2010/10/24/
of-turbans-and-alien-writing/

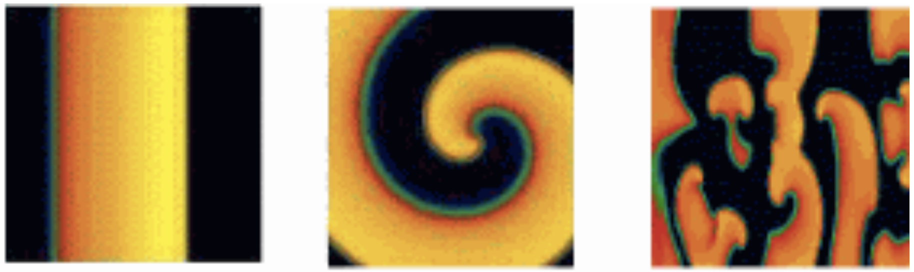
2. Spiral patterns in BZ reaction



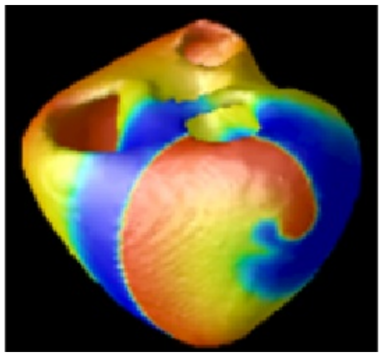
E. Mihailov et al.,
Faraday Discuss
(120),2001

Winfree (1974)

3. Wave in Cardiac tissue

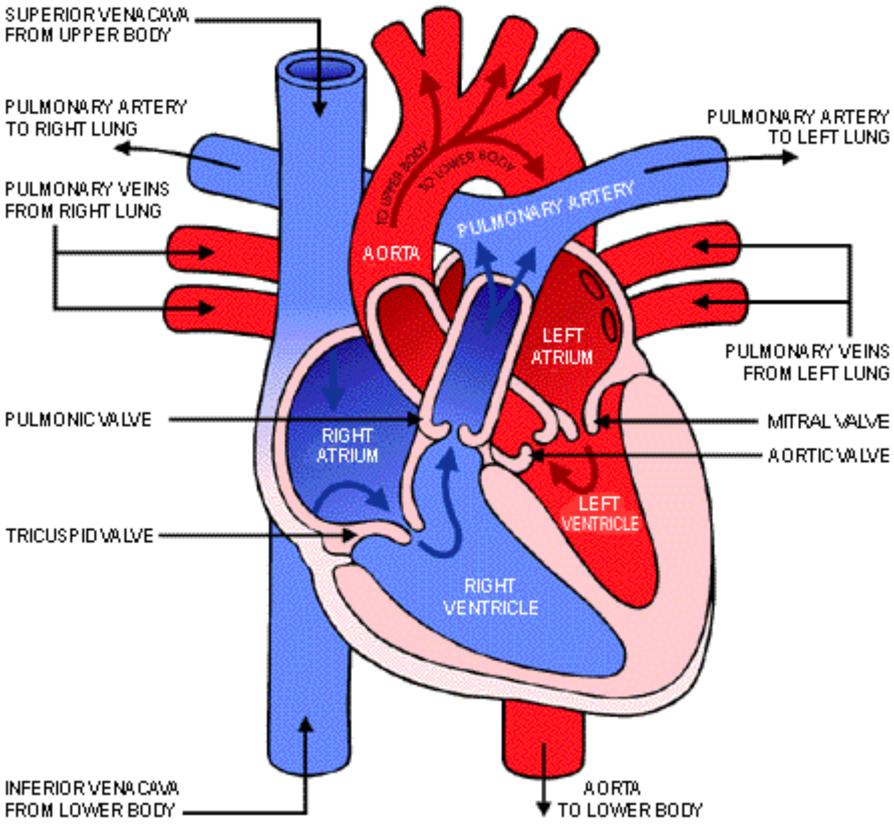


http://thevirtualheart.org



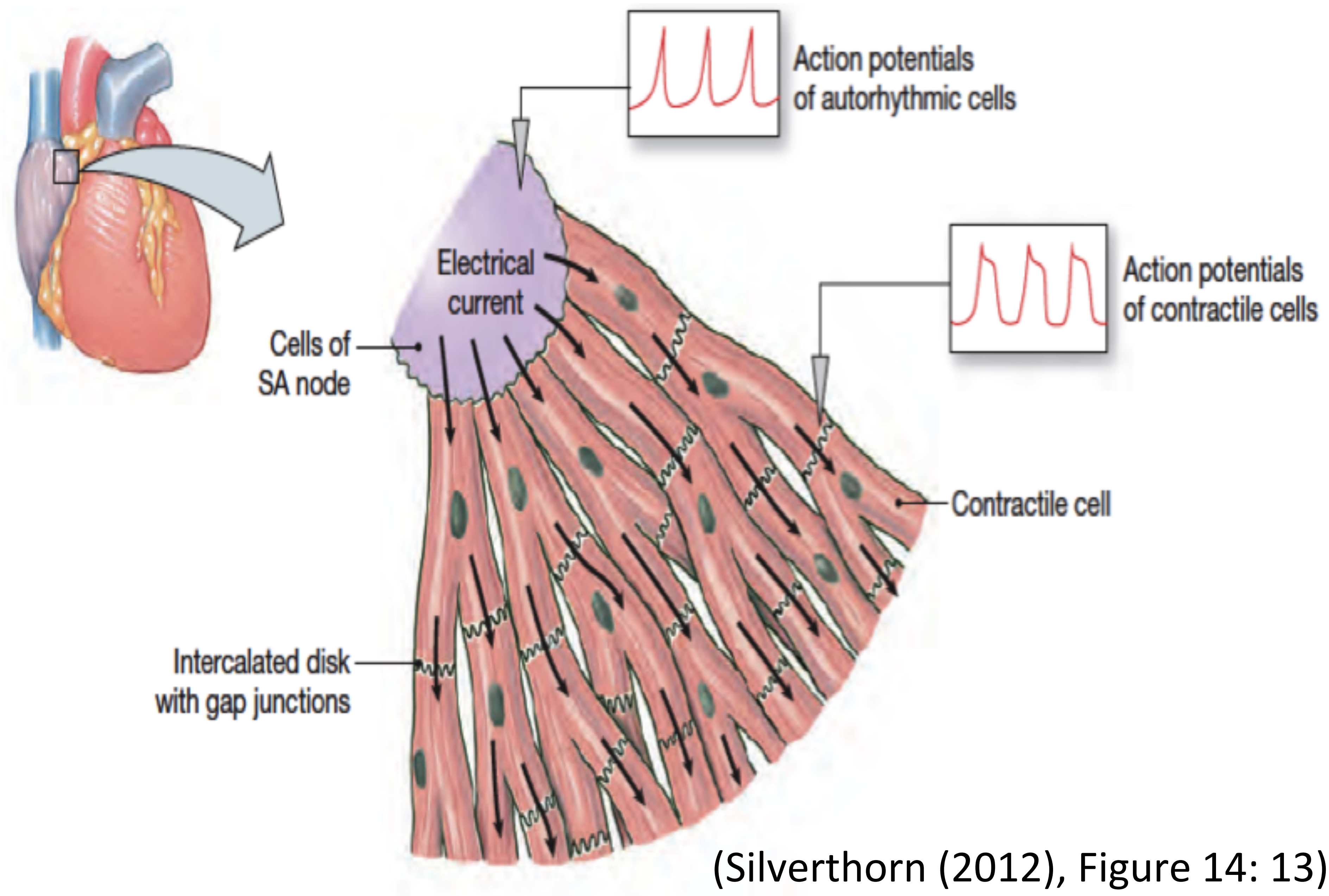
www.rit.edu/cos/sms/
acm/research/
cardiac.php

What is the heart?



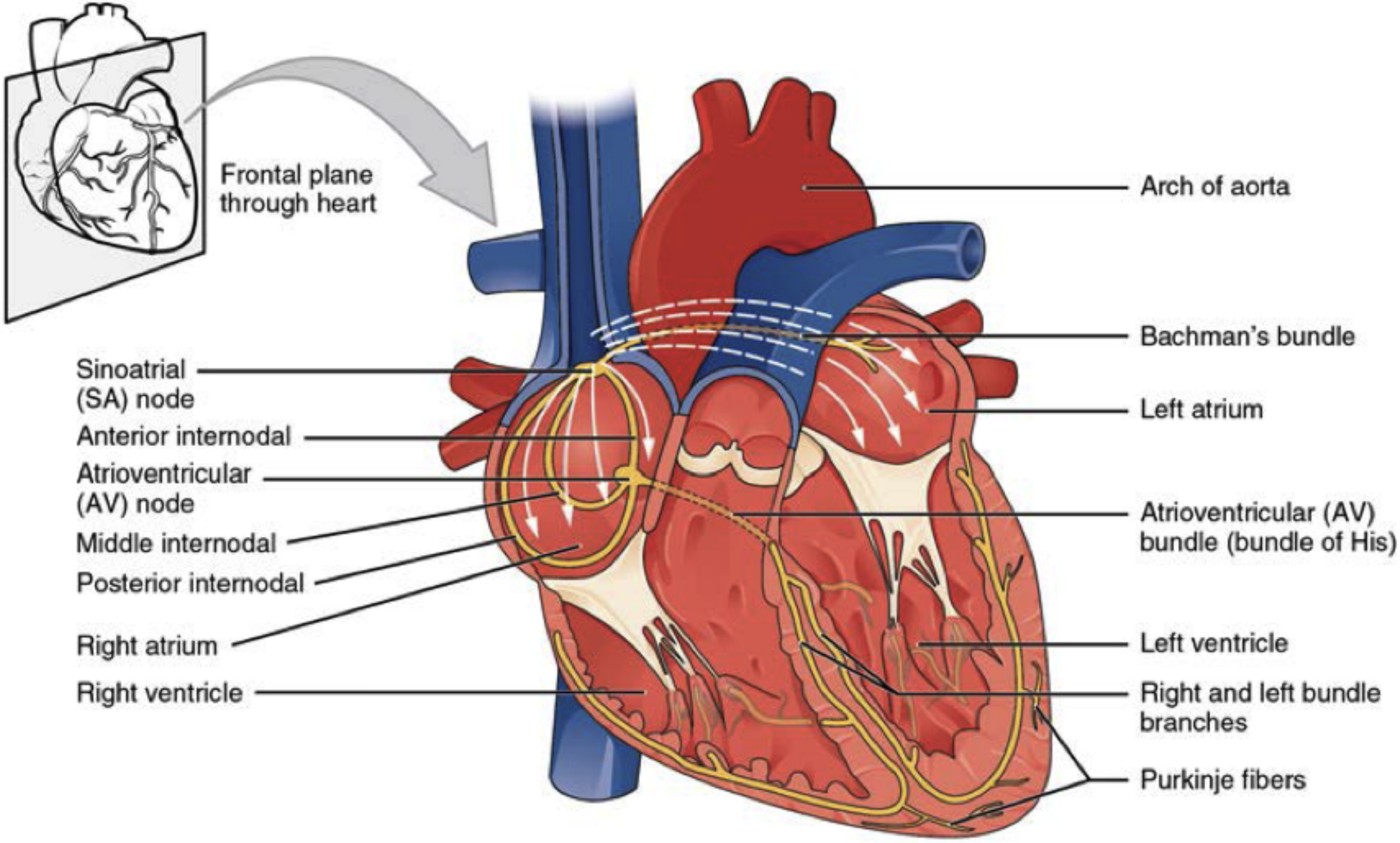
Flow of blood:= inferior vena cava and superior vena cava (from the body) ➔ right atrium ➔right ventricle➔ lungs ➔ left atrium ➔ left ventricle ➔ aorta (to the body).

Electrical Activities in Cardiac Cells



(Silverthorn (2012), Figure 14: 13)

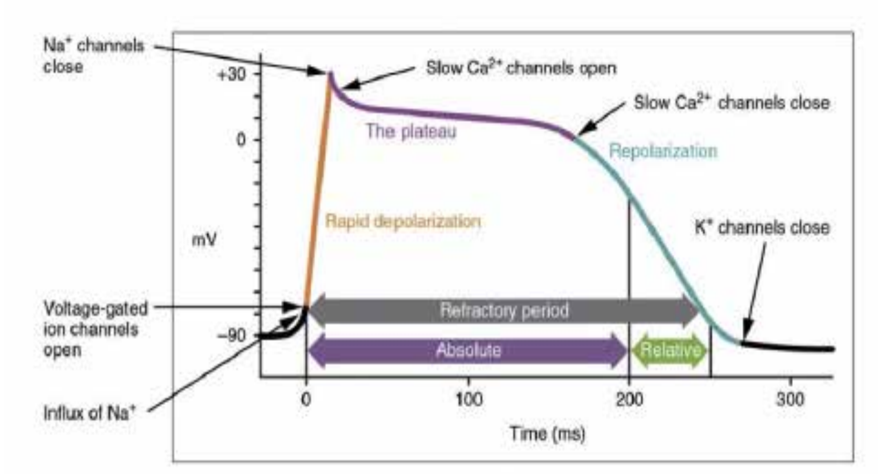
Cardiac Conduction System



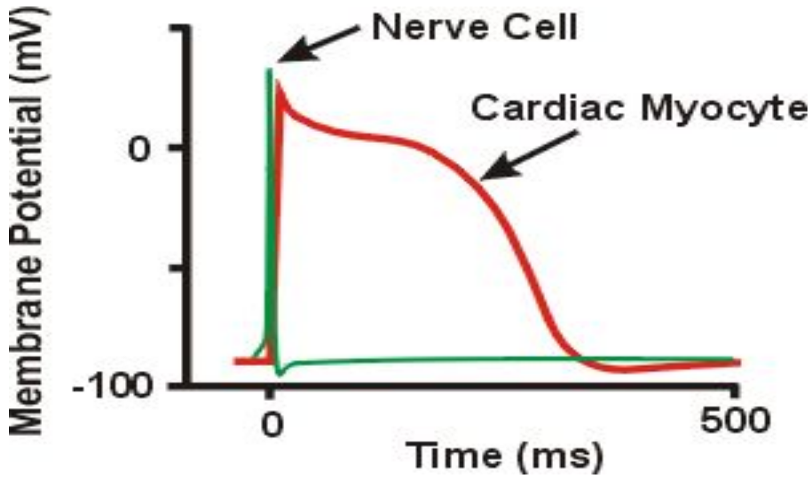
Anterior view of frontal section

Gordon (2013)

Cardiac Action Potential



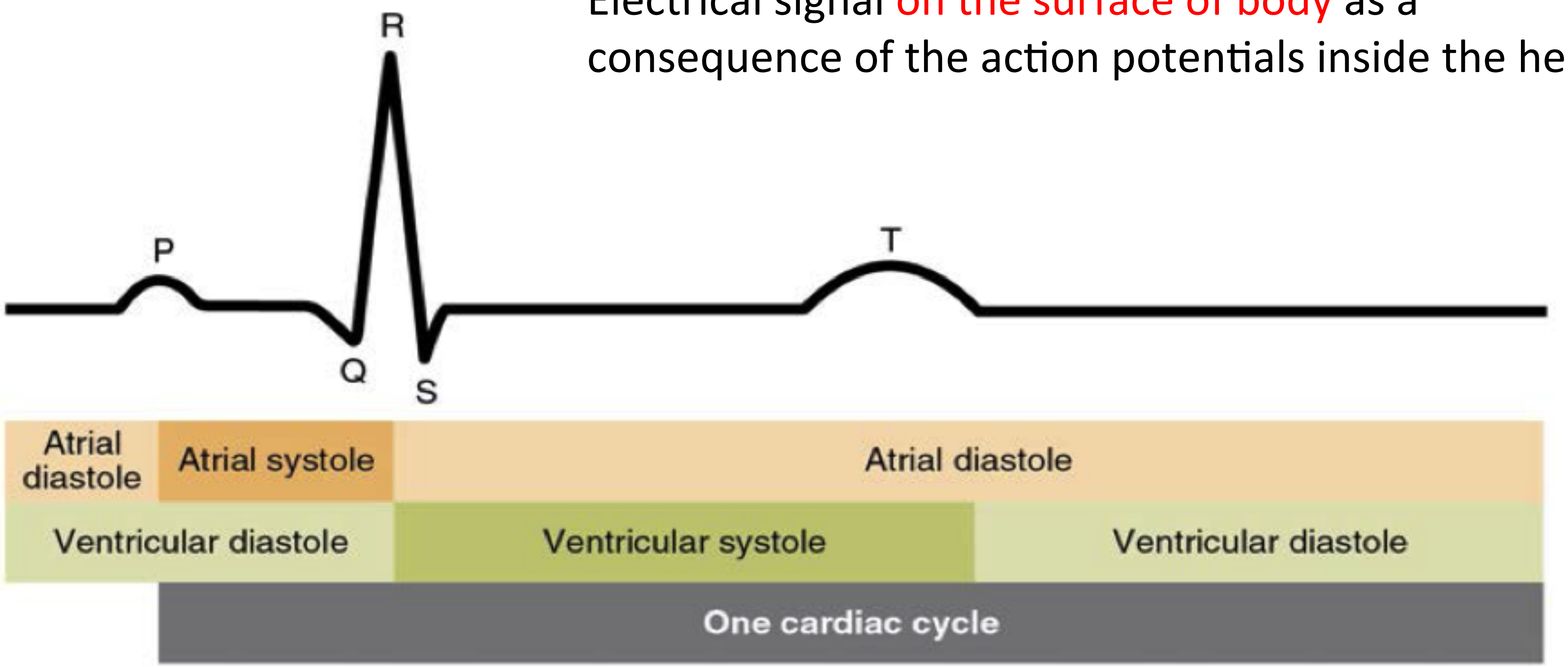
Gordon (2013)



Klabunde(2011)

Electrocardiogram (ECG/EKG)

Electrical signal on the surface of body as a consequence of the action potentials inside the heart

