心筋細胞における脈動パルスの構成に向けて

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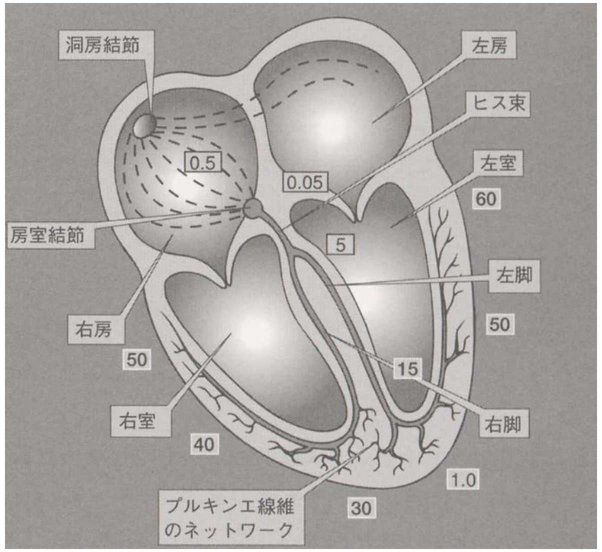
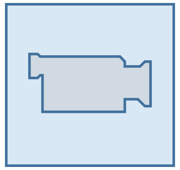
心筋細胞の興奮

心臓

心筋細胞、興奮性細胞

洞房結節とよばれる場所（ペースメーカー領域）に自発的に発火する細胞群があり、ここから興奮が心臓全体に広がる。





From YouTube

不整脈と心室細動

不整脈　心臓の拍動の異常

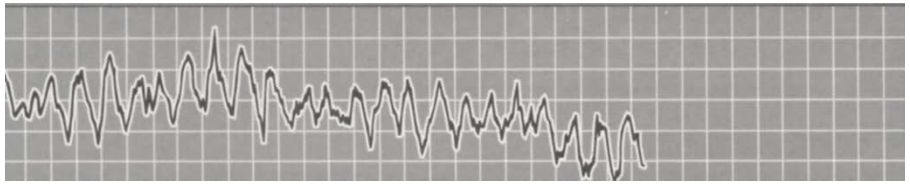
　頻脈　心拍数が増加

　徐脈　心拍数が低下

心室細動　放置すると死に至る危険な不整脈。

　心電図では細かい速い振動が見られるだけで、血液が心臓から出ていかない。

正常状態心電図



心室細動状態

スパイラルリエントリー

- スパイラルパターン:　興奮がスパイラル中心のまわりで循環し、リエントリーが生じ頻脈が起こる。

- 心房細動:　興奮波が旋回しながら心房が連続的に興奮

　心房の速すぎる興奮は房室結節で一部せき止められるので危険性は心室細動ほど高くないが、脳梗塞の原因になったりする。

- 心室頻拍(VT):　脈拍が200程度になるが心電図は規則的

　　　　安定スパイラル？

- 心室細動(VF):　脈拍が200-300程度になり心電図振幅は小さく　不規則。 スパイラルが自発的に分裂した、スパイラルカオス？

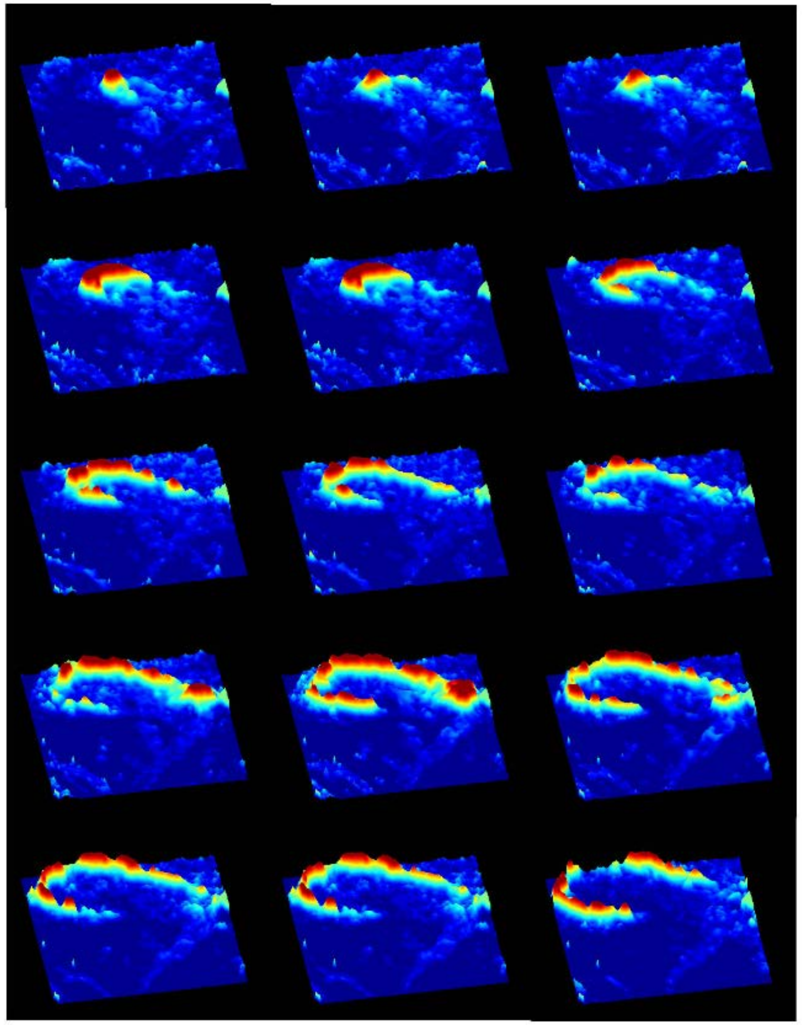
興奮系のスパイラルが不整脈に関連することがわかってきたのは

　比較的最近　Moe　1964　Winfree　1972

Visualization of spiral in real heart by optical mapping method

犬の心臓の実験から、スパイラル波動やその分裂が心室細動と関連することが示唆されている。

スパイラル波動が電位依存化学物質を利用して観測できるようになっている(光学マッピング)



Spiral in dog heart

F.W.Witkowski et al.
Nature 392,78(1998)