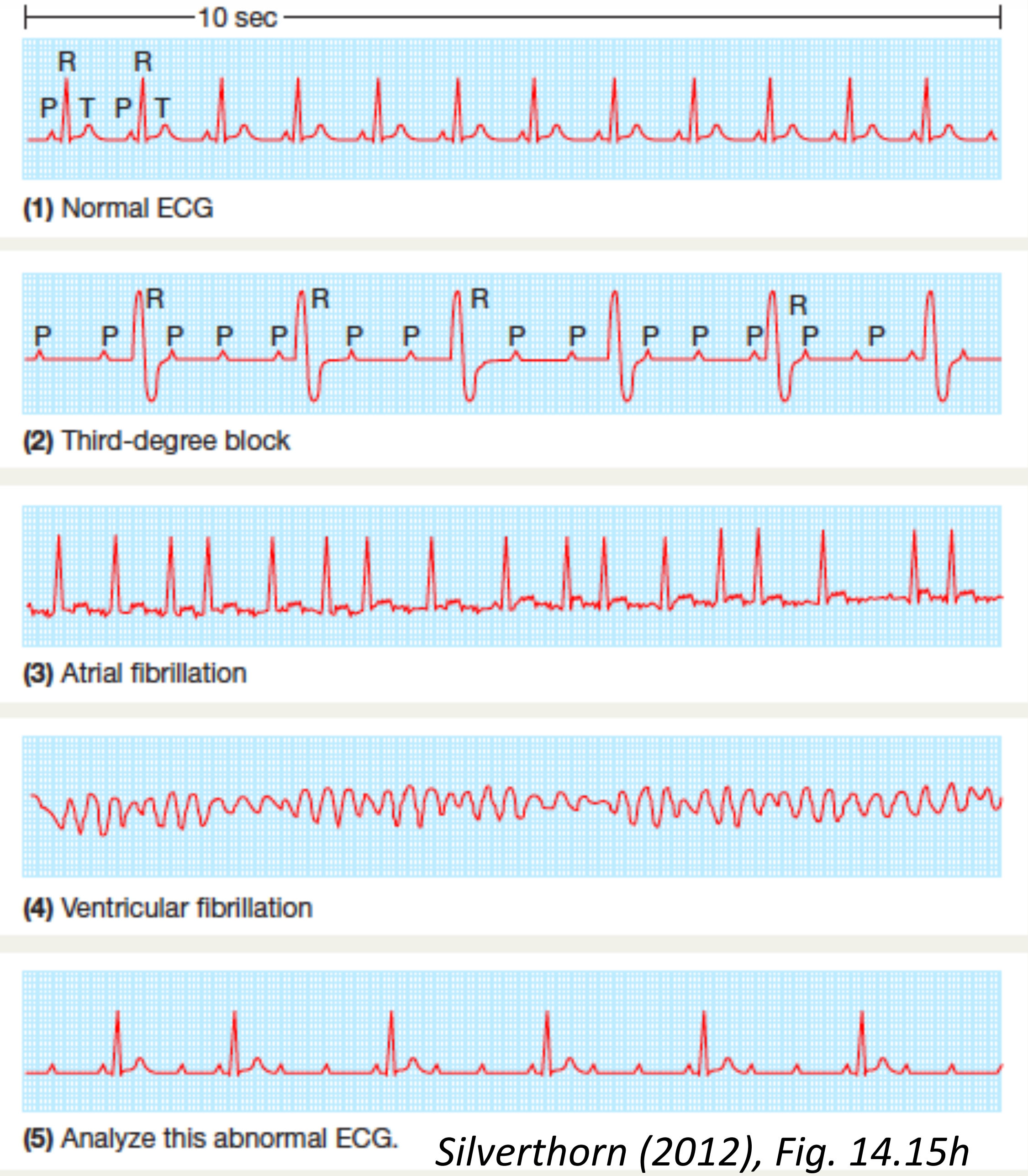


Gordon (2013)

- P wave: depolarization of the atria during atrial systole
- QRS complex: depolarization of the ventricles during ventricular systole
- T wave : repolarization of the ventricles during the relaxation phase

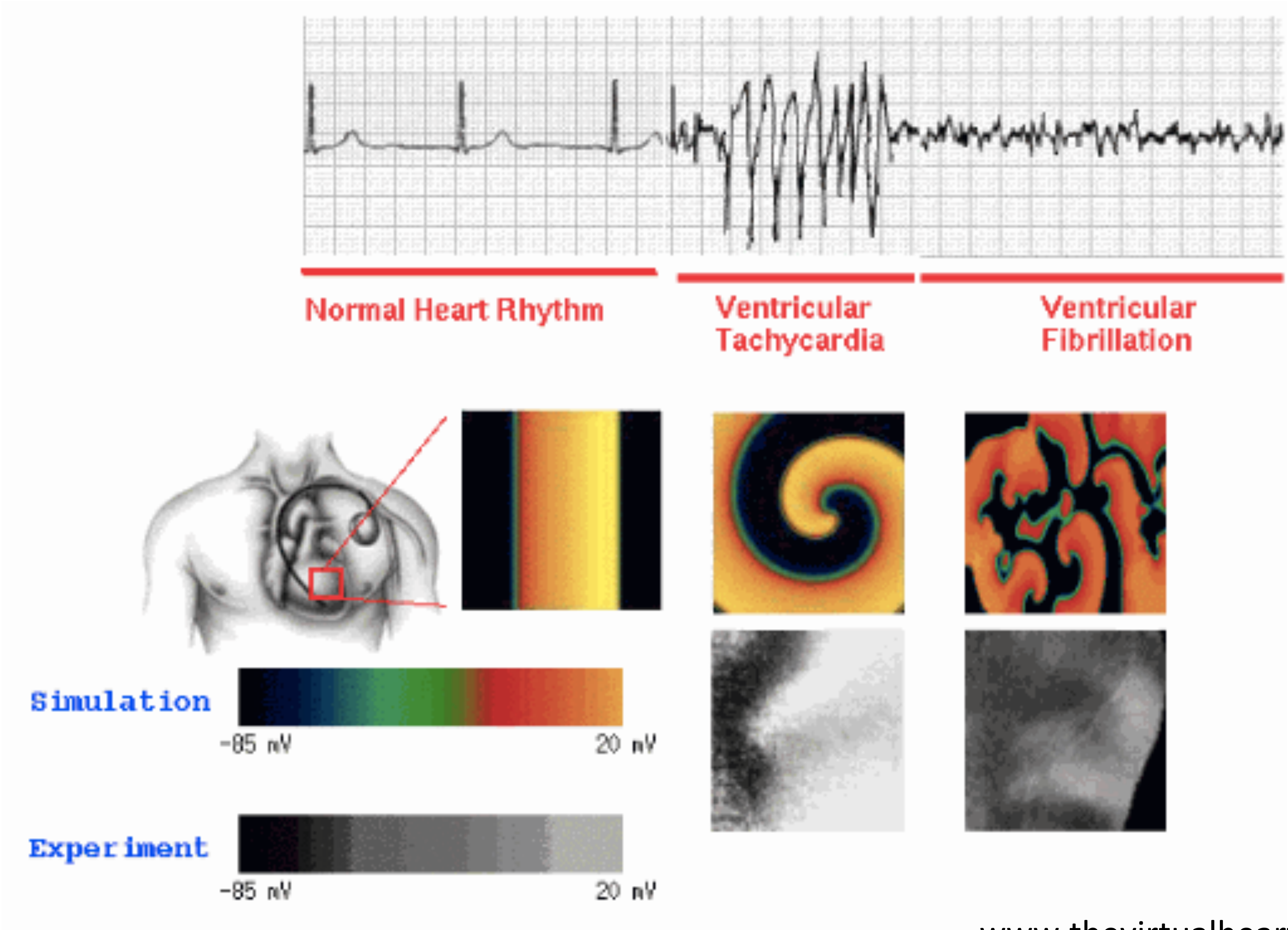
◆ Normal Heart Cycle=70/min.

ECG abnormalities



Silverthorn (2012), Fig. 14.15h

1D and 2D wave Patterns



www.thevirtualheart.org

Fast-slow system

Many models in mathematical physiology have a system of differential equations:

$$(1)\quad \begin{cases} \varepsilon \dfrac{du}{dt} = f(u,v); & u \in R^n \\ \dfrac{dv}{dt} = g(u,v); & v \in R^m \end{cases}$$

Here ε is very small time constant and t is a slow time

Now if we scale time by $t = \varepsilon\tau, \quad 0 \le \varepsilon << 1, \quad \tau,$ is a fast time

, then the above equations will take the form

$$(2)\quad \begin{cases} \dfrac{du}{d\tau} = f(u,v) \\ \dfrac{dv}{d\tau} = \varepsilon\, g(u,v) \end{cases}$$

Fast-slow system

Now , if we take the formal limit $\varepsilon = 0$,then (1) and (2) implies:

$$(1)_0 \quad \begin{cases} 0 = f(u,v) \\ \dfrac{dv}{dt} = g(u,v) \end{cases}$$

,which is slow dynamics and solutions lie on the slow manifold (cubic curve) or critical manifold

$$(2)_0 \quad \begin{cases} \dfrac{du}{d\tau} = f(u,v) \\ \dfrac{dv}{d\tau} = 0 \end{cases}$$

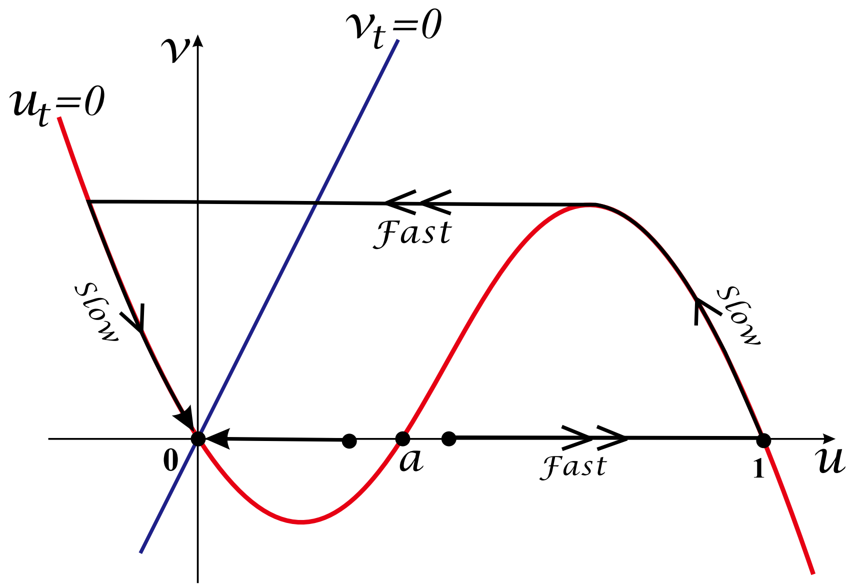
,which is fast dynamics and we say for fixed v, the equation $\dfrac{du}{d\tau} = f(u,v)$ is a fast dynamics or fast subsystem

As for example:

- FitzHugh-Nagumo Equation:

$$\varepsilon \dot{u} = u(1-u)(u-a) - v$$

$$\dot{v} = u - \gamma v$$



Hodgkin-Huxley Model (1952)

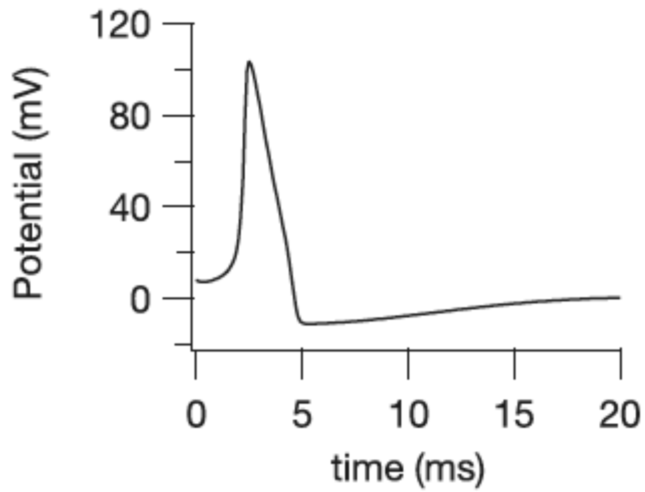
In order to describe the action potential propagation on squids (a large nerve cell)

$$C_m \frac{dv}{dt} = -\bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_K n^4 (v - v_K) - \bar{g}_L (v - v_L) + I_{app}$$

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v) m$$

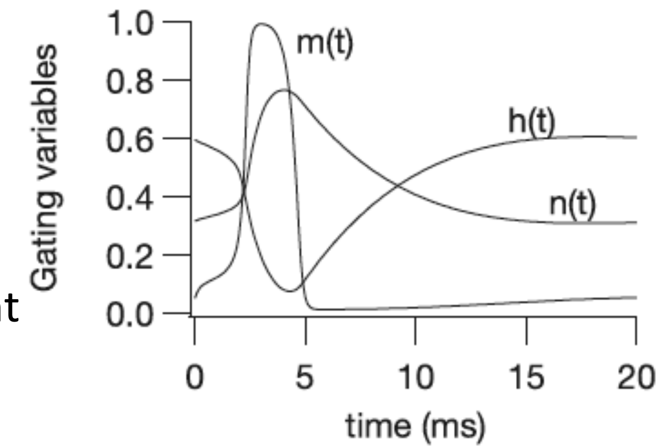
$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v) h$$

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v) n$$



where *"v"* is the membrane potential (fast variable),
"m" is the sodium activation variable (fast variable),
"*h*" is the sodium inactivation variable (slow variable),
"*n*" is the potassium activation variable (fast variable).

m, *n*, and *h* are called gating variables, I_{app} is the applied current C_m is the membrane capacitance, V_{Na}, V_K, V_L are constant equilibrium potentials and the other parameters are constant.

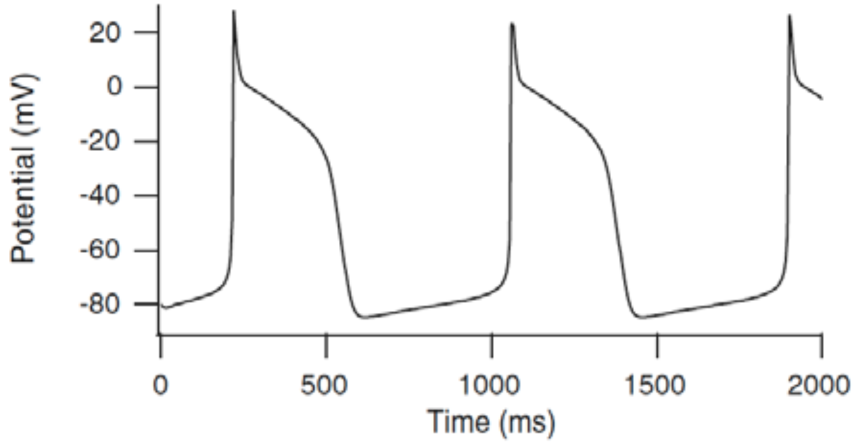


Keener and Sneyd (2010)

Noble Model (1962)

(For the Cardiac Cell Dybnamics)

Based on the Hodgkin-Huxley model Noble in 1962 proposed the first physiological model for the dynamics of Purkinje fiber cardiac cells.



Keener and Sneyd (2010)

The main motivation with the Noble model was to have a prolong plateau phase in the action potential.

Several Ionic Models: McAllister et al. (1975); Beeler and Reuter (1977); Sharp and Joyner (1980); Ebihara and Johnson (1980); Luo and Rudy (1991); Winslow et al. (1993); Luo and Rudy (1994a,b), etc.

Two-variable Reduction of HH Model

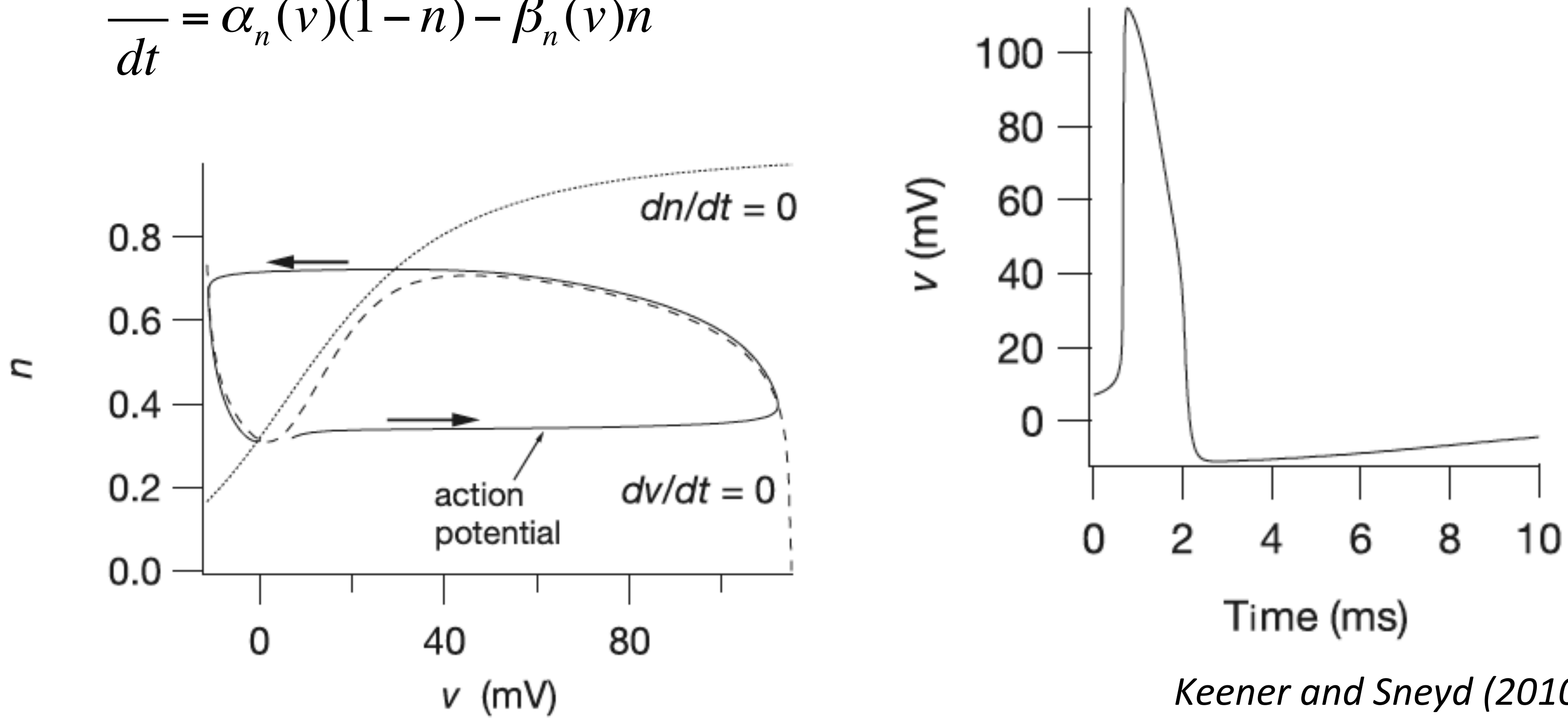
[FitzHugh's Fast-Slow approach(1960,1961)]

Set $h + n = 0.8$ and $m = m_\infty(v)$.