除細動

心室細動を押さえるために緊急処置として行うのが心臓全体に短時間に大きな電気パルスを与える電気ショックである。

AED：自動体外式除細動器

緊急処置：内蔵する心電図計で自動的に心室細動か判断し電気ショックを加える

ICD：植え込み型除細動器

ペースメーカのように体のなかに植え込んで細動が起こると自動的に電気ショックが加わる

心筋に見られる波

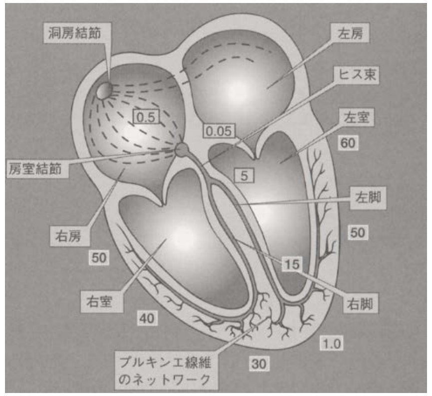
不整脈 ⇒ らせん波の発生

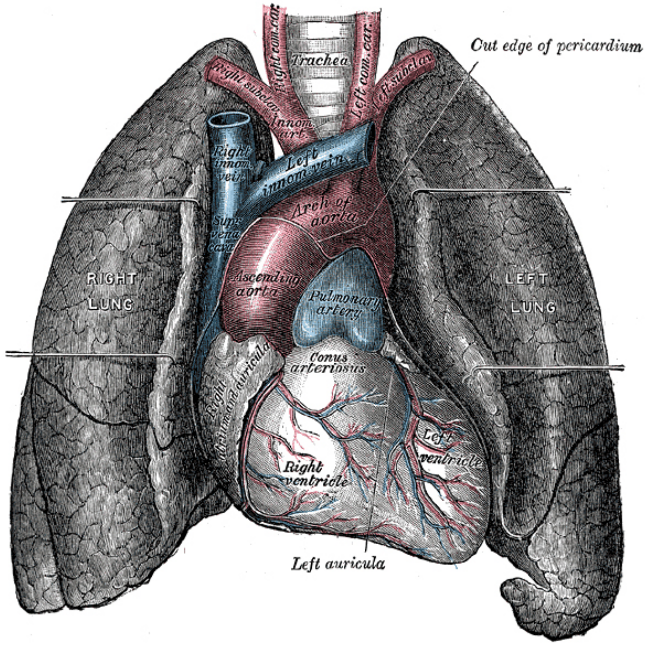
Osaka etl.al.

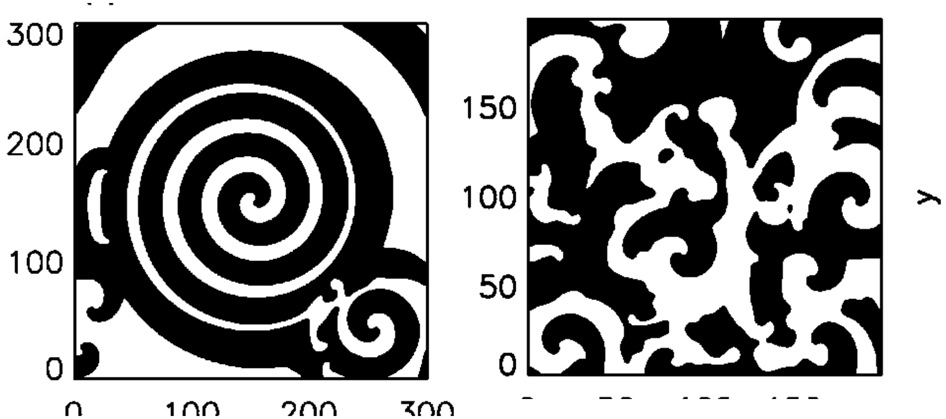
Study of traveling waves, trains

Panfilov et.al 00, H.Sakaguchi 03, 05, T.Ogawa 14

Consider one dimensional problems





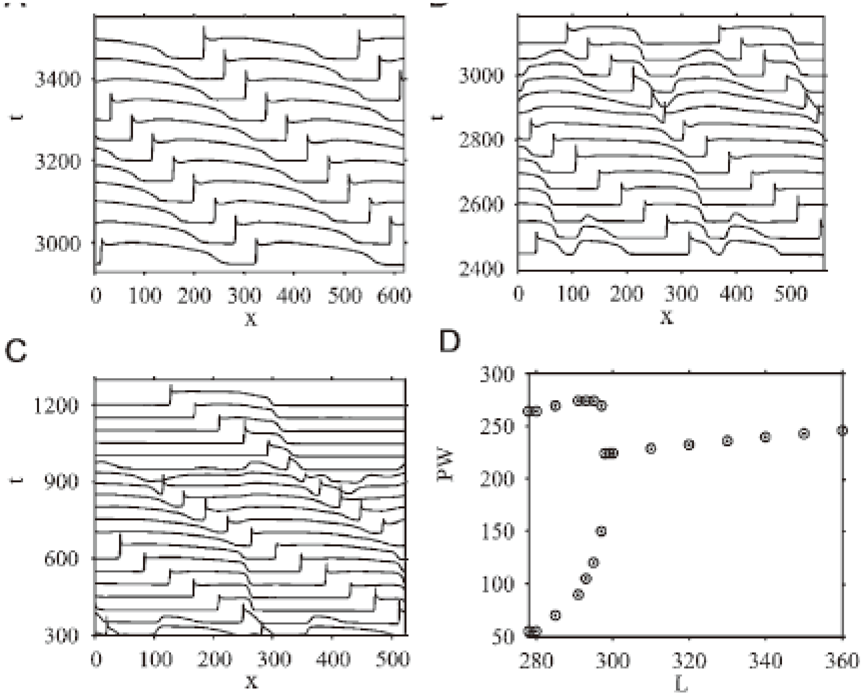


Ludy-Ruoモデル

心筋細胞の興奮の数理モデル（Hodgkin-Huxley型方程式）

実験と定量的に比較可能

電位とイオンチャネルの8変数の連立微分方程式



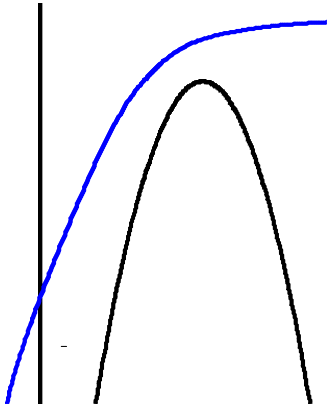
Luo-Rudy モデル（一次元）でシステムサイズL（L は無次元化）が 620 の際の定常興奮（A）と L が 560（B），524（C）における活動電位持続時間（APD）の交互不安定化．D はパルス幅（PW：APD に相当）と L の関係．E

空間長さLを短くすると定常パルスが脈動化し、消滅

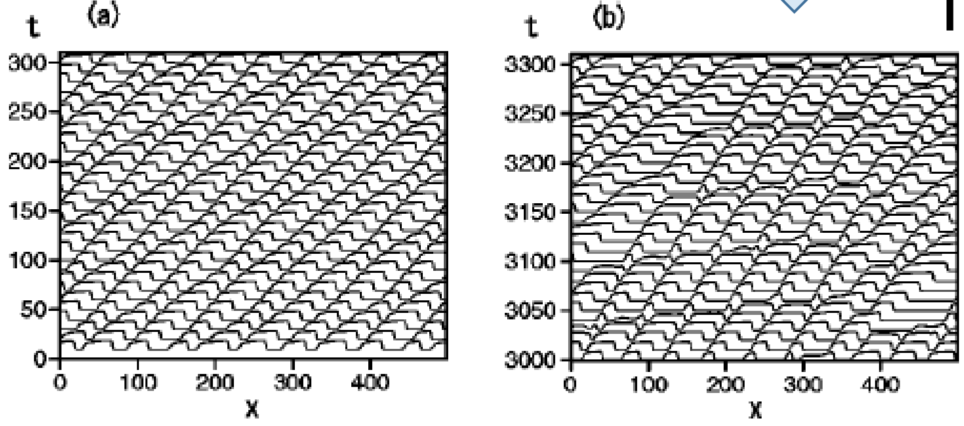
Mathematical models for waves in Cardiac activity

Aliev-Panfilov model (1996)