This reduces to a two-variable fast-slow system as follows:

$$C_m \frac{dv}{dt} = -\bar{g}_{Na} m_\infty(v)(0.8 - n)(v - v_{Na}) - \bar{g}_K n^4 (v - v_K) - \bar{g}_L (v - v_L)$$

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v) n$$



Keener and Sneyd (2010)

Two-variable FitzHugh-Nagumo Model
(Simplified HH Model)

$$\frac{du}{dt} = u(1-u)(u-a) - v$$

$$\frac{dv}{dt} = \varepsilon(u - \gamma v)$$

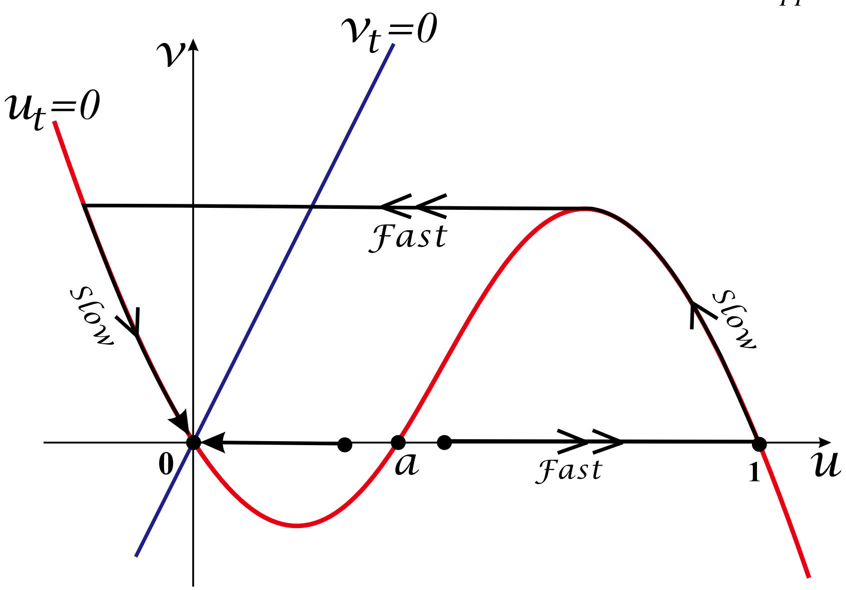
$$0 < a < 1/2$$

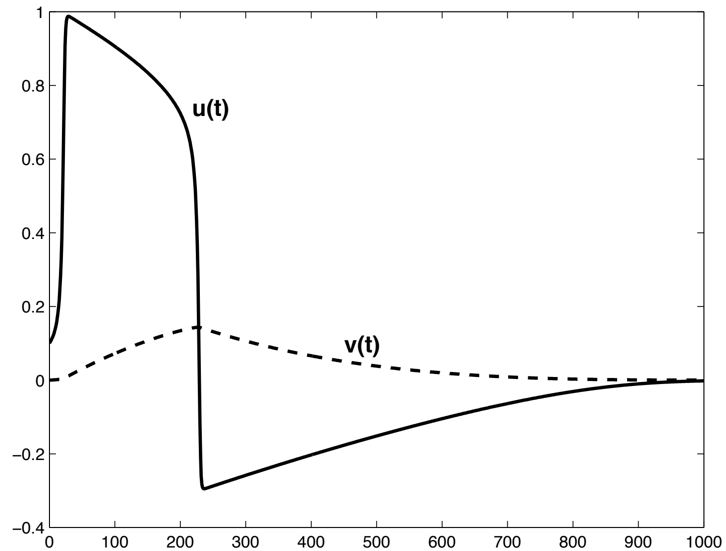
$$0 < \varepsilon << 1$$

u: fast activator (excitable) variable,
v: slow inhibitor (recovery) variable

u works like membrane potential and
v plays the role of gating variables

$I_{app} = 0$





$$a = 0.07, \varepsilon = 0.001, \gamma = 2.0$$

Other two-variable models: Pertsov et al. (1984); Karma (1993); Panfilov and Hogeweg (1993); Aliev and Panfilov (1996); Panfilov (1998); etc.

Goal

The purpose of this work is to study the existence and stability of Periodic Traveling Wave solutions (PTWs) in the FHN model and in a proposed variant of the FHN model.

Standard FitzHugh-Nagumo model

$$u_t = d_u \Delta u + u(1-u)(u-a) - v$$
$$v_t = d_v \Delta v + \varepsilon(u - \gamma v)$$

$0 < a < 1/2$

$0 < \varepsilon << 1$

$d_u >> d_v$

"u": fast activator (excitable) variable, *"v"*: slow inhibitor (recovery) variable

"u" works like membrane potential and
"v" plays the role of gating variables

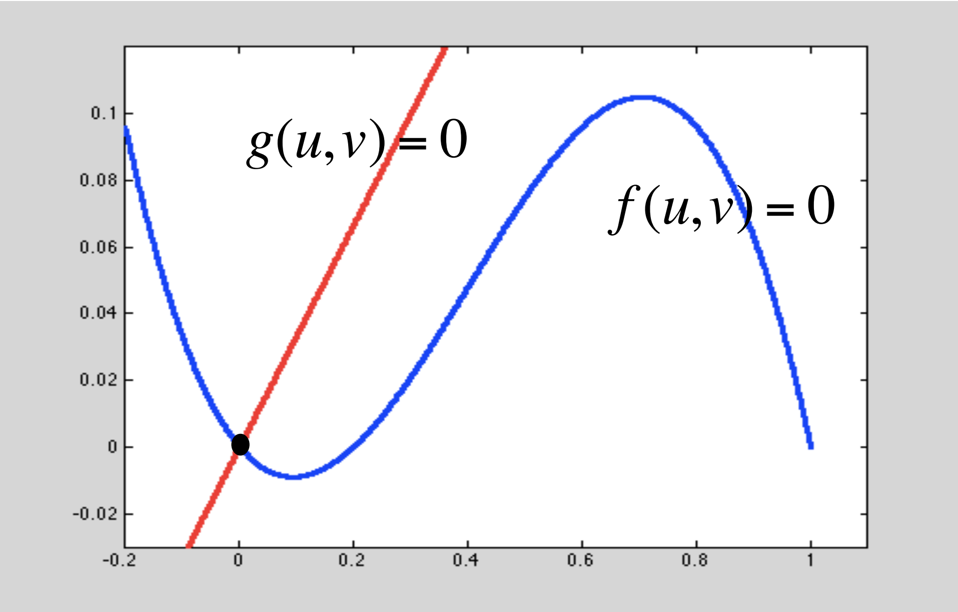
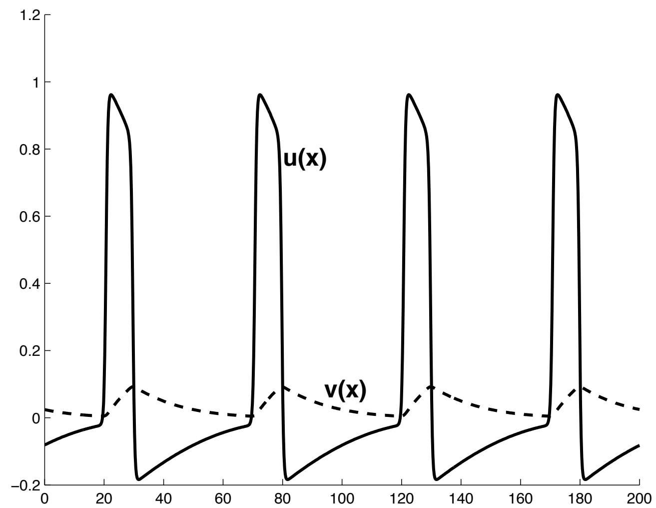


Fig: Nullclines of the FHN model



Pulse profile

$a = 0.2, \varepsilon = 0.001, \gamma = 2.5, d_u = 0.05, d_v = 0.005$

What is PTW solution?

Substituting $u(x,t) = U(z)$ and $v(x,t) = V(z)$, where $z = x - ct$

is a travelling wave coordinate, in the model equations we have a system of ODE of the form :

$$d_u U'' + cU' + f(U,V) = 0$$
$$d_v V'' + cV' + g(U,V) = 0$$

where ' denotes w.r.to z

After reducing the first order the above system yields:

$$U' = P$$
$$P' = (-cP - f(U,V)) / d_u$$
$$V' = Q$$
$$Q' = (cQ - g(U,V)) / d_v$$

where '*c*' is the wave speed

A PTW solution is a limit cycle solution of this ODE system.

Stability of PTWs

Again Substituting $u(x,t) = U(z)$ and $v(x,t) = V(z)$ where $z = x - ct$ and neglecting the non-linear terms yields a linearized PDE :

$$\frac{\partial}{\partial t}\vec{u}_{lin} = D\frac{\partial^2}{\partial x^2}\vec{u}_{lin} + \vec{u}_{lin}.\,\Delta\vec{F}$$

where $\vec{u}_{lin}(x,t) = \vec{u}(x,t) - \vec{U}(z)$. Again substituting $\vec{u}_{lin}(x,t) = e^{\lambda t}\vec{U}(z)$

We obtain the eigenvalue problem:

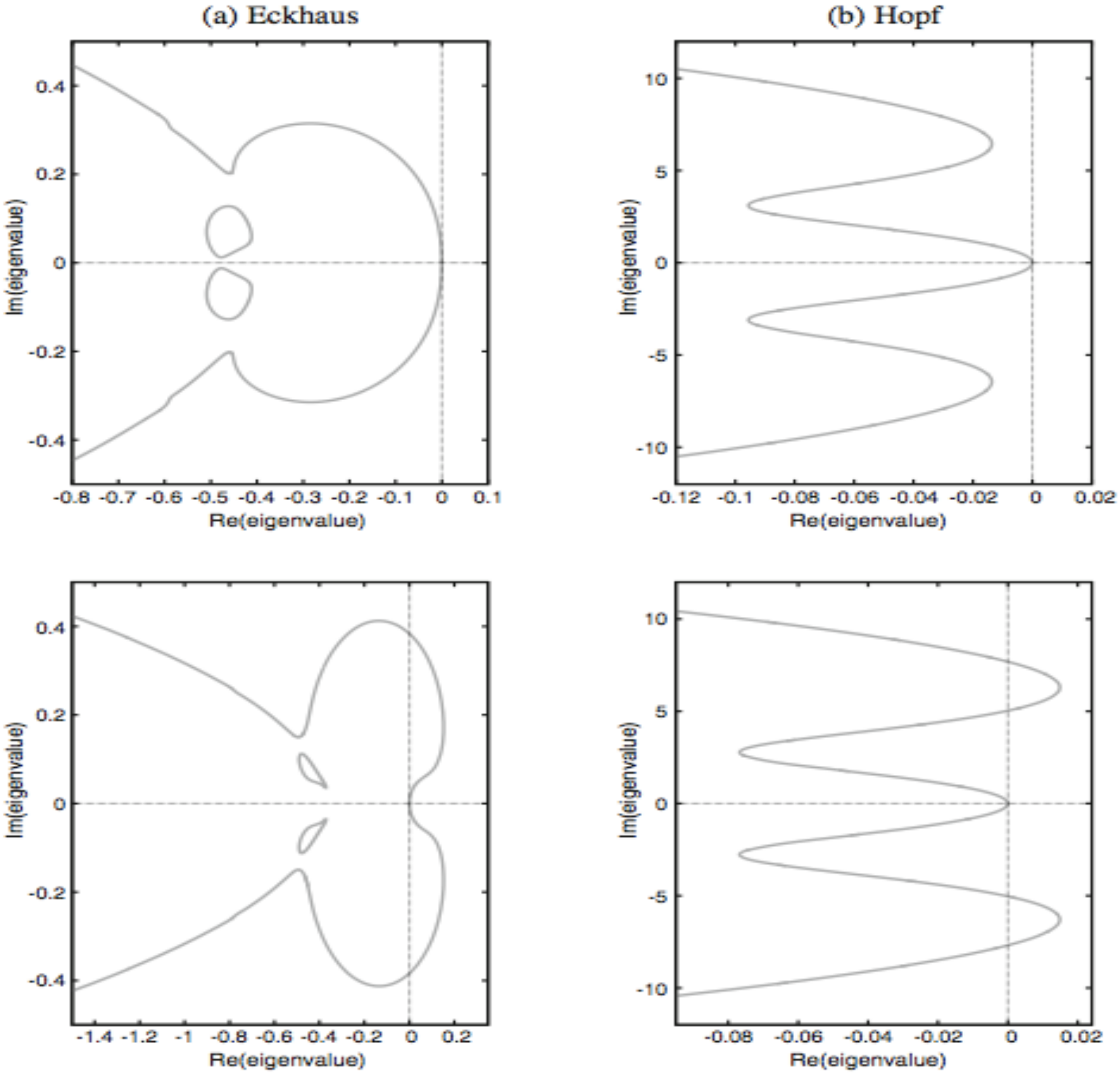
$$\lambda\vec{U} = c\frac{d}{dz}\vec{U} + D\frac{d^2}{dz^2}\vec{U} + \vec{U}.\,\Delta\vec{F}$$

with boundary condition $\vec{U}(L) = \vec{U}(0)\exp(i\gamma), \ \ for\ some\ \gamma \in R,$

Where L is the period of the PTW, γ is the phase shift across one period of the wave, $\Delta\vec{F}$ is the Jacobian matrix of $(f(u,v), g(u,v))$ along the PTW, D is the diffusion matrix , $\vec{U}$ is the eigenfunction and λ is the eigenvalue.

In order to understand the stability of PTWs our interest is to calculate the essential spectra of the PTWs.

Eckhaus and Hopf Instabilities of the PTWs



J. A. Sherratt,
Adv Comput Math
(2013)

Method of Continuation (FHN Model)

1. 4-dim ODE system:

$$U' = P$$
$$P' = (-cP - U(1-U)(U-a) + V)/d_u$$
$$V' = Q$$
$$Q' = (cQ - \varepsilon(U - \gamma V))/d_v$$

Where,

$$u(x,t) = U(z)$$
$$v(x,t) = V(z)$$
$$z = x - ct$$

2. Linearized PDE:

$$\frac{\partial u_{lin}}{\partial t} = d_u \frac{\partial^2 u_{lin}}{\partial x^2} + u_{lin}(-3U^2 + 2(1+a)U - a) + v_{lin}(-1)$$
$$\frac{\partial v_{lin}}{\partial t} = d_v \frac{\partial^2 v_{lin}}{\partial x^2} + u_{lin}(\varepsilon) + v_{lin}(-\varepsilon\gamma)$$

where

$$u_{lin}(x,t) = u(x,t) - U(z)$$
$$v_{lin}(x,t) = v(x,t) - V(z)$$

3. First order eigenvalue problem:

$$\frac{d}{dz}\begin{bmatrix} U_{lin} \\ M_{lin} \\ V_{lin} \\ N_{lin} \end{bmatrix} = (A(z) + \lambda B)\begin{bmatrix} U_{lin} \\ M_{lin} \\ V_{lin} \\ N_{lin} \end{bmatrix}$$

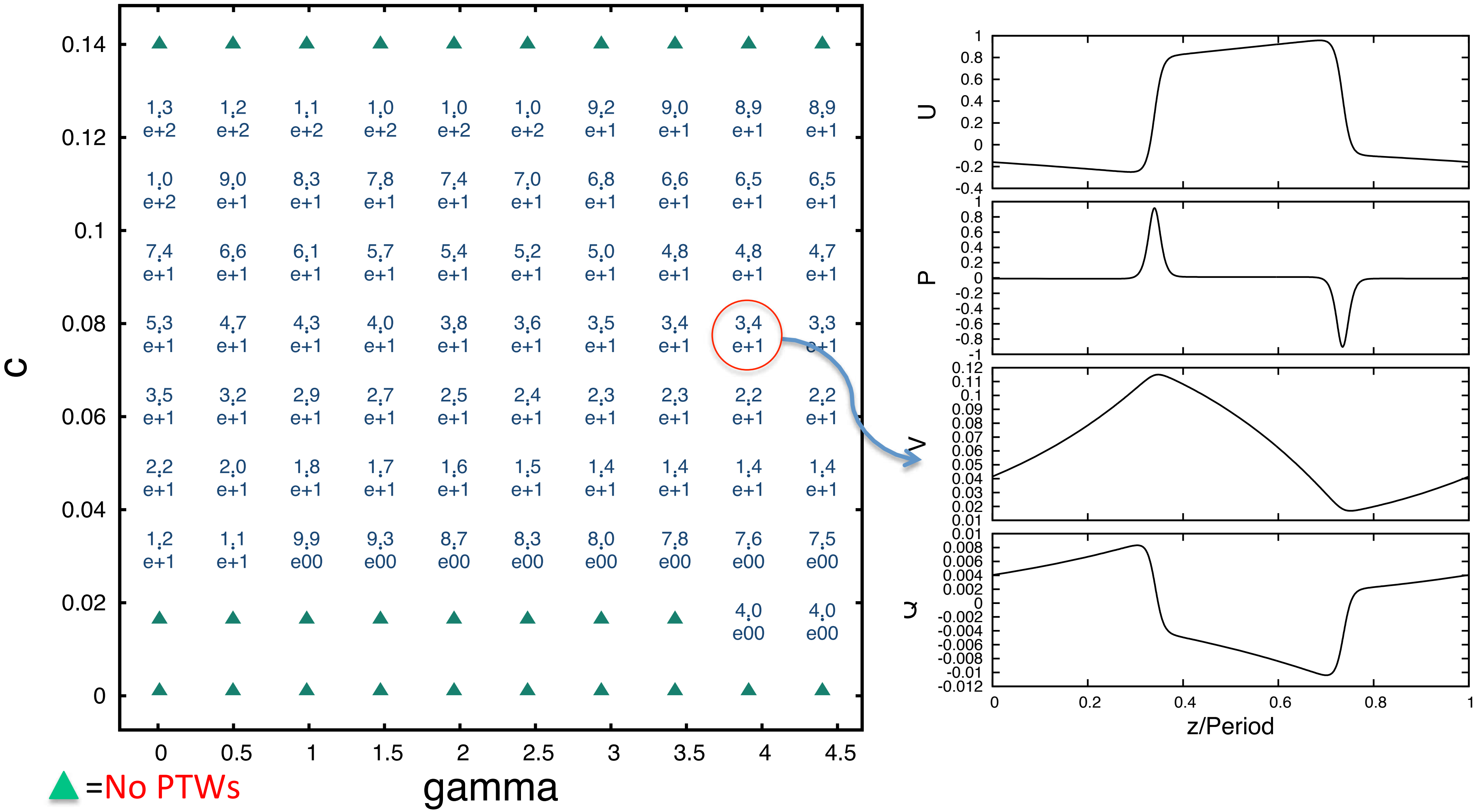
where

$$A = \begin{bmatrix} 0 & 1 & 0 & 0 \\ -\frac{1}{d_u}(-3U^2 + 2(1+a)U - a) & \frac{-c}{d_u} & \frac{1}{d_u} & 0 \\ 0 & 0 & 0 & 1 \\ \frac{-\varepsilon}{d_v} & 0 & \frac{\varepsilon\gamma}{d_v} & \frac{-c}{d_v} \end{bmatrix}$$