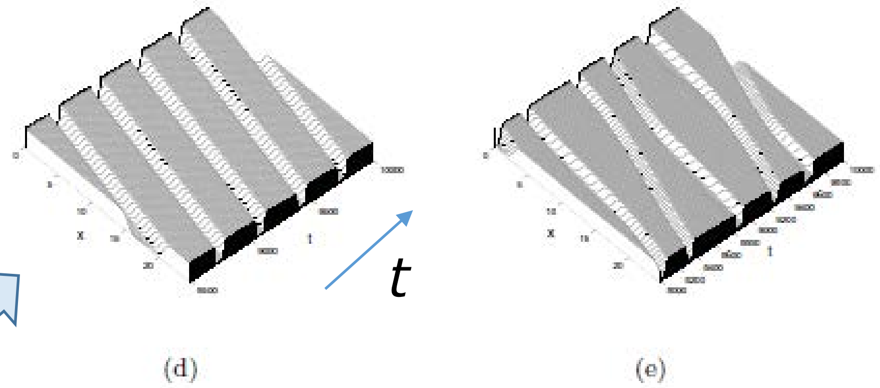
$$\begin{cases} u_t &= \varepsilon^2 u_{xx} - k_0 u(u-a)(u-1) - uv =: f(u,v), \\ \tau v_t &= \varepsilon(k_1 + k_2 v/(k_3+u))[-v - k_4 u(u-k_5-v)] =: g(u,v), \end{cases}$$



Sakaguchi 03



Traveling trains

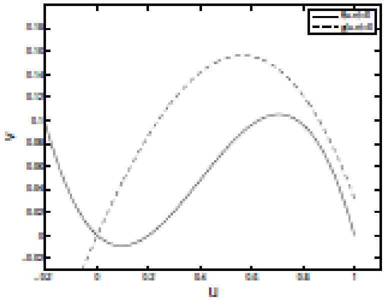


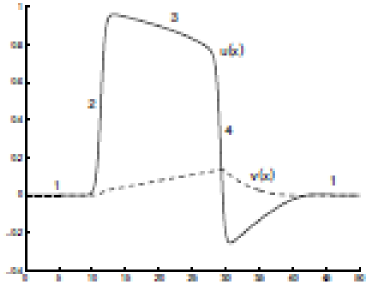
Gani, Ogawa 14

Eckhaus instability

Modified FHN equation

$$\begin{cases} u_t &= d_1 u_{xx} - u(u-a)(u-1) - v, \\ \tau v_t &= d_2 v_{xx} + \varepsilon[(k_1 u(k_2-u)(u+k_3) - v], \end{cases}$$





Traveling pulse solutions in Cardiac activity

Stable traveling pulse in cardiac models

Not overshooting

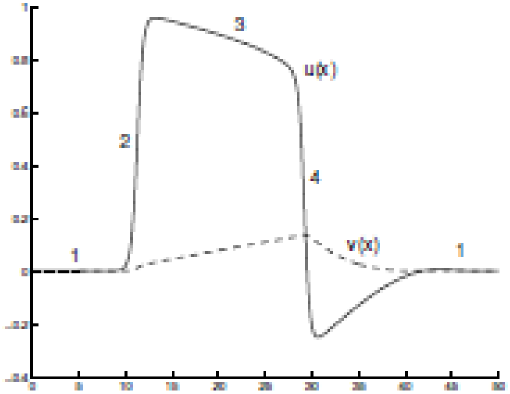
e.g. Sakaguchi 03

Aliev-Panfilov model (1996)

$$\begin{cases} u_t &= \varepsilon^2 u_{xx} - k_0 u(u-a)(u-1) - uv, \\ \tau v_t &= \varepsilon(k_1 + k_2 v/(k_3+u))[-v - k_4 u(u - k_5 - v)], \end{cases}$$

Modified FHN equation

$$\begin{cases} u_t &= d_1 u_{xx} - u(u-a)(u-1) - v, \\ \tau v_t &= d_2 v_{xx} + \varepsilon[(k_1 u(k_2 - u)(u + k_3) - v], \end{cases}$$



Gani, Ogawa 14

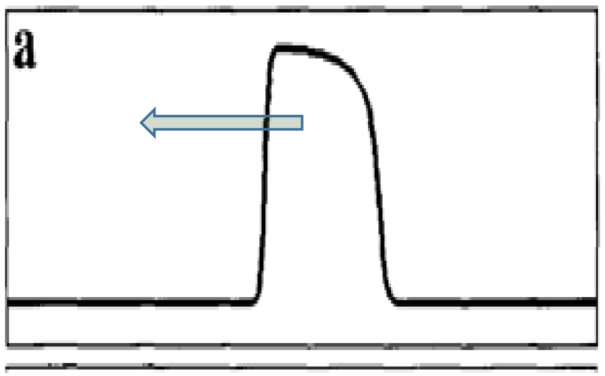
overshooting

Comparison between pulses in cardiac tissues and nerve impulses

Comparison between two examples

Aliev-Panfilov model (1996) AP model

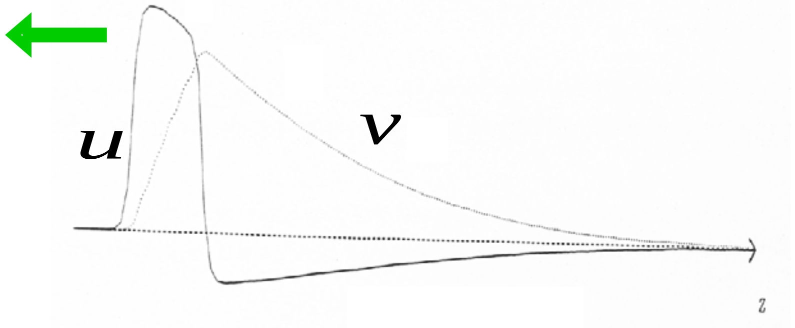
$$\begin{cases} u_t &= \varepsilon^2 u_{xx} - k_0 u(u-a)(u-1) - uv, \\ \tau v_t &= \varepsilon(k_1 + k_2 v/(k_3+u))[-v - k_4 u(u-k_5-v)], \end{cases}$$



In both, existence of stable traveling pulses with node type

FitzHugh-Nagumo equation FHN model

$$\begin{cases} u_t &= \varepsilon^2 u_{xx} + f(u) - v, \\ \tau v_t &= \varepsilon(u - \gamma v), \end{cases}$$