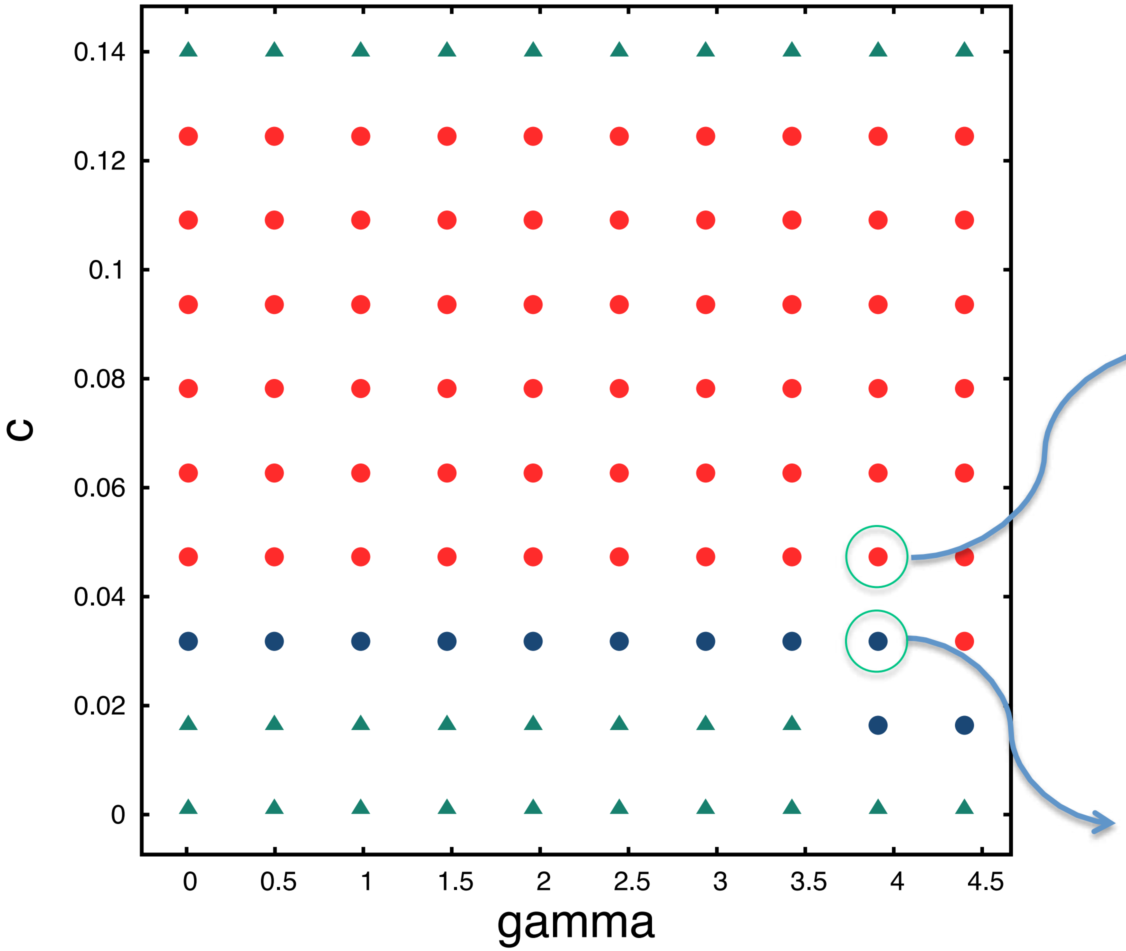
and

$$B = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \frac{1}{d_u} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{d_v} & 0 \end{bmatrix}$$

Existence of PTWs as a function of the parameter “γ”

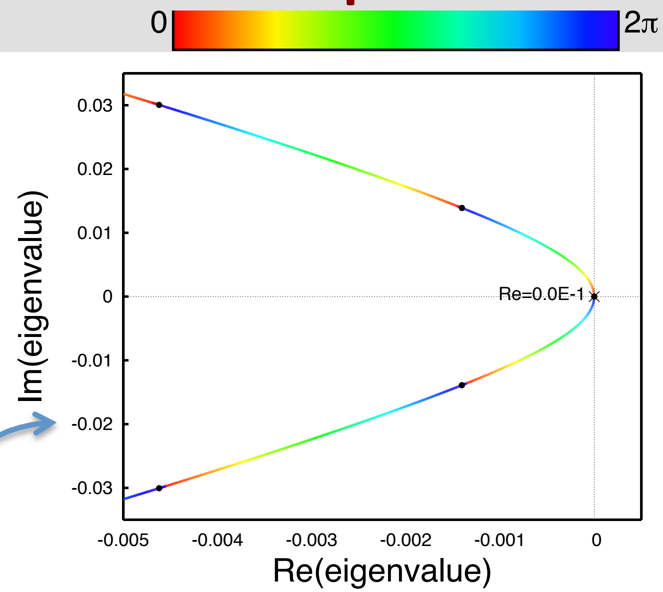


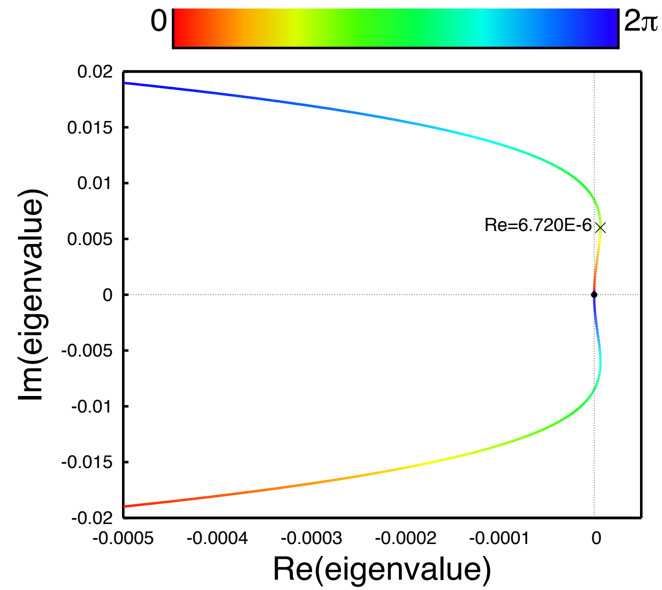
Stability of PTWs and Essential Spectra



=Stable PTW

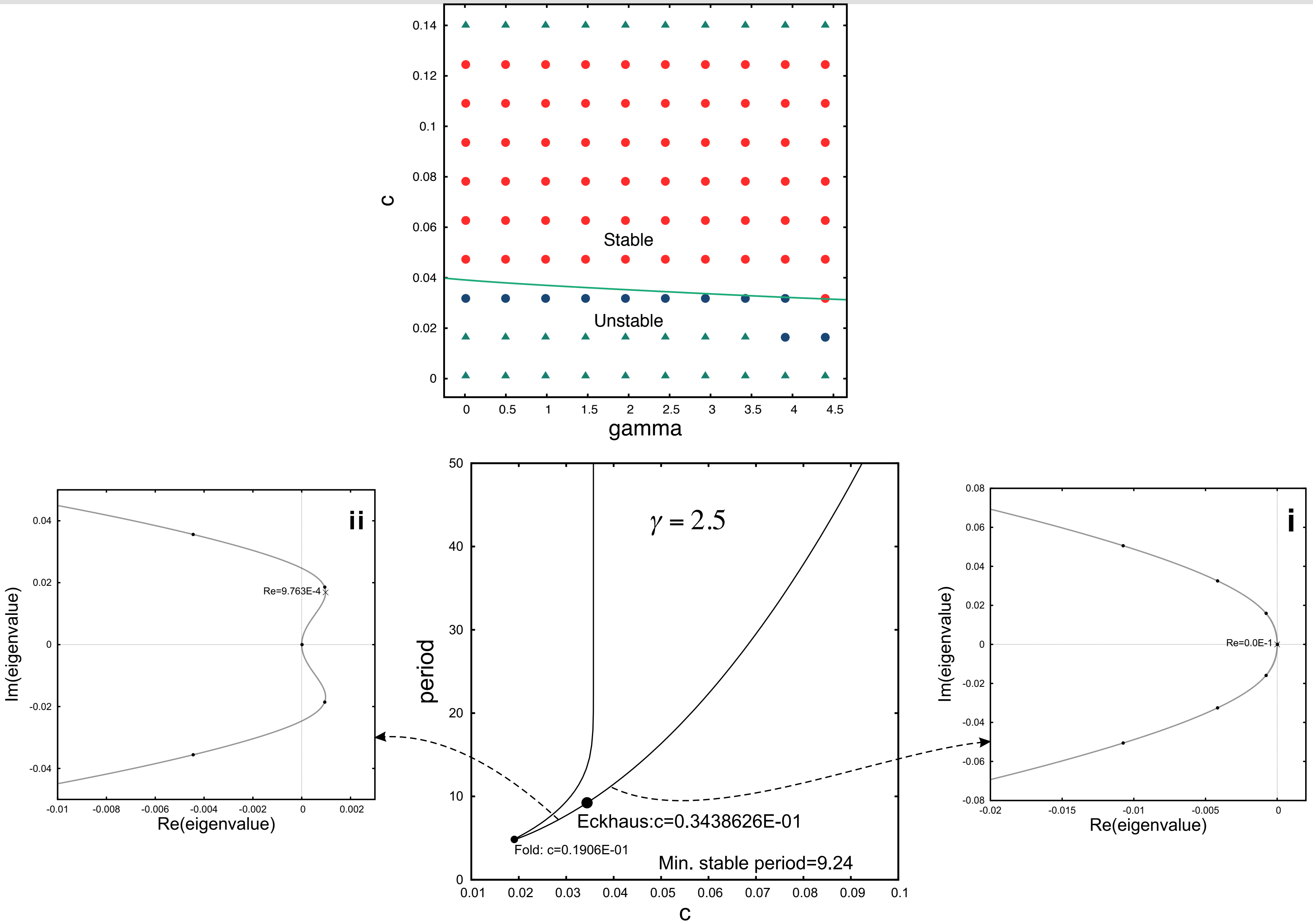
=Unstable PTW





Since the curvature of the spectrum changes sign at the origin, This indicate a stability change of Eckhaus type.

Stability Boundary of Eckhaus type



Our proposed model

$$u_t = d_u \Delta u + u(1-u)(u-a) - v$$
$$v_t = d_v \Delta v + \varepsilon(du(b-u)(u+c) - v)$$

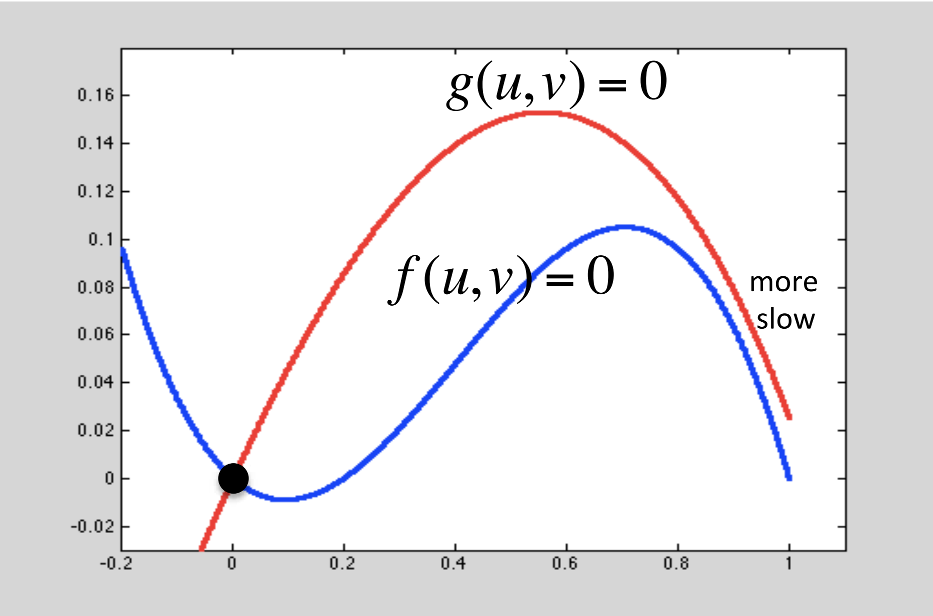
$0 < a < 1/2$

$0 < \varepsilon << 1$

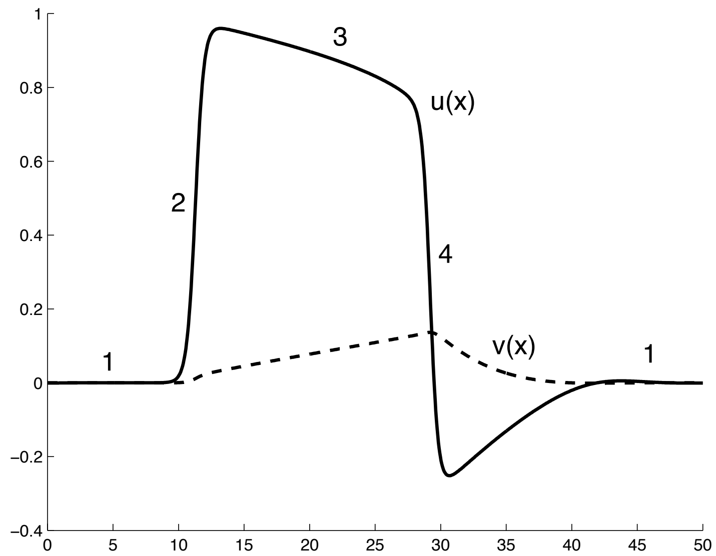
$b > 1$

u: fast activator (excitable) variable, v: slow inhibitor (recovery) variable

$a, b, c, d, \varepsilon, d_u, d_v$ are parameters; $d_u >> d_v$

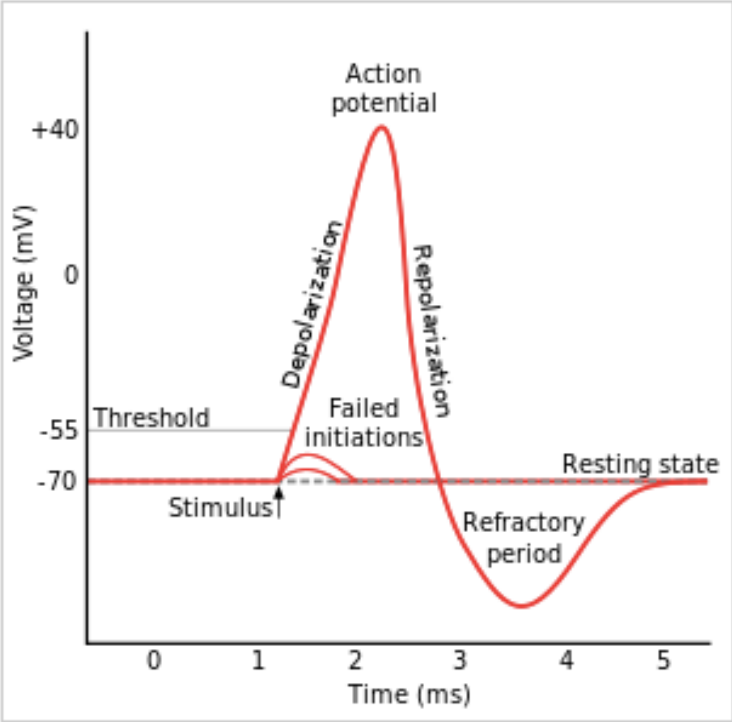


Nullclines of the model

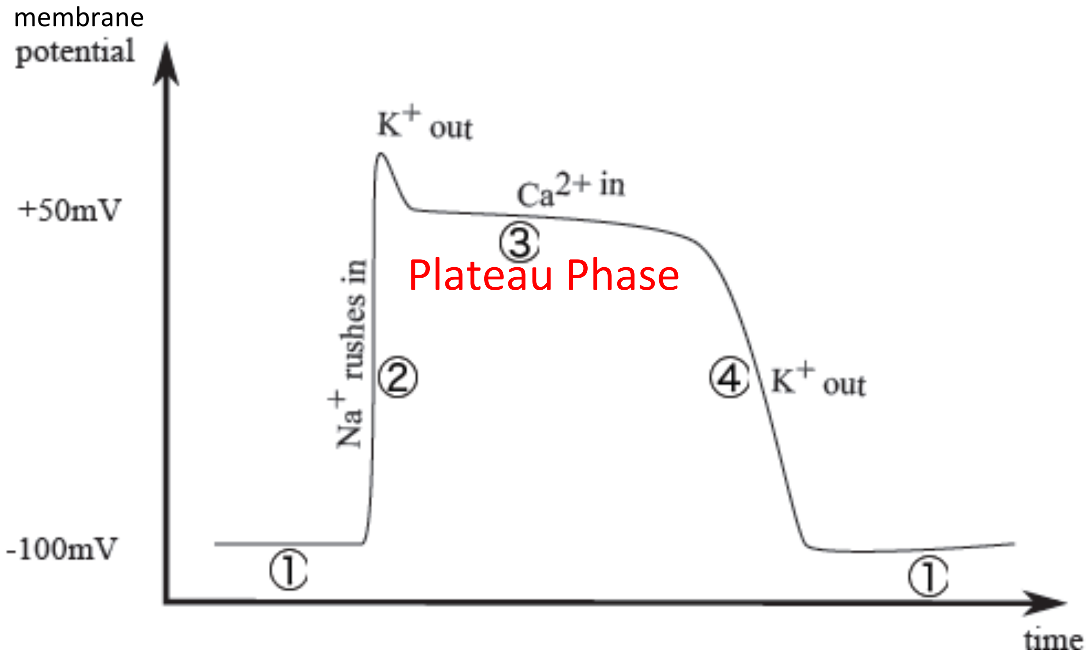


Pulse Profile

Neuron and Cardiac Action Potentials



Neuron AP
(FHN)