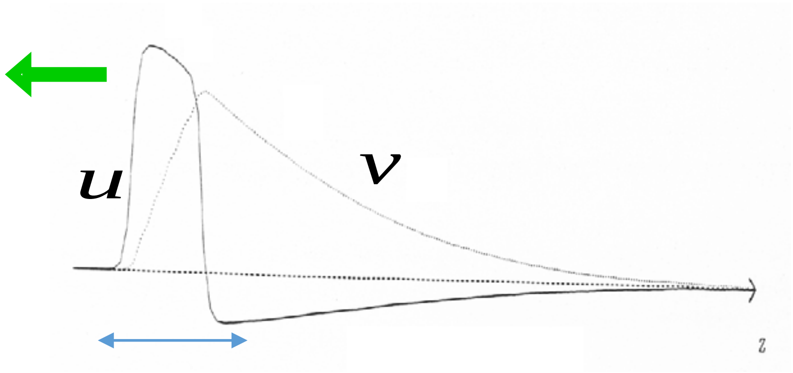


Difference between pulses of AP and FHN

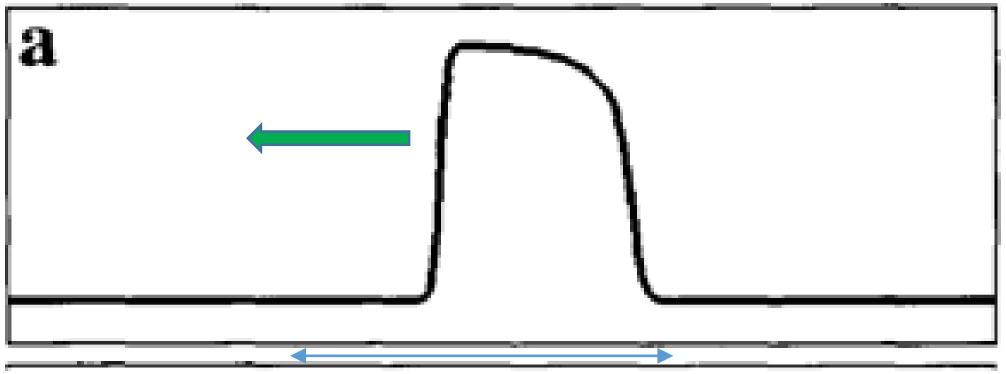
FHN

AP

Active region



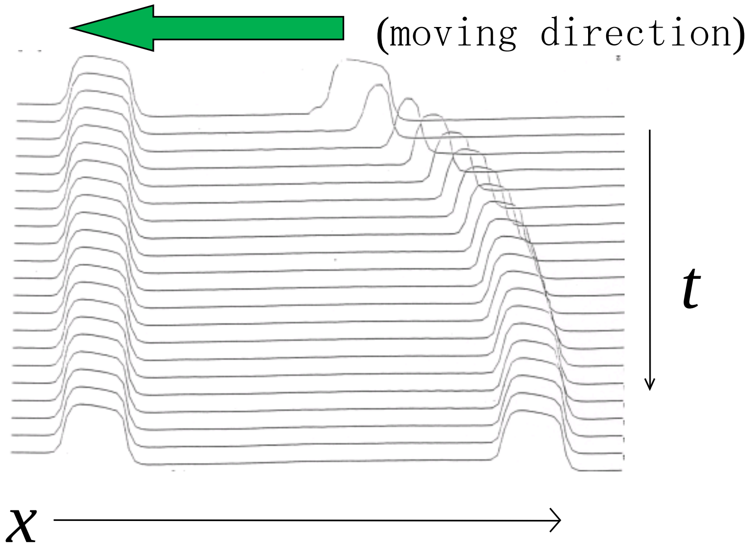
narrow

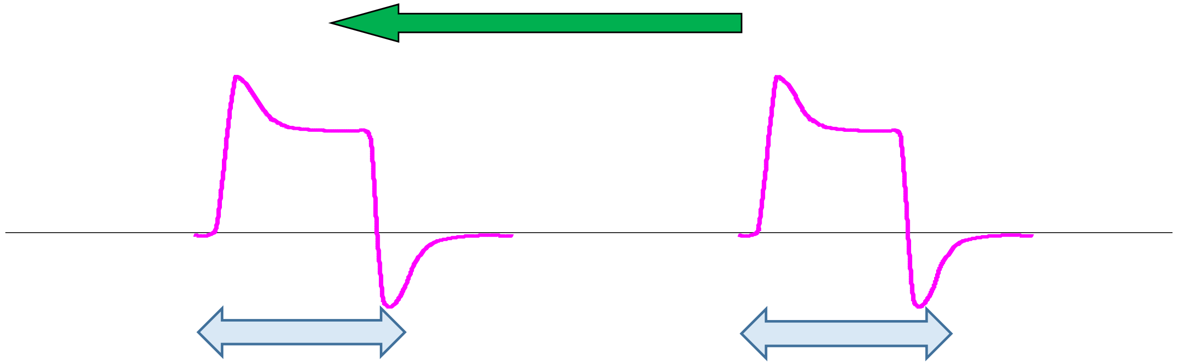


wide

Interaction of pulses

repulsive





Oscillatory interaction appear

Problems

Theoretical explanation that

・single traveling pulse is stable with node type,

・multi stable single traveling pulses interact oscillatory

Construction of solutions with above properties

Bi-stable reaction-diffusion system

$$U_t = DU_{xx} + F(U;k),\ t > 0,\ x \in \boldsymbol{R} \qquad U \in \boldsymbol{R}^N$$

$$P_\pm = P_\pm(k);\ F(P_\pm(k);k) = 0$$ Stable equilibria

P_+; excitable state
P_-; rest state

The modified m-FHN2 model :

$$u_t = d_u u_{xx} + u(1-u)(u-a) - v$$
$$v_t = d_v v_{xx} + \varepsilon G_b(u - \gamma v)$$

i.e.,

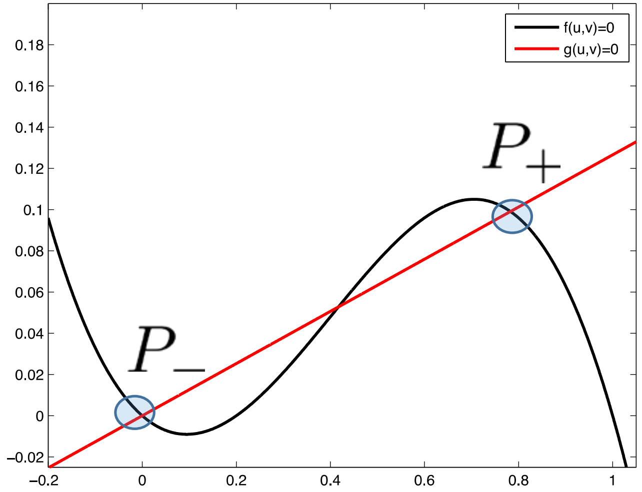
$$u_t = d_u u_{xx} + u(1-u)(u-a) - v$$

$$v_t = d_v v_{xx} + \varepsilon\left(\frac{(u-\gamma v)e^{-b(u-\gamma v)}}{e^{b(u-\gamma v)} + e^{-b(u-\gamma v)}}\right)$$

$0 < a < 1/2$

$b > 0$

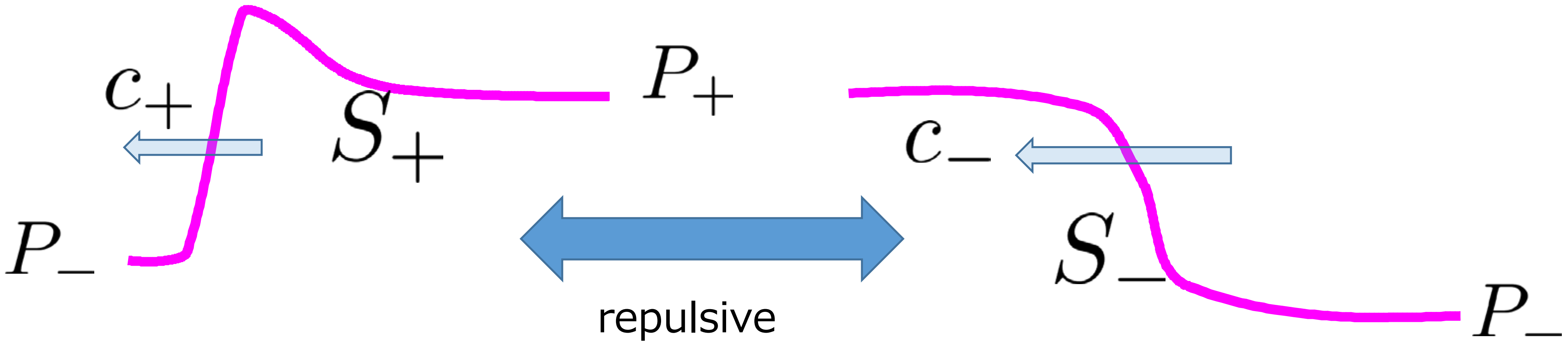
γ is a bit smaller than γ^*



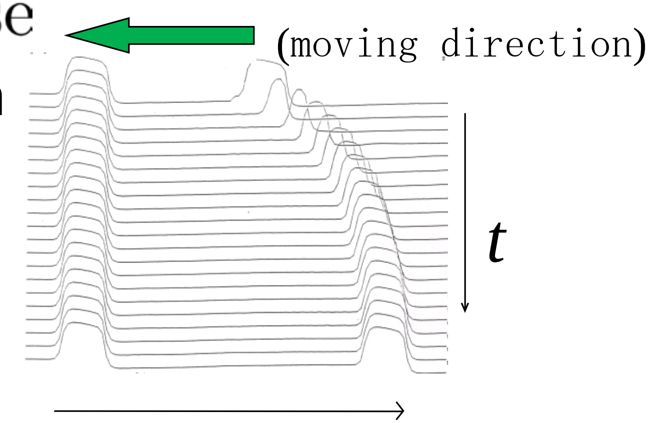
γ^* makes the nullclines symmetric (i.e., the areas between two nullclines at upper pick and lower pick is equal)

Stable front solutions

<u>Assume</u> stable traveling front solutions: $S_\pm(x+c_\pm t);\ S_\pm(\pm\infty)=P_\pm$



<u>REM:</u> $c_+ < c_-$, repulsive interaction $\Rightarrow$ stable traveling pulse with <u>wide</u> excitable region



Dynamics of front solution near bifurcation point

$$U_t = DU_{xx} + F(U;k),\ t>0,\ x\in \boldsymbol{R}$$

Assume: $k=k_c$; bifurcation point s.t.

S_- has a singularity at $k=k_c$ satisfying: $S_- = S_-(z)\ (z := x + c_- t)$

$$L_- := D\partial_z^2 + F'(S_-;k_c) - c_-\partial_z \quad (L_-\partial_z S_- = 0)\ L_-\Psi_- = -\partial_z S_-$$

$$L_-^* := D\partial_z^2 + {}^tF'(S_-;k_c) + c_-\partial_z \ \ L_-^*\Phi_-^* = 0\ L_-^*\Psi_-^* = -\Phi_-^*$$

Theorem

If $\eta := k - k_c$ is sufficiently small, then

$$U(t,x) = S_-(x + c_-t - l_-(t)) + r(t)\Psi_-(x + c_-t - l_-(t)) + O(|\eta|),$$

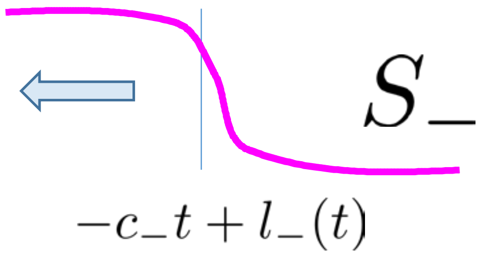
$$\begin{cases} \dfrac{dl_-}{dt} = r + O(|\eta|), \\ \dfrac{dr}{dt} = K(r) + O(r^4 + |\eta|^{3/2}) \end{cases}$$

$$K(r) := -M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3$$

Bifurcation structure of $S\_$

$$U(t,x) = S_-(x + c_- t - l_-(t)) + r(t)\Psi_-(x + c_- t - l_-(t)) + O(|\eta|),$$

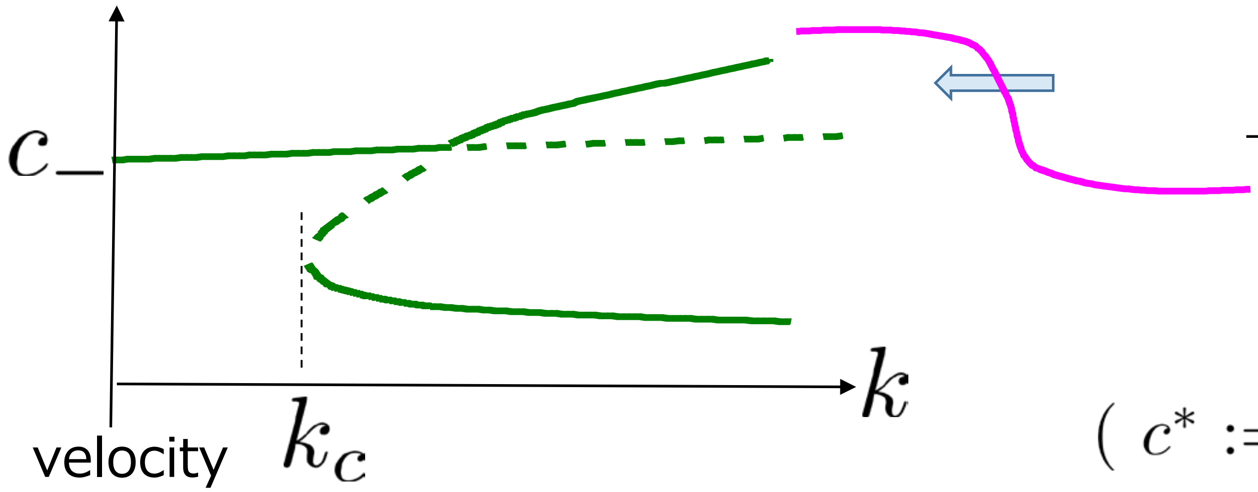
$$\begin{cases} \dfrac{dl_-}{dt} &= r, \\ \dfrac{dr}{dt} &= K(r) \end{cases} \qquad \eta := k - k_c \qquad K(r) := -M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3$$

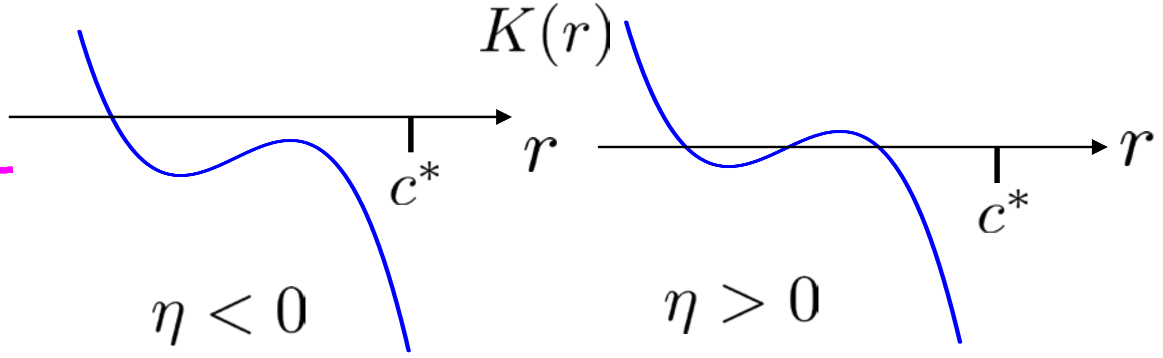


In the case of sufficiently small $c\_$ and $S\_$ close to odd symmetry

⇨ M_0, M_2 sufficiently small

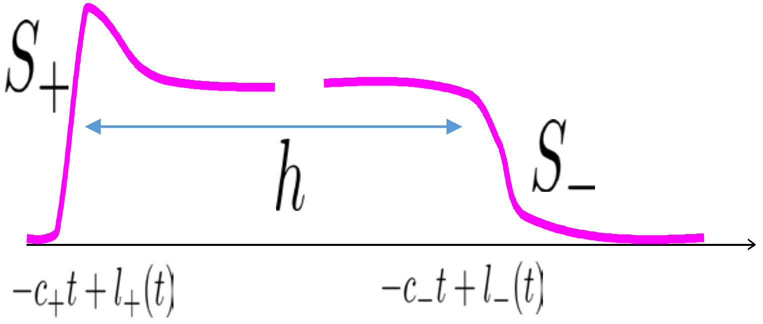
<u>Assume</u> all coefficients are positive and M_0, M_2 sufficiently small