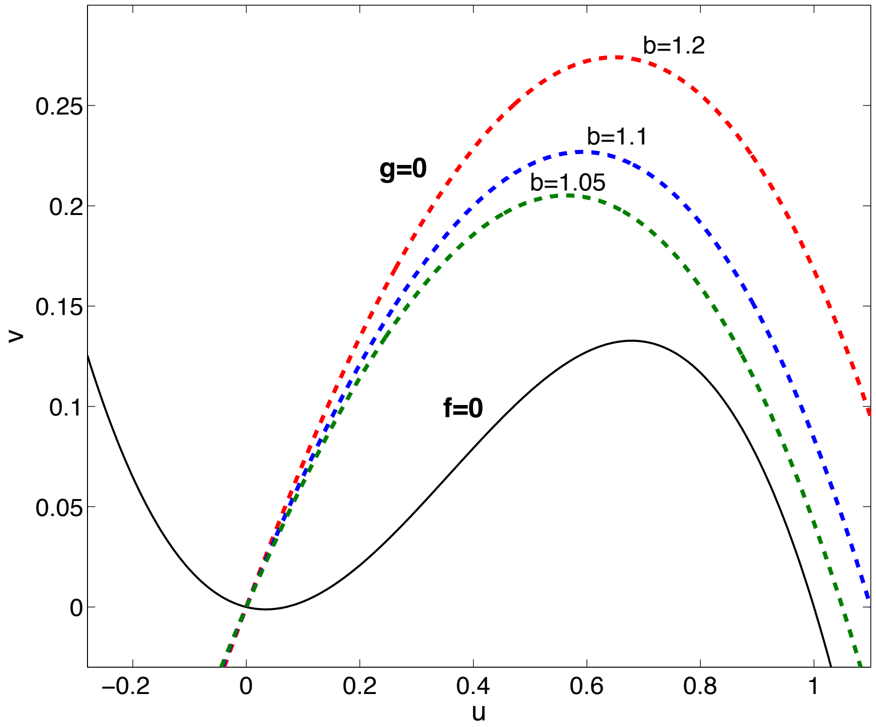


Cardiac AP
m-FHN

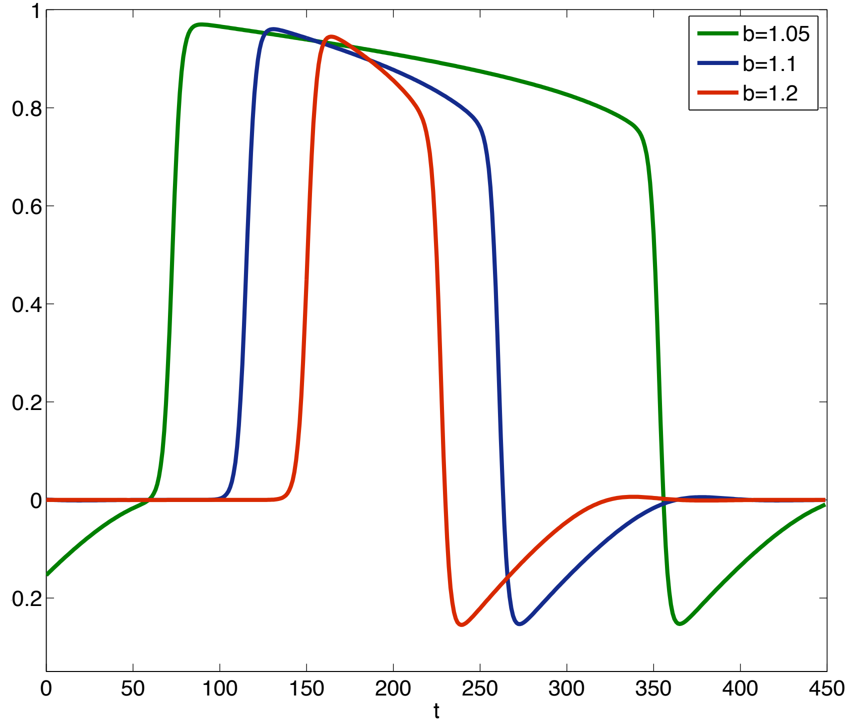
- Cardiac AP has a prolonged plateau phase lasting around 300 millisecond (ms) compared with 1 ms in nerves.
- An **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls

Action Potentials as a function of parameter "b"

a	b	c	d	d_u	d_v	ε
0.07	free	3.0	0.21	0.05	0.005	0.011

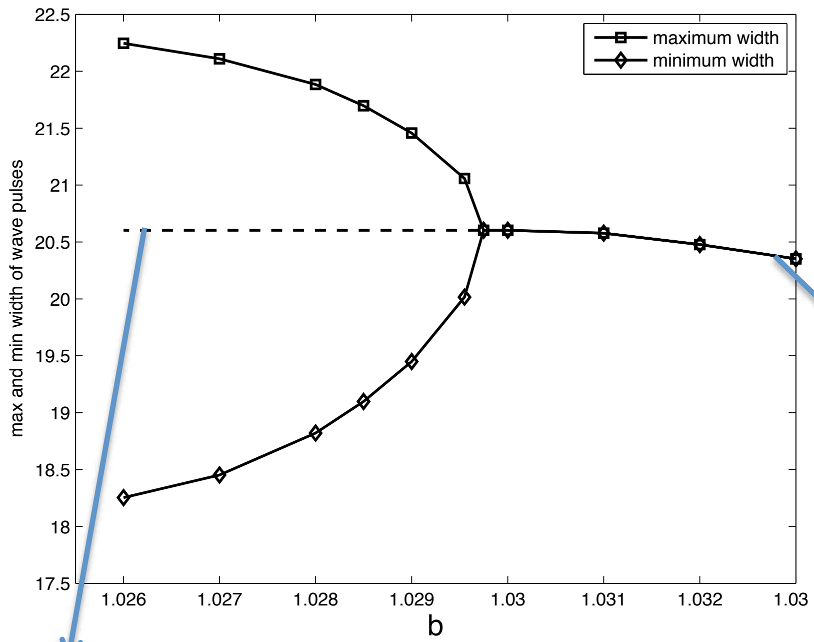


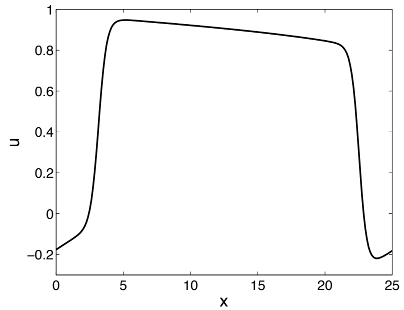
Nullclines

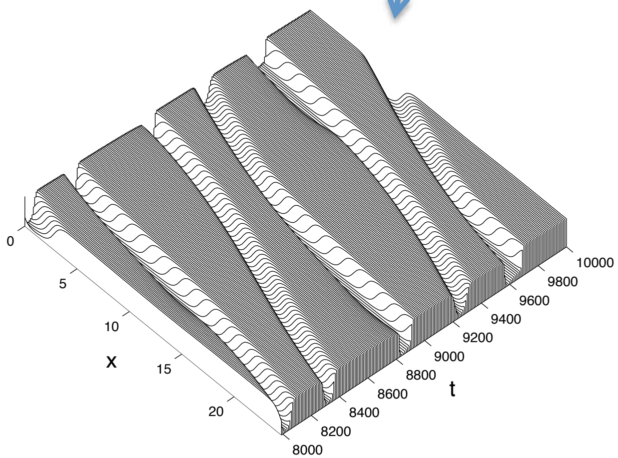


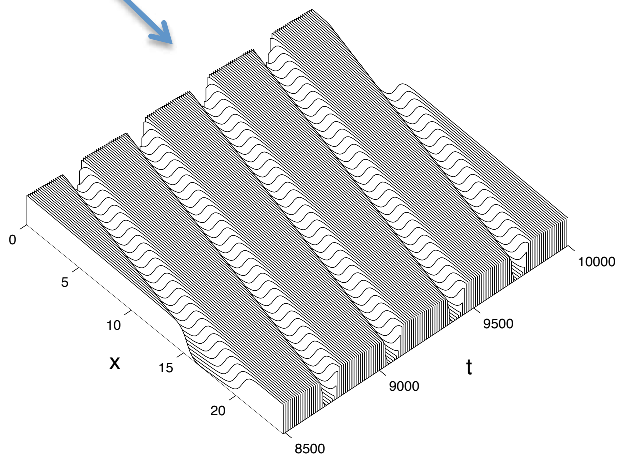
Action Potentials

PDE Simulation
(Bifurcation Diagram)





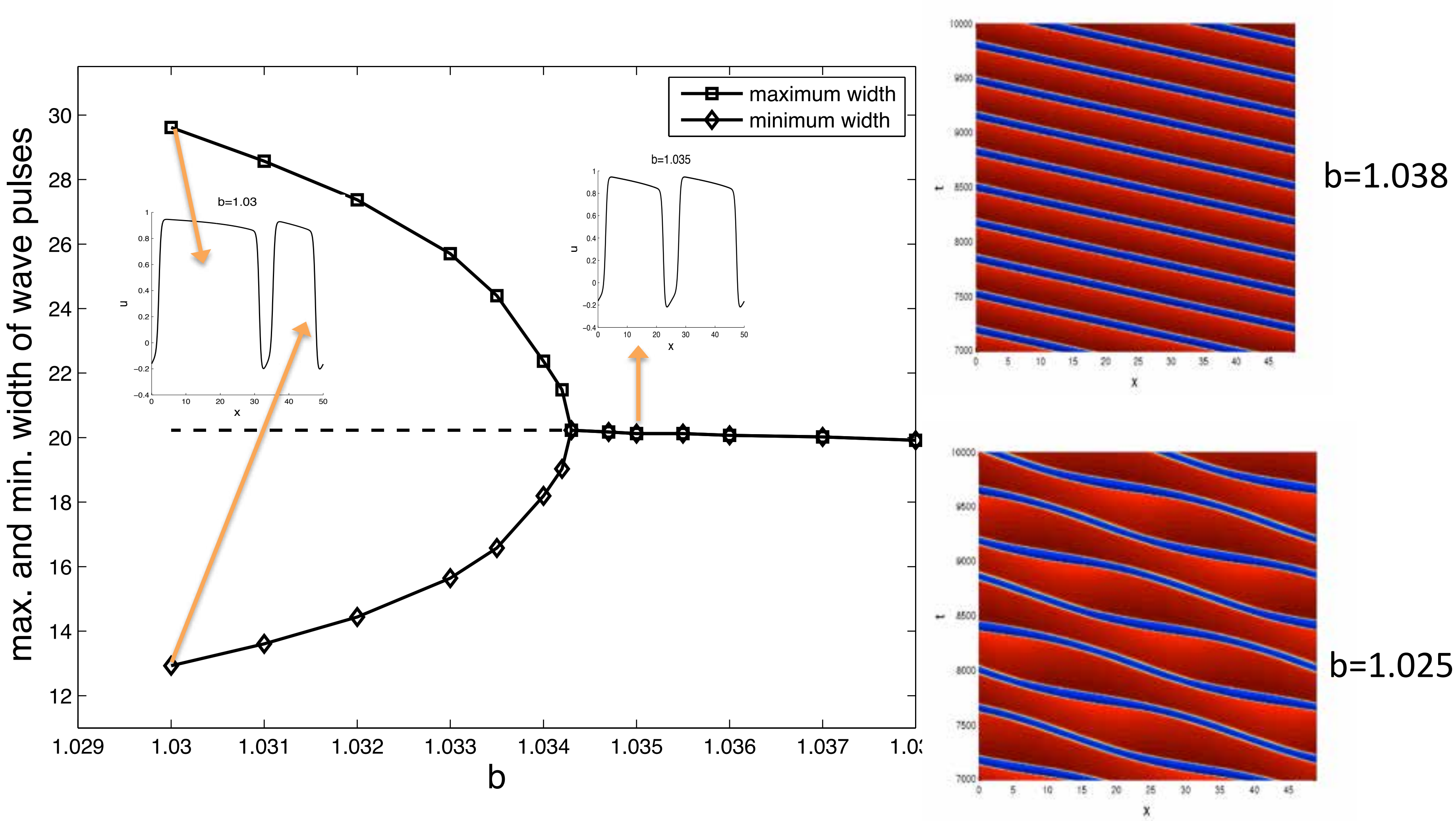




The bifurcation point is found at b=1.0295.
Let us say this critical value b_1

System size = Spatial period, i.e. L= l=25

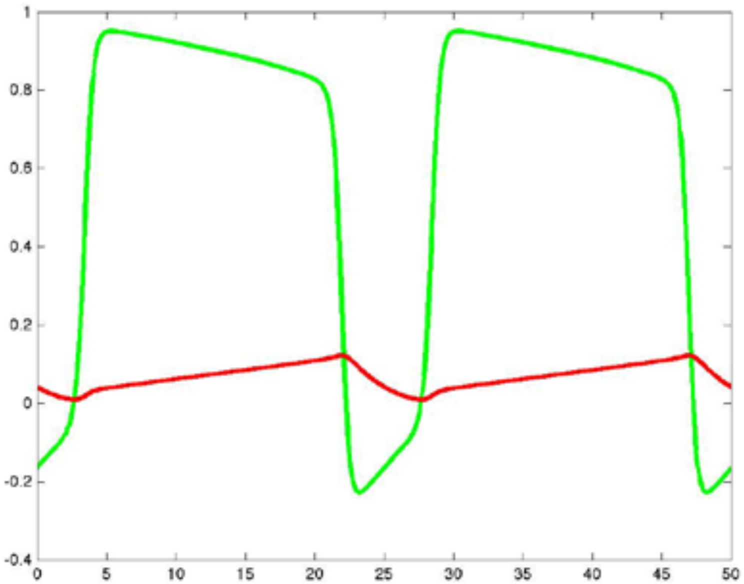
Bifurcation Diagram (L=50, l=25)



The bifurcation point is detected here at b = 1.0343. Let us say this critical value b_2

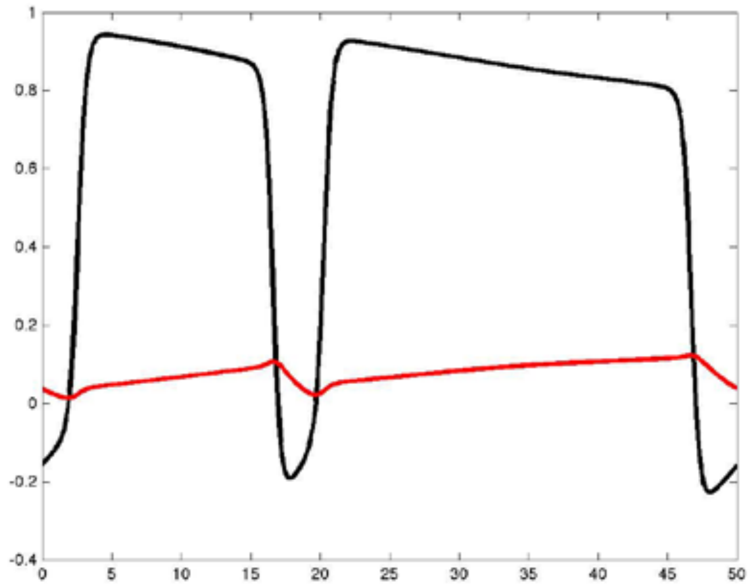
So one can expect: $b_1 < b_2 < \cdots\cdots$

Stable and Oscillatory Pattern of Solutions



b=1.038

Stable pattern



b = 1.03

Oscillatory Pattern

For Continuation Technique in the Proposed Model

1. 4-dim ODE system:

$$U' = P$$
$$P' = (-cP - U(1-U)(U-a) + V)/d_u$$
$$V' = Q$$
$$Q' = (-cQ - \varepsilon(dU(b-U)(U+c) - V))/d_v$$

Where,

$$u(x,t) = U(z)$$
$$v(x,t) = V(z)$$
$$z = x - ct$$

2. Linearized PDE:

$$\frac{\partial u_{lin}}{\partial t} = d_u \frac{\partial^2 u_{lin}}{\partial x^2} + u_{lin}(-3U^2 + 2(1+a)U - a) + v_{lin}(-1)$$

$$\frac{\partial v_{lin}}{\partial t} = d_v \frac{\partial^2 v_{lin}}{\partial x^2} + u_{lin}(\varepsilon(-3dU^2 + 2(db-dc)U + dbc)) + v_{lin}(-\varepsilon)$$

where

$$u_{lin}(x,t) = u(x,t) - U(z)$$
$$v_{lin}(x,t) = v(x,t) - V(z)$$

3. First order eigenvalue problem:

$$\frac{d}{dz}\begin{bmatrix} U_{lin} \\ M_{lin} \\ V_{lin} \\ N_{lin} \end{bmatrix} = (A(z) + \lambda B)\begin{bmatrix} U_{lin} \\ M_{lin} \\ V_{lin} \\ N_{lin} \end{bmatrix}$$