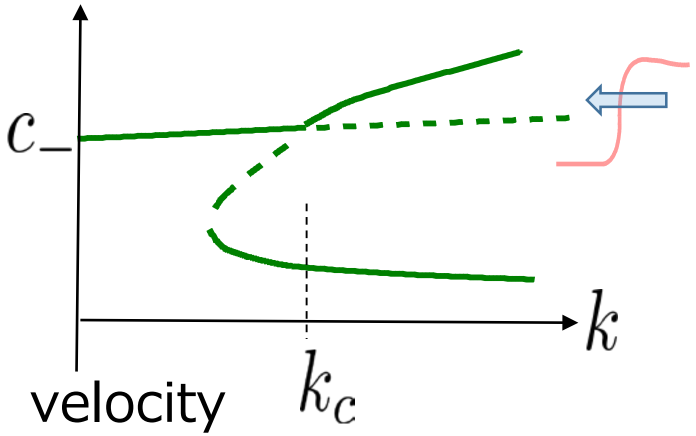




($c^* := c_- - c_+$) $\quad c_- - r > c_+ \iff r < c^*$

Bifurcation structure of S_+ and $S\_$





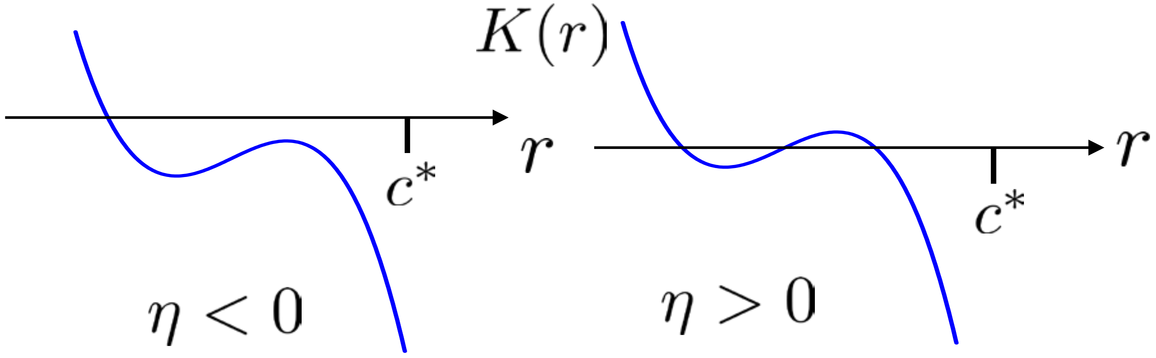
$$\begin{cases} \dfrac{dl_-}{dt} &= r, \\ \dfrac{dr}{dt} &= K(r) \end{cases}$$

Assume

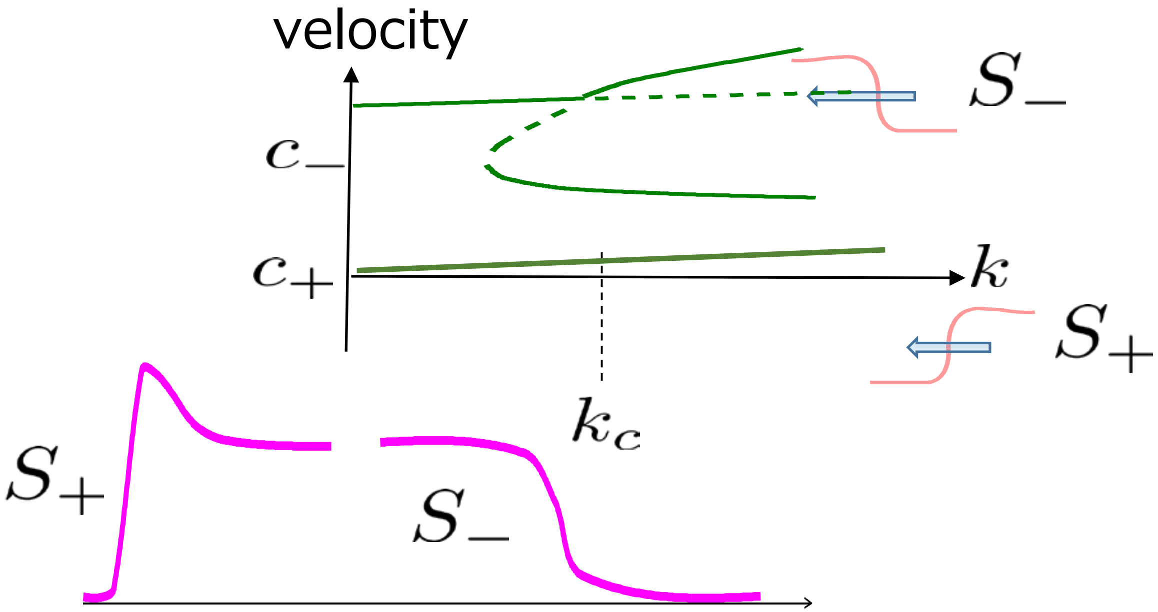
S_- is always faster than S_+

$$c_- - r > c_+ \iff r < c^*$$

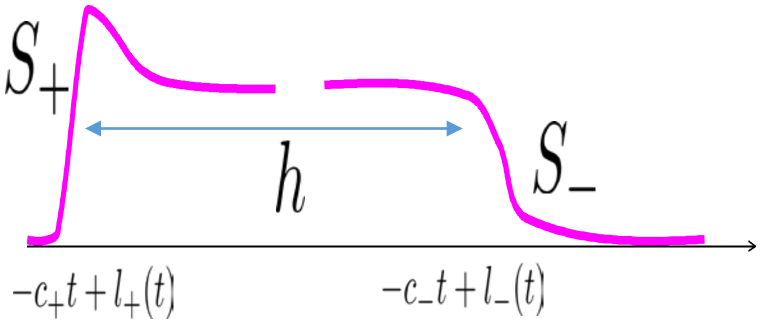
$$(\ c^* := c_- - c_+ \ )$$

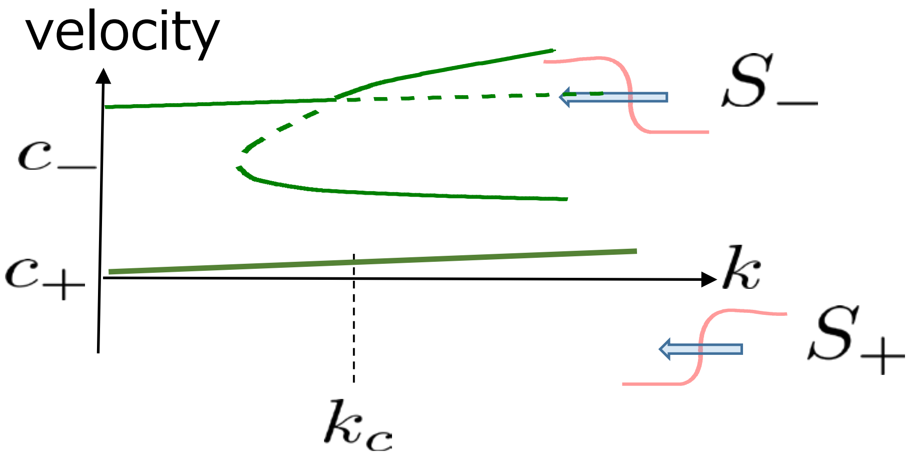


Assume S_+ is stable near $k = k_c$



Pulse solution consisting with S_+ and $S\_$ near $k = k_c$





$$K(r) := M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3$$

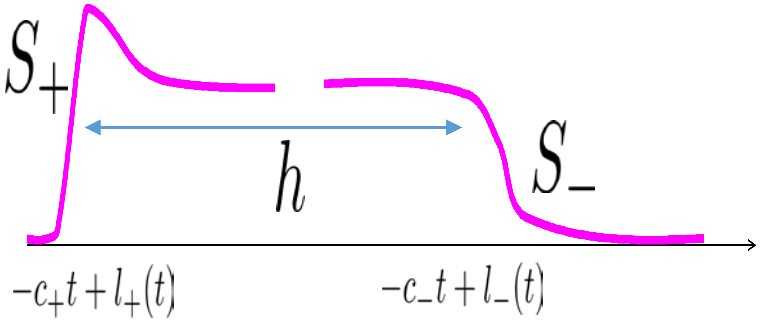
$$k = k_c + \eta \ (0 < \eta << 1)$$

<u>Theorem</u> Suppose $S_+(z) \to e^{-\alpha z}\boldsymbol{a} + P_+,\ S_-(z) \to e^{\alpha z}\boldsymbol{a} + P_+ \quad 0 < c_- - c_+ << 1$

$$U(t,x) = S_+(x + c_+t - l_+(t)) + S_-(x + c_-t - l_-(t)) + r(t)\Psi_-(x + c_-t - l_-(t)) + O(|\eta|),$$

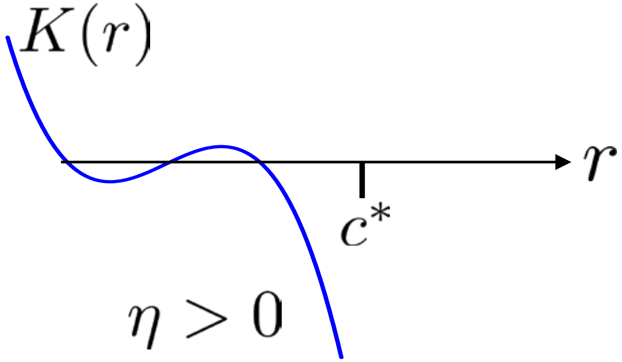
$$\left\{\begin{array}{rcl} \dfrac{dl_+}{dt} & = & -N_1 e^{-\alpha h} + O(e^{-2\alpha h} + r^2 + |\eta|), \\ \dfrac{dr}{dt} & = & N_2 e^{-\alpha h} + K(r) + O(e^{-2\alpha h} + r^4 + |\eta|^{3/2}), \\ \dfrac{dl_-}{dt} & = & N_3 e^{-\alpha h} + r + O(e^{-2\alpha h}) \end{array}\right.$$

Existence of stable traveling pulse



$$\begin{cases} \dfrac{dl_+}{dt} = -N_1 e^{-\alpha h}, \\ \dfrac{dr}{dt} = N_2 e^{-\alpha h} + K(r), \\ \dfrac{dl_-}{dt} = N_3 e^{-\alpha h} + r \end{cases}$$

$$K(r) := -M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3$$



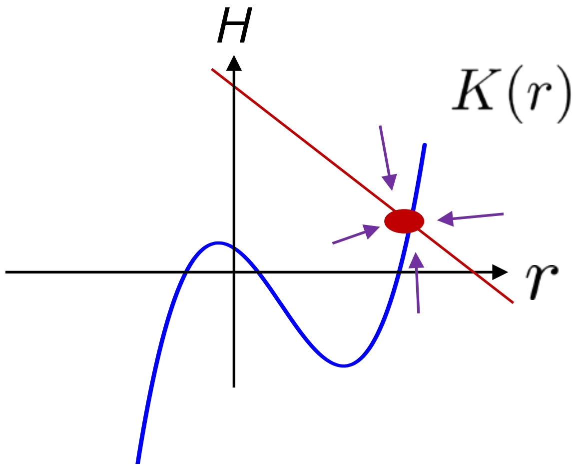
$$h := l_- - l_+ - c^* t$$

$$c^* := c_- - c_+$$

$$\begin{cases} \dfrac{dh}{dt} = (N_1 + N_3)e^{-\alpha h} + r - c^*, \\ \dfrac{dr}{dt} = N_2 e^{-\alpha h} + K(r) \end{cases}$$

Analysis of reduced ODE

$$\begin{cases} \dfrac{dh}{dt} = (N_1 + N_3)e^{-\alpha h} + r - c^*, \\ \dfrac{dr}{dt} = N_2 e^{-\alpha h} + K(r) \end{cases} \quad H(t) := e^{-\alpha h(t)} \Longrightarrow \begin{cases} \dfrac{dH}{dt} = -\alpha H\{(N_1 + N_3)H + r - c^*\}, \\ \dfrac{dr}{dt} = N_2 H + K(r) \end{cases}$$

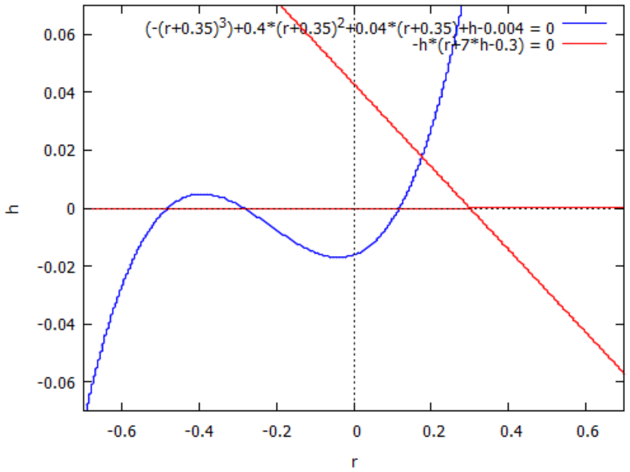


$$K(r) := -M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3$$

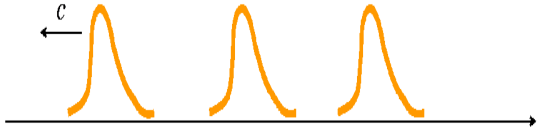
PROP There is one stable equilibrium with node type.