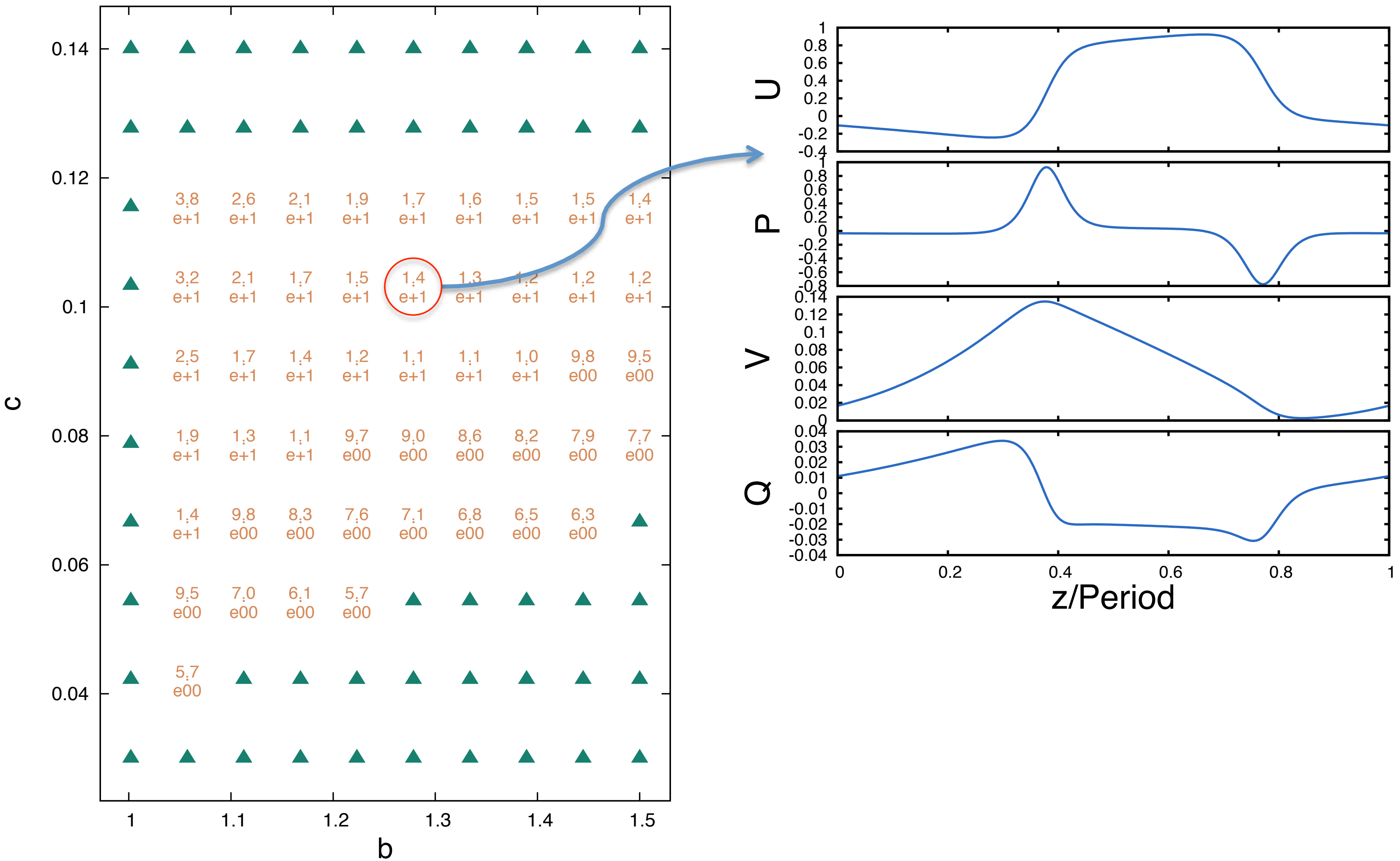
where

$$A = \begin{bmatrix} 0 & 1 & 0 & 0 \\ -\frac{1}{d_u}(-3U^2 + 2(1+a)U - a) & \frac{-c}{d_u} & \frac{1}{d_u} & 0 \\ 0 & 0 & 0 & 1 \\ \frac{-\varepsilon}{d_v}[-3dU^2 + 2(db-dc)U + dbc] & 0 & \frac{\varepsilon}{d_v} & \frac{-c}{d_v} \end{bmatrix}$$

and

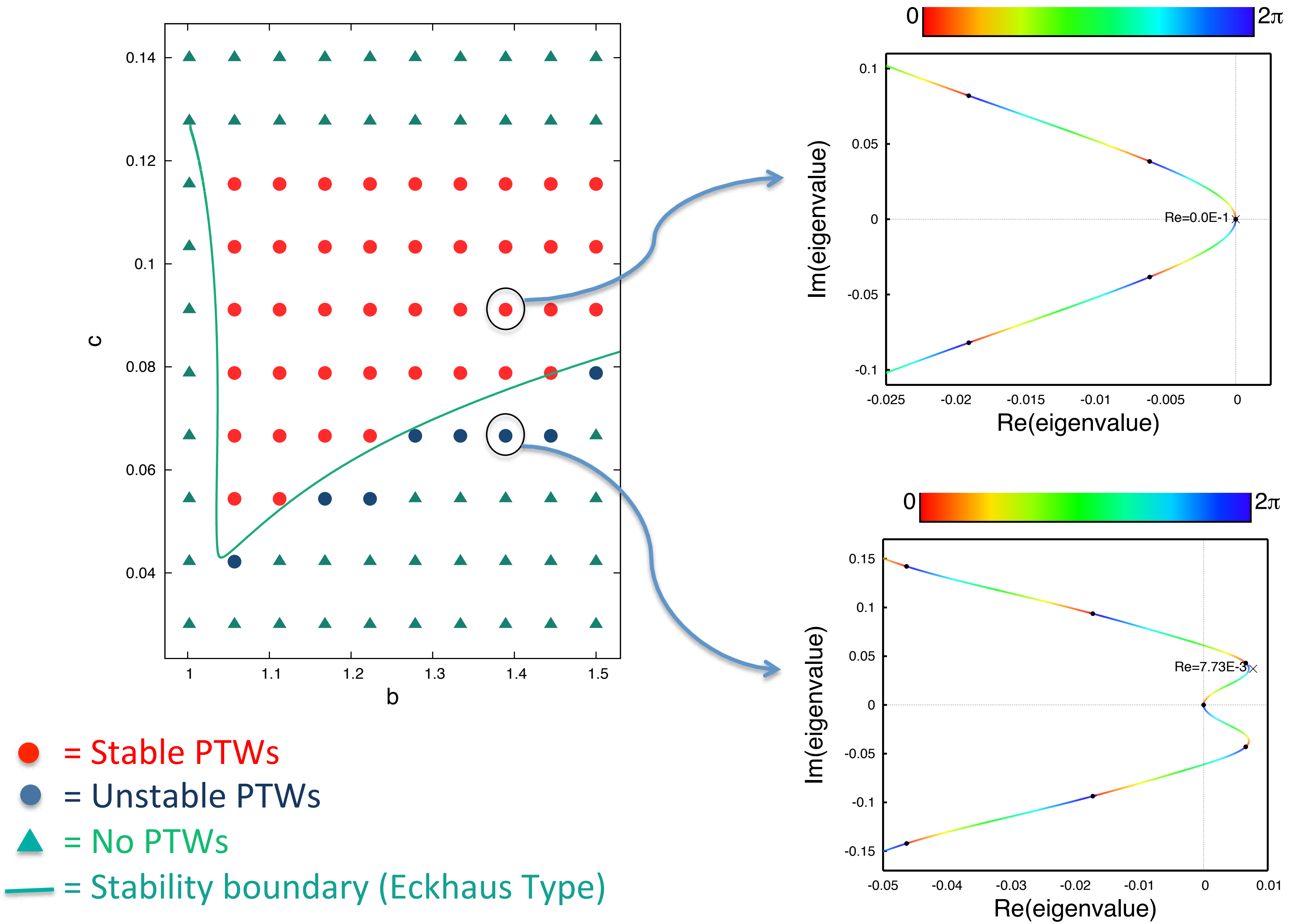
$$A = \begin{bmatrix} 0 & 0 & 0 & 0 \\ \frac{1}{d_u} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{d_v} & 0 \end{bmatrix}$$

Existence of PTWs in the Proposed Model

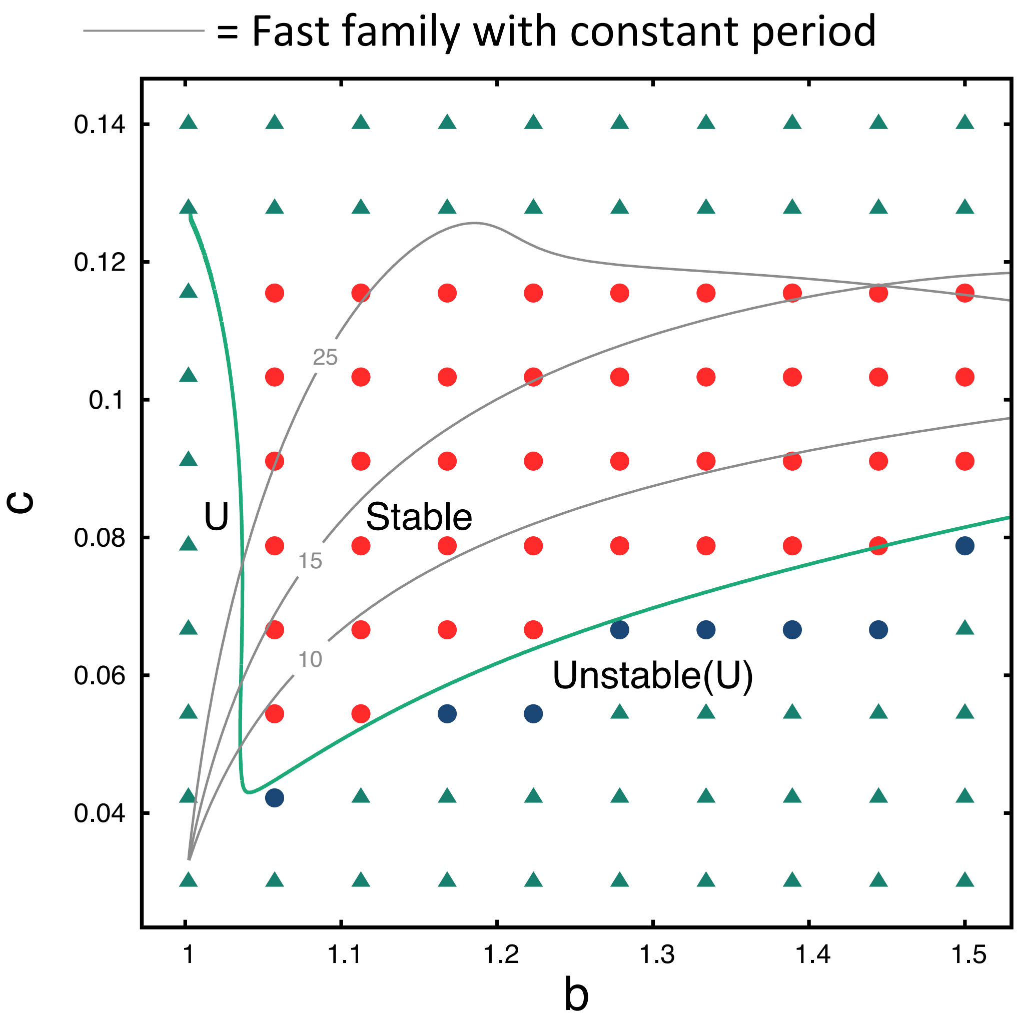


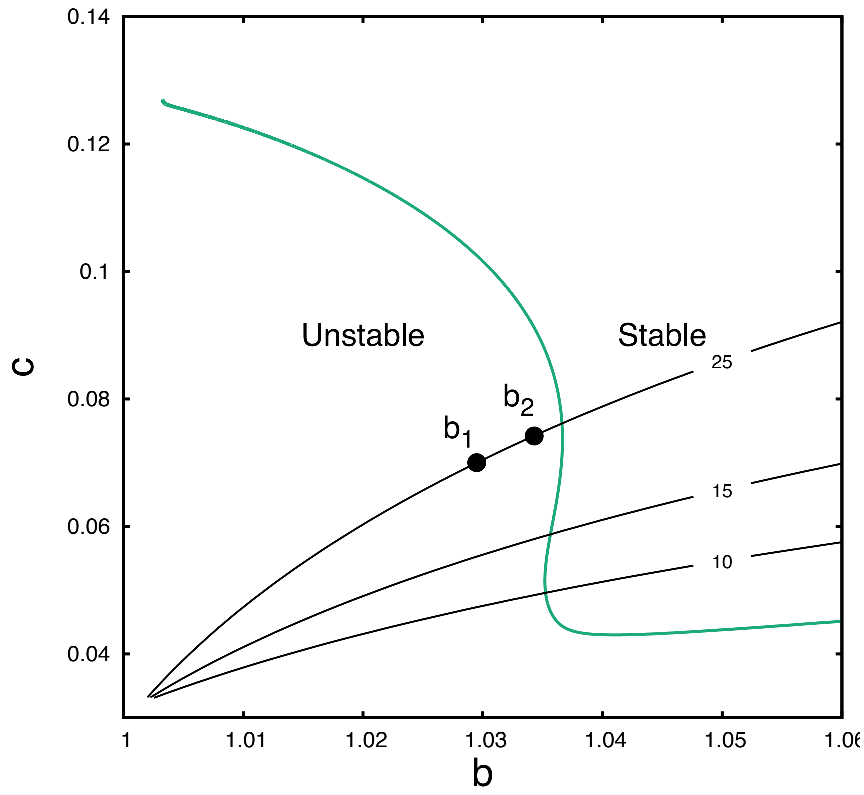
▲ = No PTWs

Stability of the PTWs Through Essential Spectra



Fast Family of PTWs

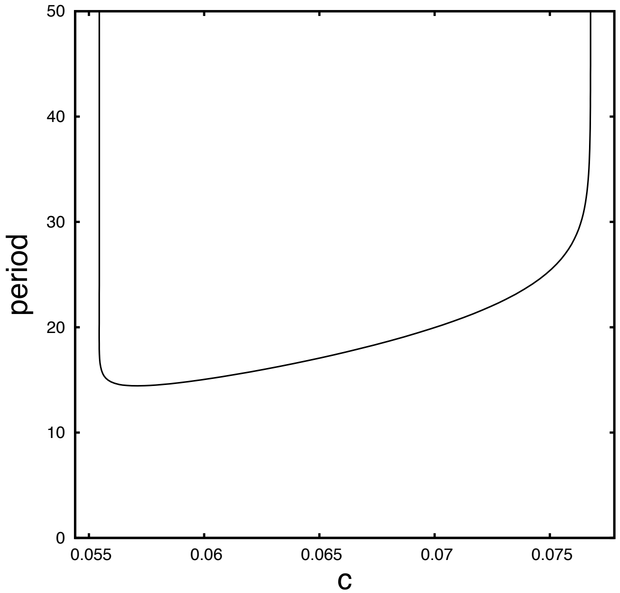




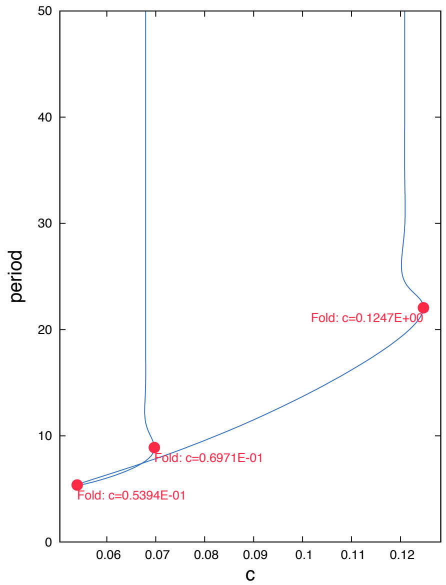
Magnification

- Fast Family crosses the stability boundary in our model
- The bifurcation points b_1 and b_2 lie in the unstable area

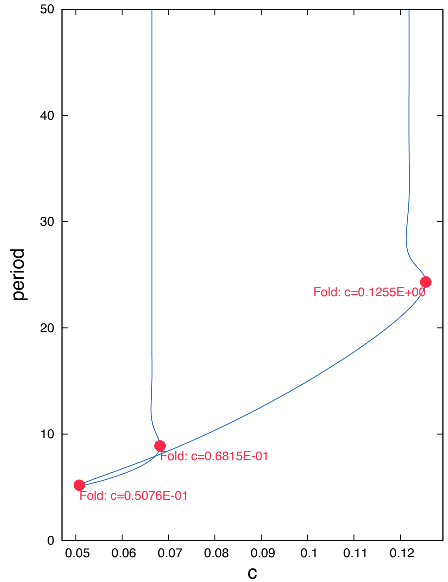
Bifurcation Diagrams or Dispersion Curves



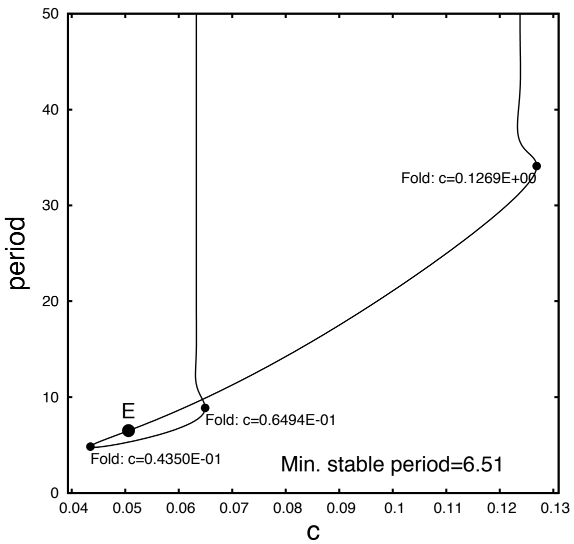
b=2.2



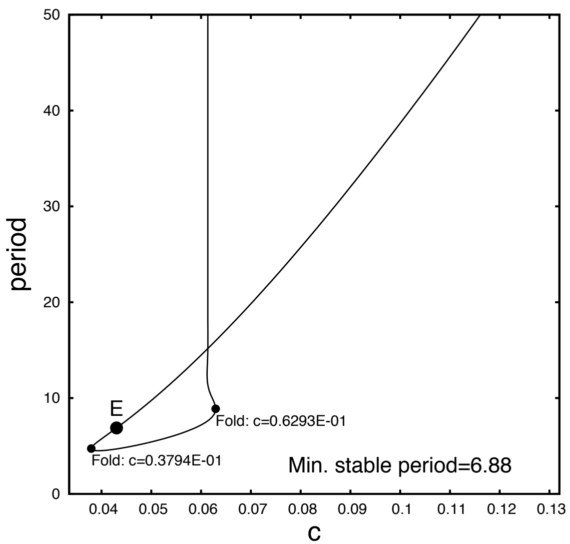
b=1.25



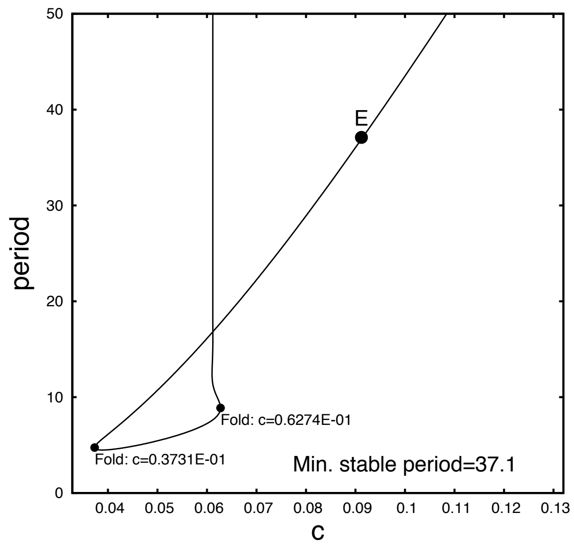
b=1.2



b=1.1

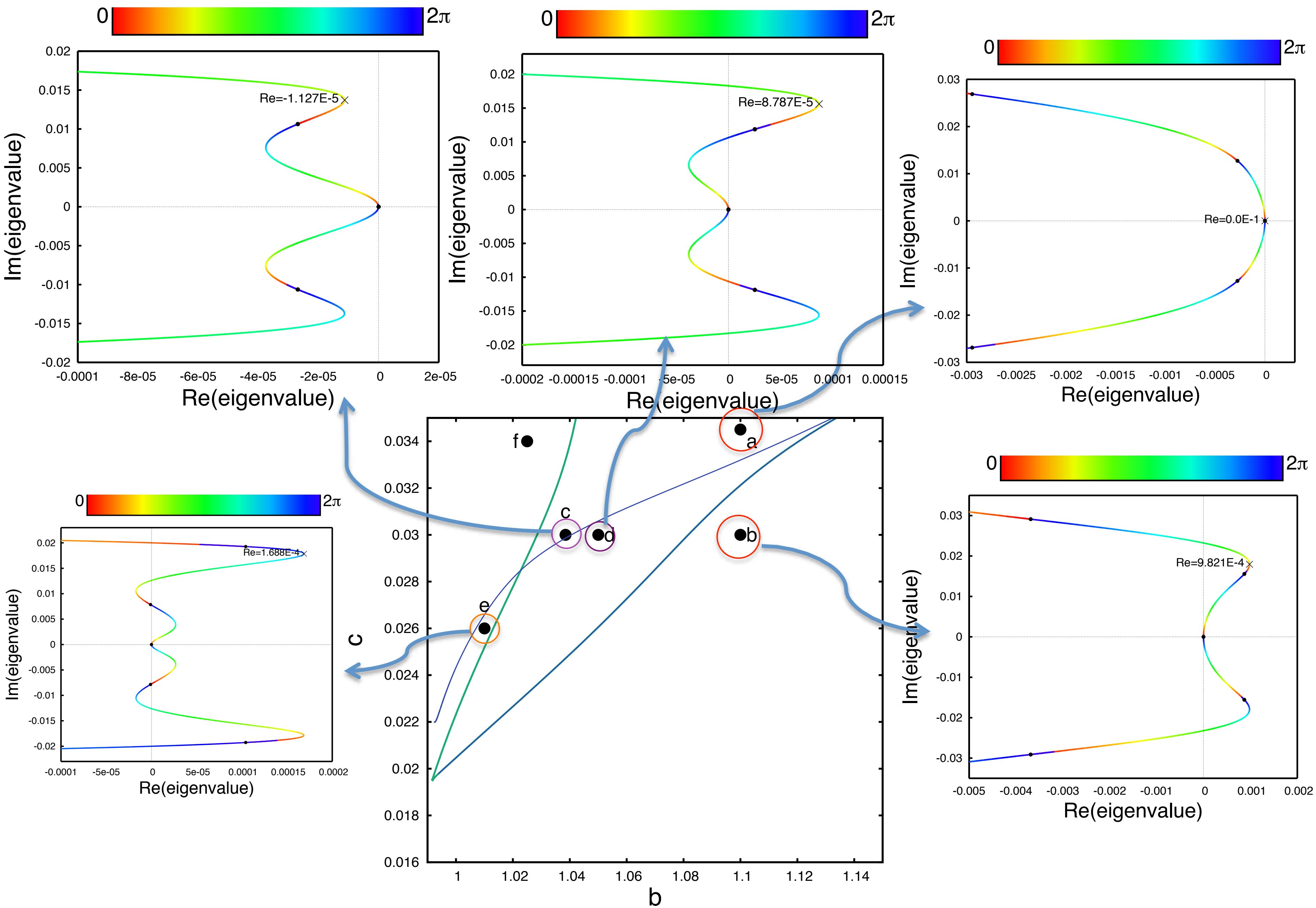


b=1.04

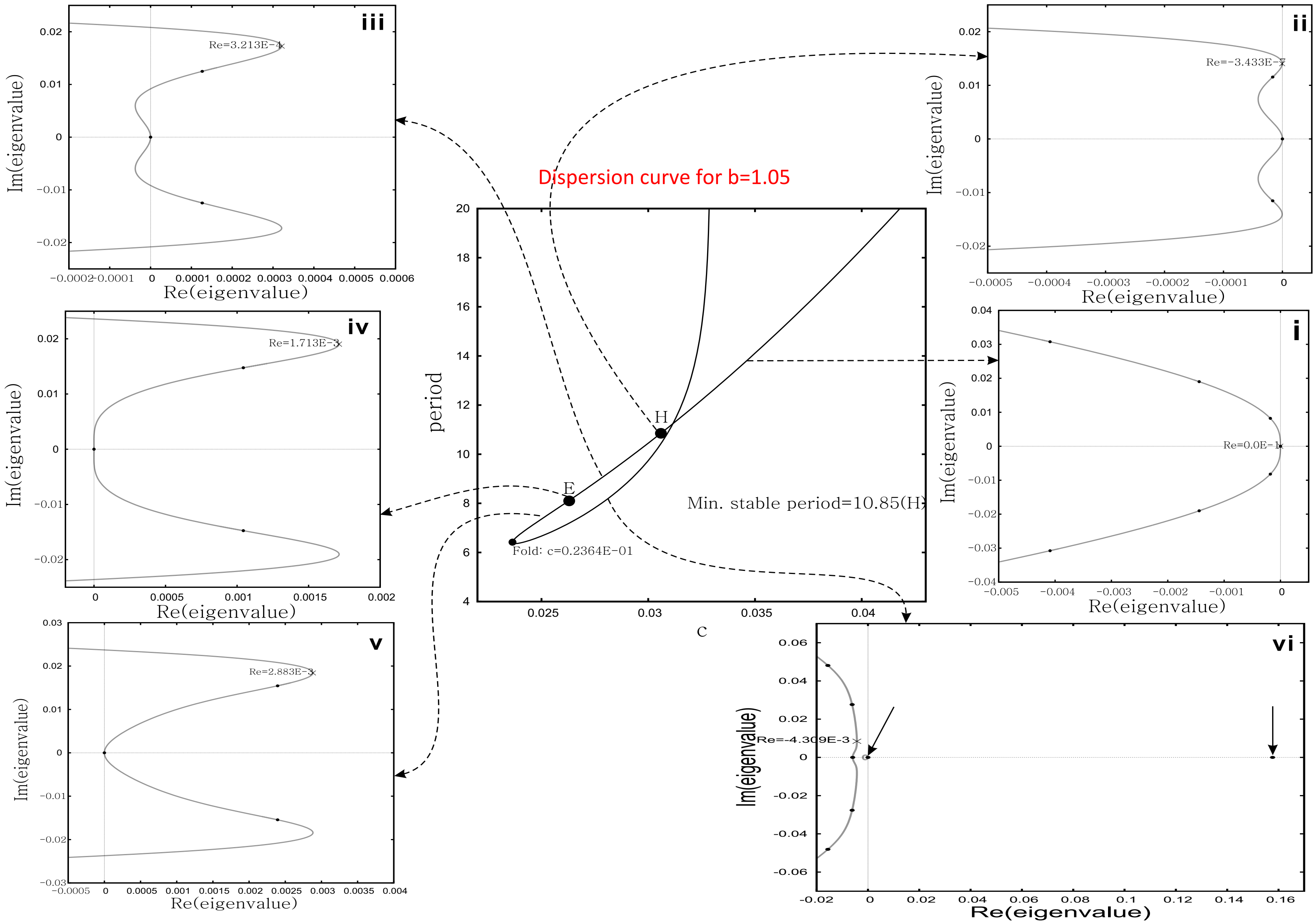


$b = b_2 = 1.0343$

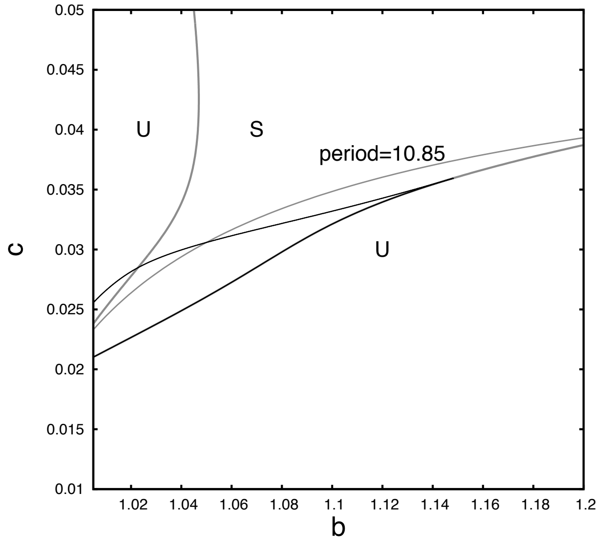
Essential Spectra (Eckhaus and Hopf instability)

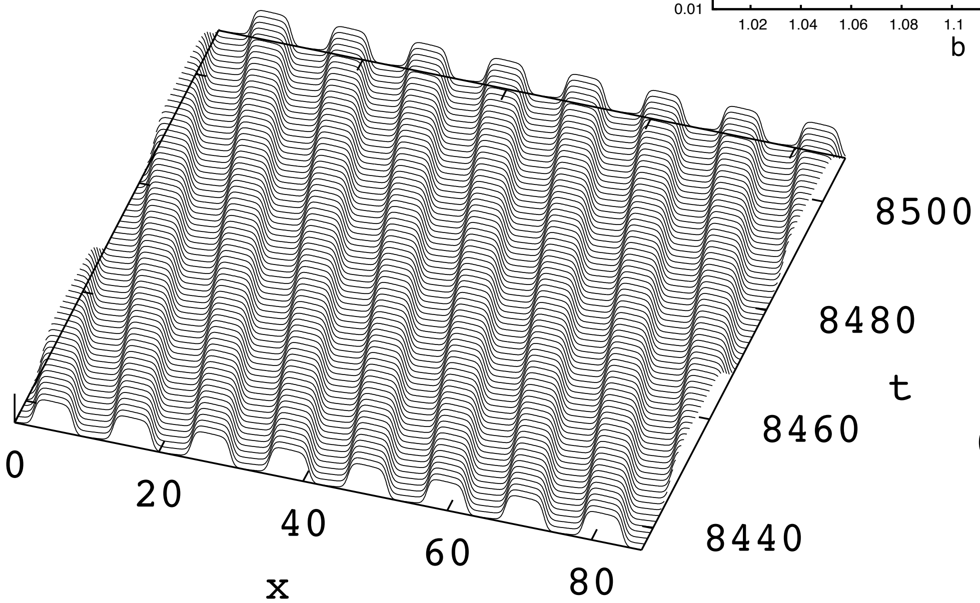


Essential Spectra in the different parts of a dispersion curve

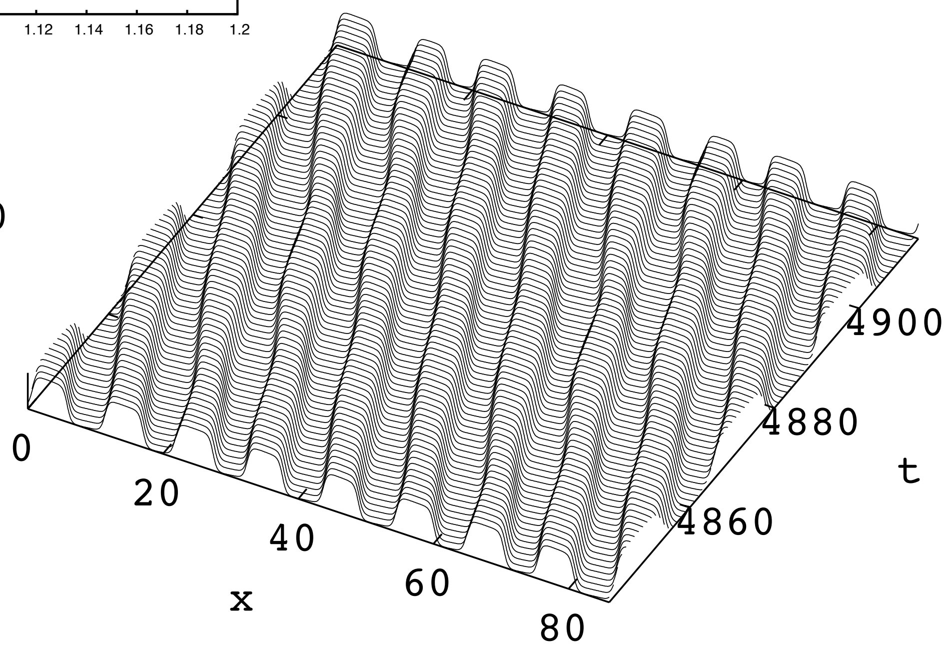


PDE Simulation as a consequence of the Hopf instability



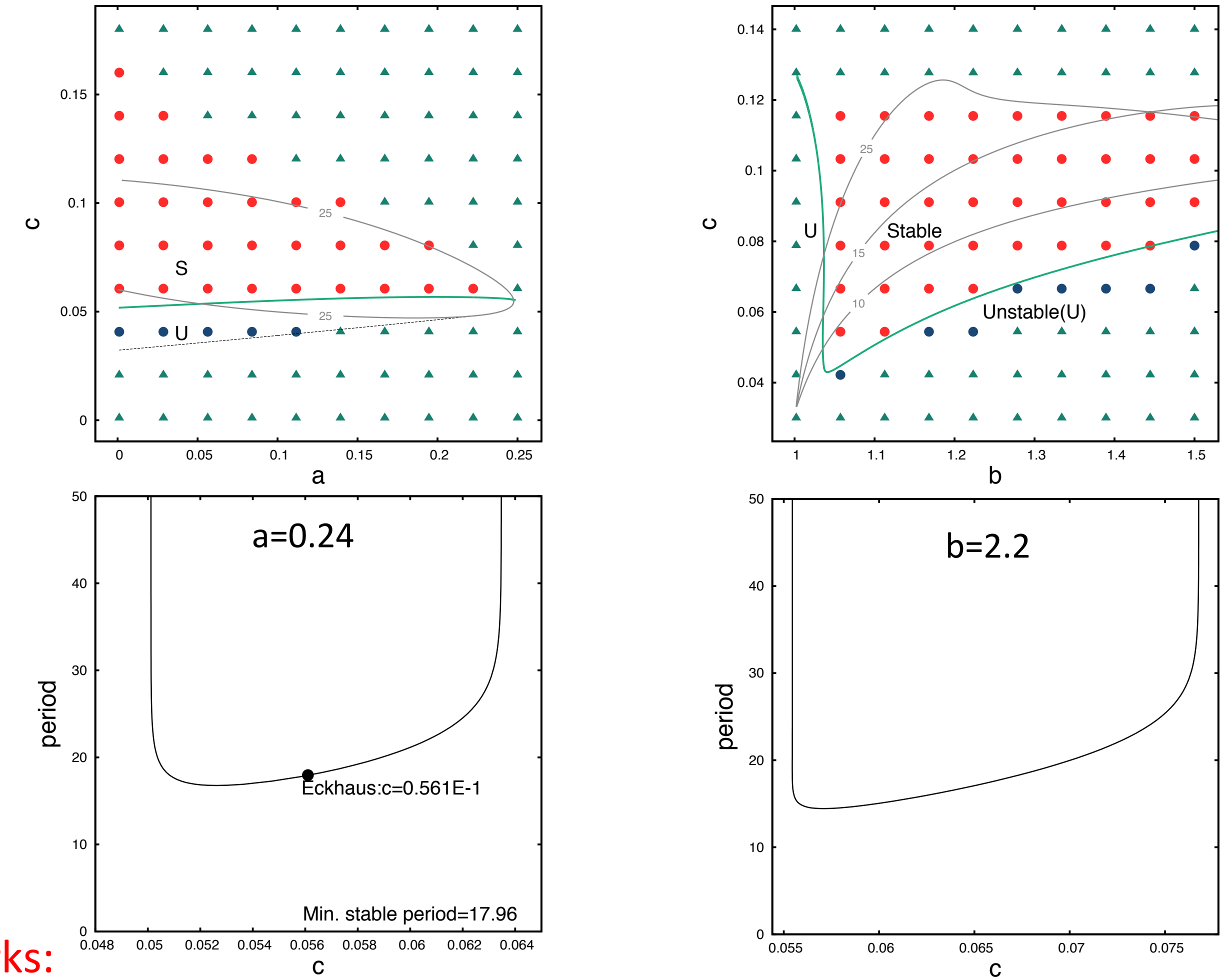


L=86.96, l=10.87



L=86.4, l=10.8

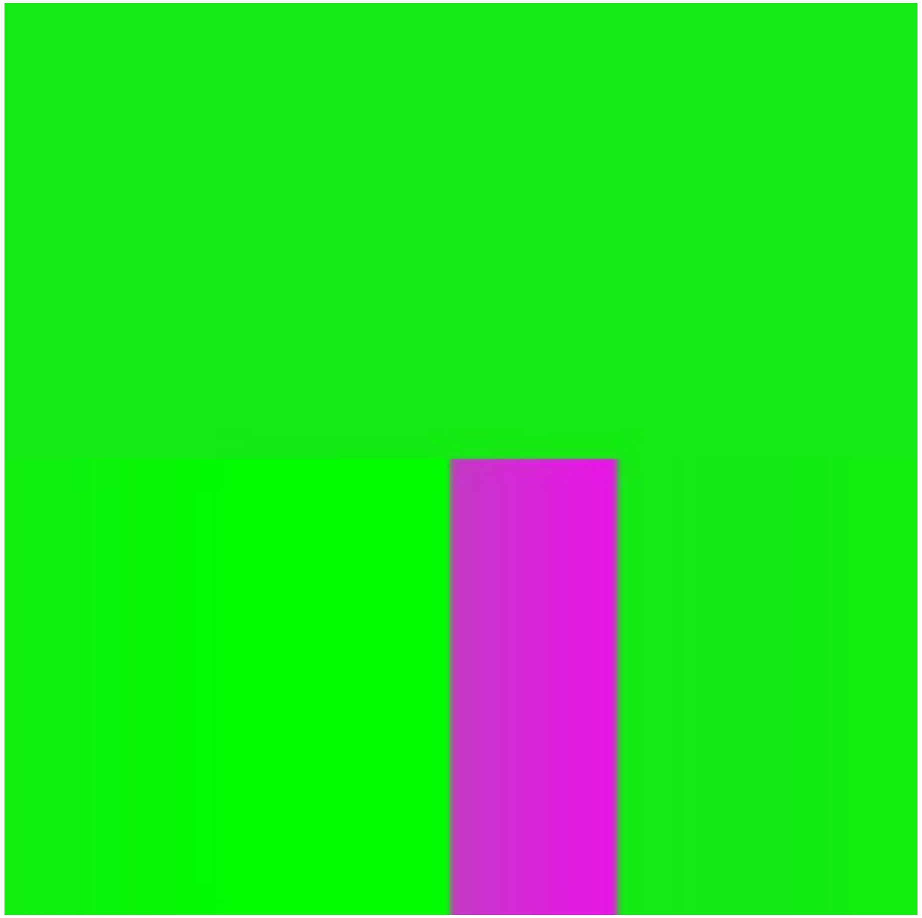
FHN vs m-FHN



Remarks:

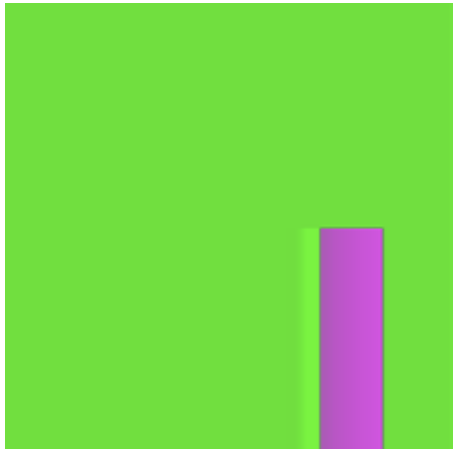
- Thus in our model by controlling the parameter *“b”* we control the stability of solutions
- The fast family with sufficiently large period always stable in the FHN model, whereas in our model they crosses the stability boundary and this is responsible for the oscillatory pattern of solution in the full PDE simulation

Spiral wave formation



$b = 1.05$

Spiral pulses widths increasing as b decreased



Initial data

b=1.3

b=1.2

b=1.1

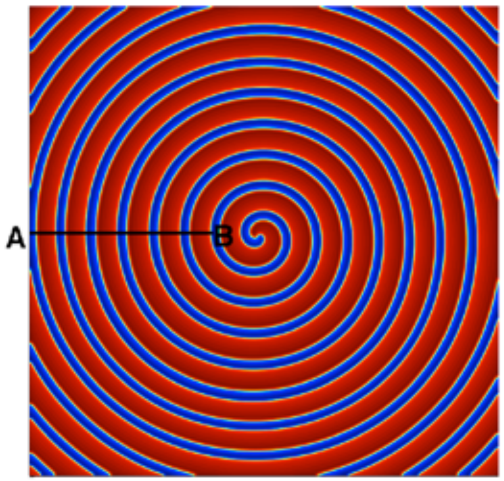
b=1.05

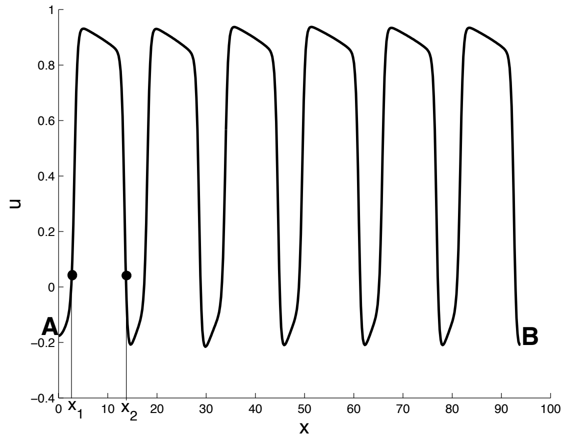
b=1.04

b=1.035

b=1.03

Calculation of Spiral Pulse widths and onset of oscillation





$$\text{Pulse width} = |x_1 - x_2|$$

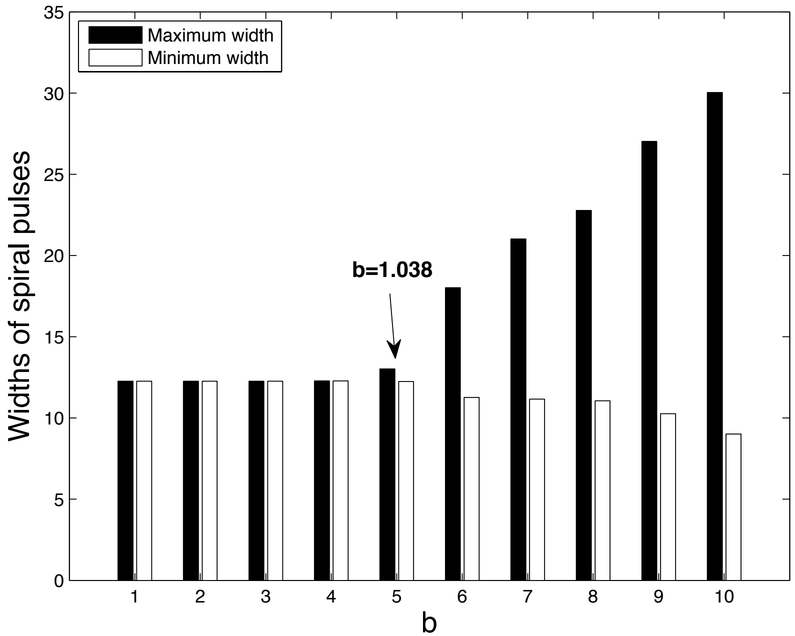
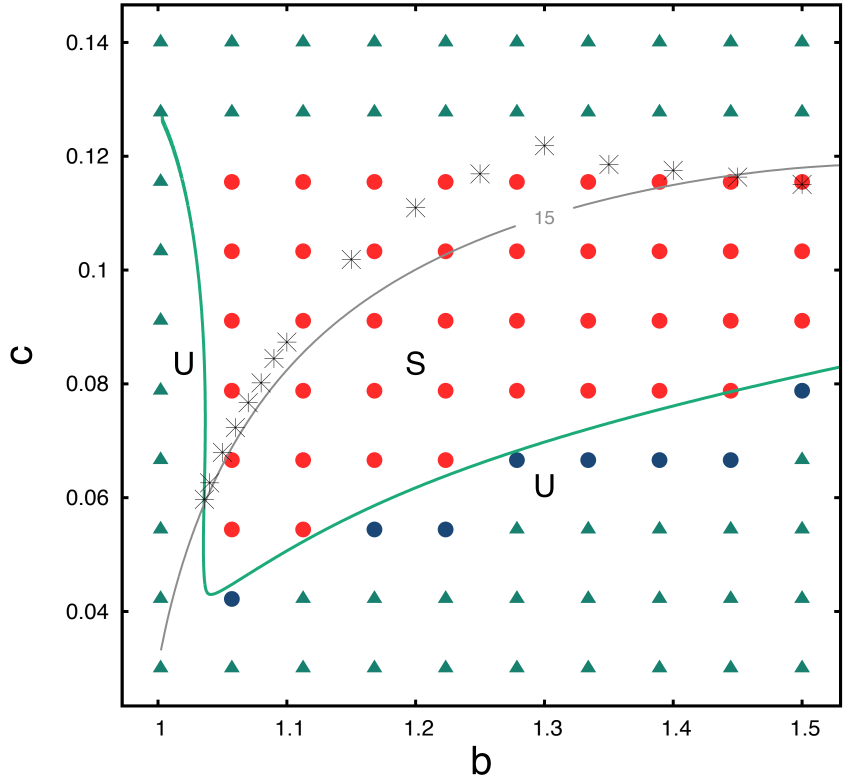
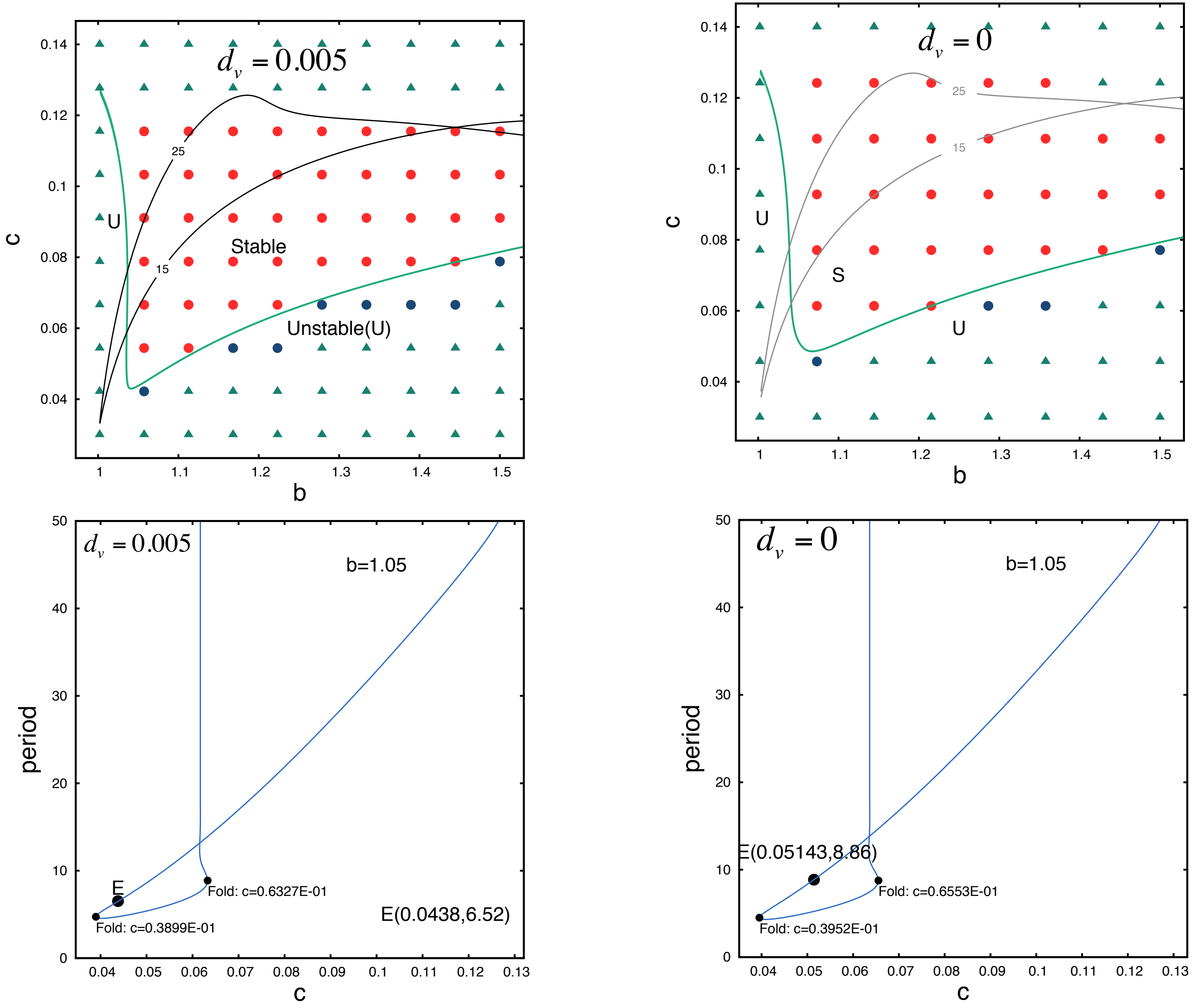


Figure: Max and Min width of spiral pulses as a function of b.

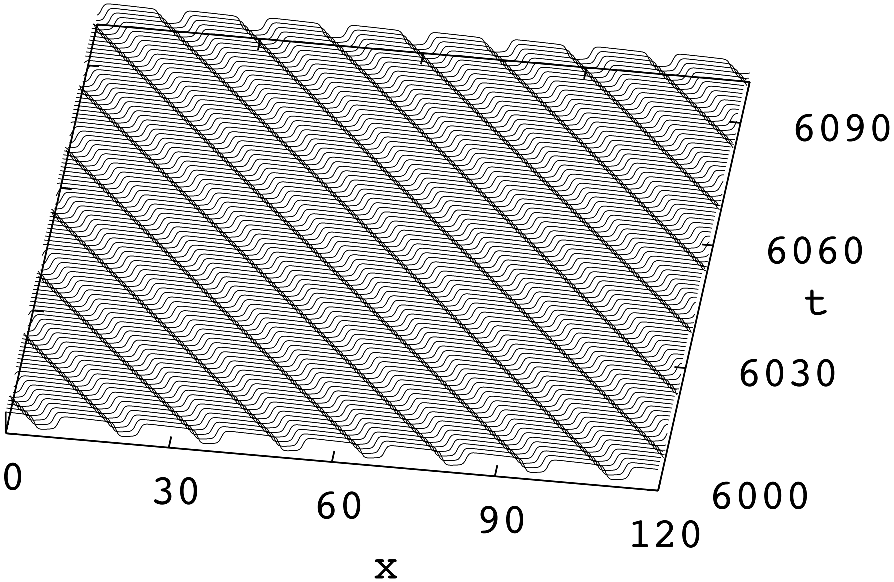


Speed of parallel wave in 2D as a function of b (asterisk line)

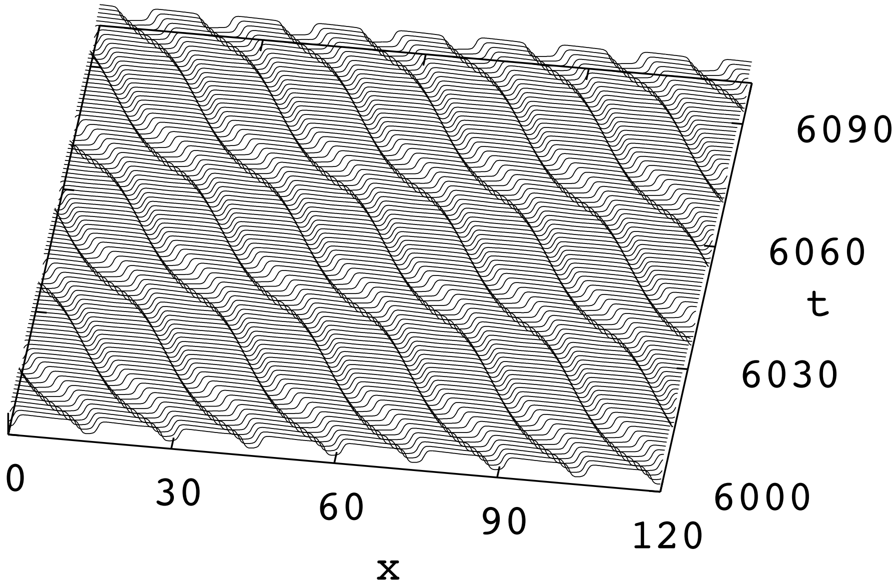
Stability of PTWs when “$d_v = 0$“



PDE Simulation, when $d_v = 0$



b=1.055



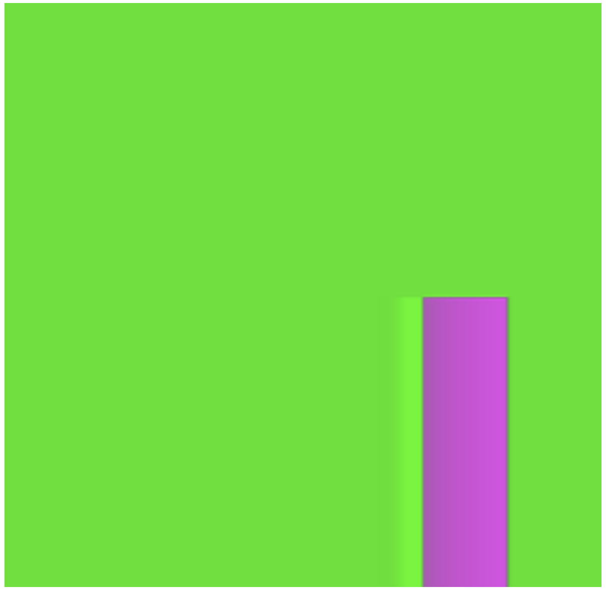
b=1.03

b=1.045

Onset of instability

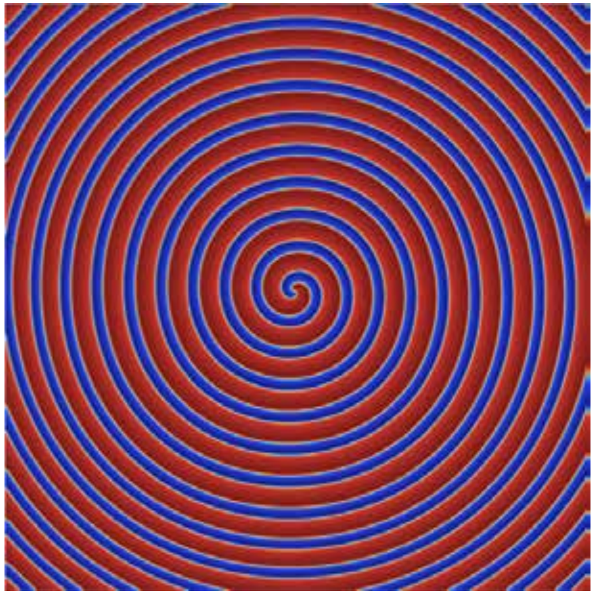
However, for d_v=0.005, the onset of instability b = 1.0355

Spiral Dynamics, when d_v=0



Initial data

b=1.2



b=1.1

b=1.05

b=1.04

Thus the stable spiral pattern bifurcate to an unstable pattern between b=1.1 and b=1.05

Summary

- We have studied the stability of PTWs numerically in FHN-type RD systems for excitable media
- We found two types of instability in the proposed model:

  Eckhaus type and Hopf type
- The fast family is stable in the FHN model, whereas it crosses the stability boundary in the proposed model.
- The alternans, i.e. the oscillation of pulse width, is a consequence of the instability of PTWs.
- The onset of spiral wave instability was observed as a consequence of Eckhaus instability of the PTWs.

Thank you for your attention!!