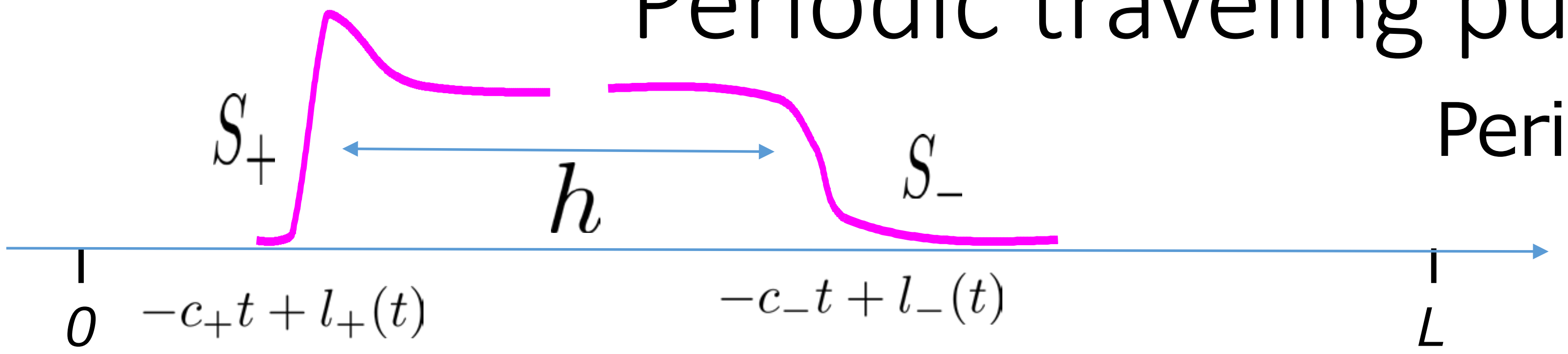
⇓

Stable traveling pulse solution with note type.



Periodic traveling pulses

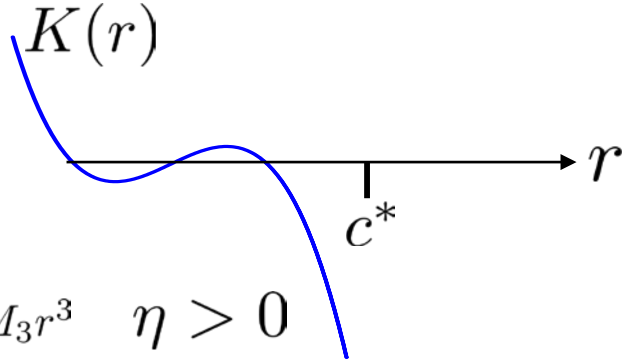




Periodic boundary condition
(Pulse train) $L >> 1$

Suppose $S_+(z) \to e^{-\beta z}\boldsymbol{b} + P_-,\ S_-(z) \to e^{\beta z}\boldsymbol{b} + P_-$

$$\begin{cases} \dfrac{dl_+}{dt} = N_4 e^{-\beta(L-h)} - N_1 e^{-\alpha h}, \\ \dfrac{dr}{dt} = -N_5 e^{-\beta(L-h)} + N_2 e^{-\alpha h} + K(r), \\ \dfrac{dl_-}{dt} = N_3 e^{-\alpha h} - N_6 e^{-\beta(L-h)} + r \end{cases}$$

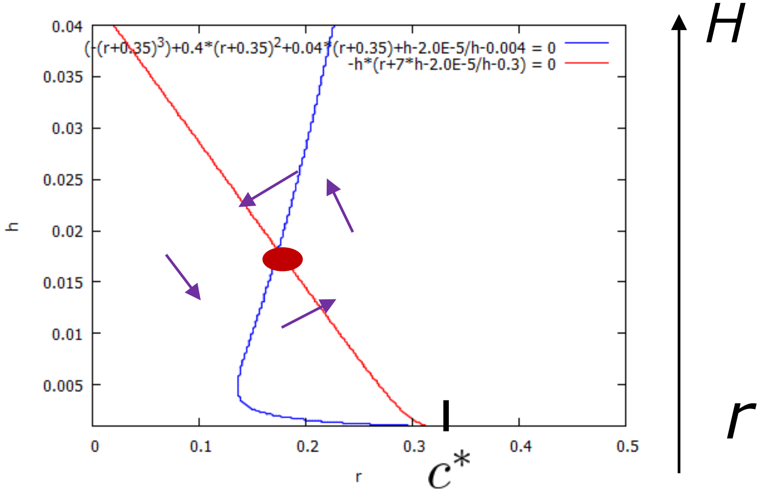


$K(r) := -M_0\eta + M_1 r\eta + M_2 r^2 - M_3 r^3 \quad \eta > 0$

$c^* := c_- - c_+$

$$\begin{cases} \dfrac{dh}{dt} = (N_1+N_3)e^{-\alpha h} - (N_4+N_6)e^{-\beta(L-h)} + r - c^*, \\ \dfrac{dr}{dt} = -N_5 e^{-\beta(L-h)} + N_2 e^{-\alpha h} + K(r) \end{cases}$$

$H(t) := e^{-\alpha h}$



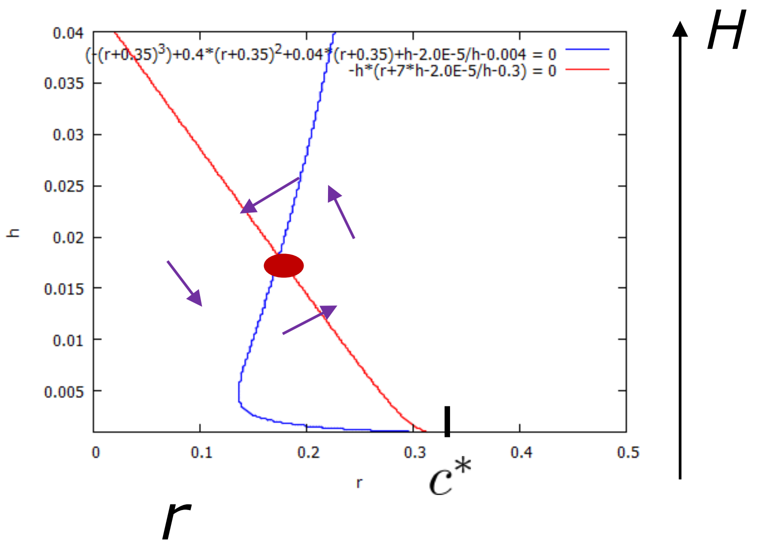
Repulsive $\iff$ all coefficients N_j positive

Analysis of reduced ODE

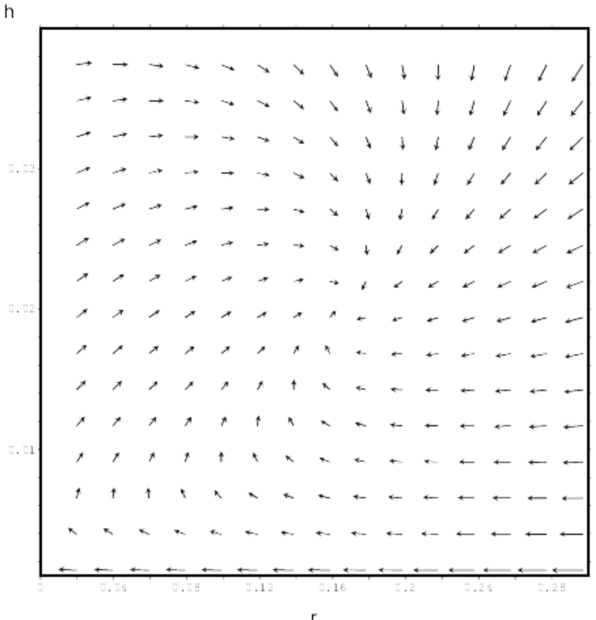
$$
\begin{cases}
\dfrac{dh}{dt} = (N_1 + N_3)e^{-\alpha h} - (N_4 + N_6)e^{-\beta(L-h)} + r - c^*, \\
\dfrac{dr}{dt} = -N_5 e^{-\beta(L-h)} + N_2 e^{-\alpha h} + K(r)
\end{cases}
$$

$$H(t) := e^{-\alpha h(t)}$$

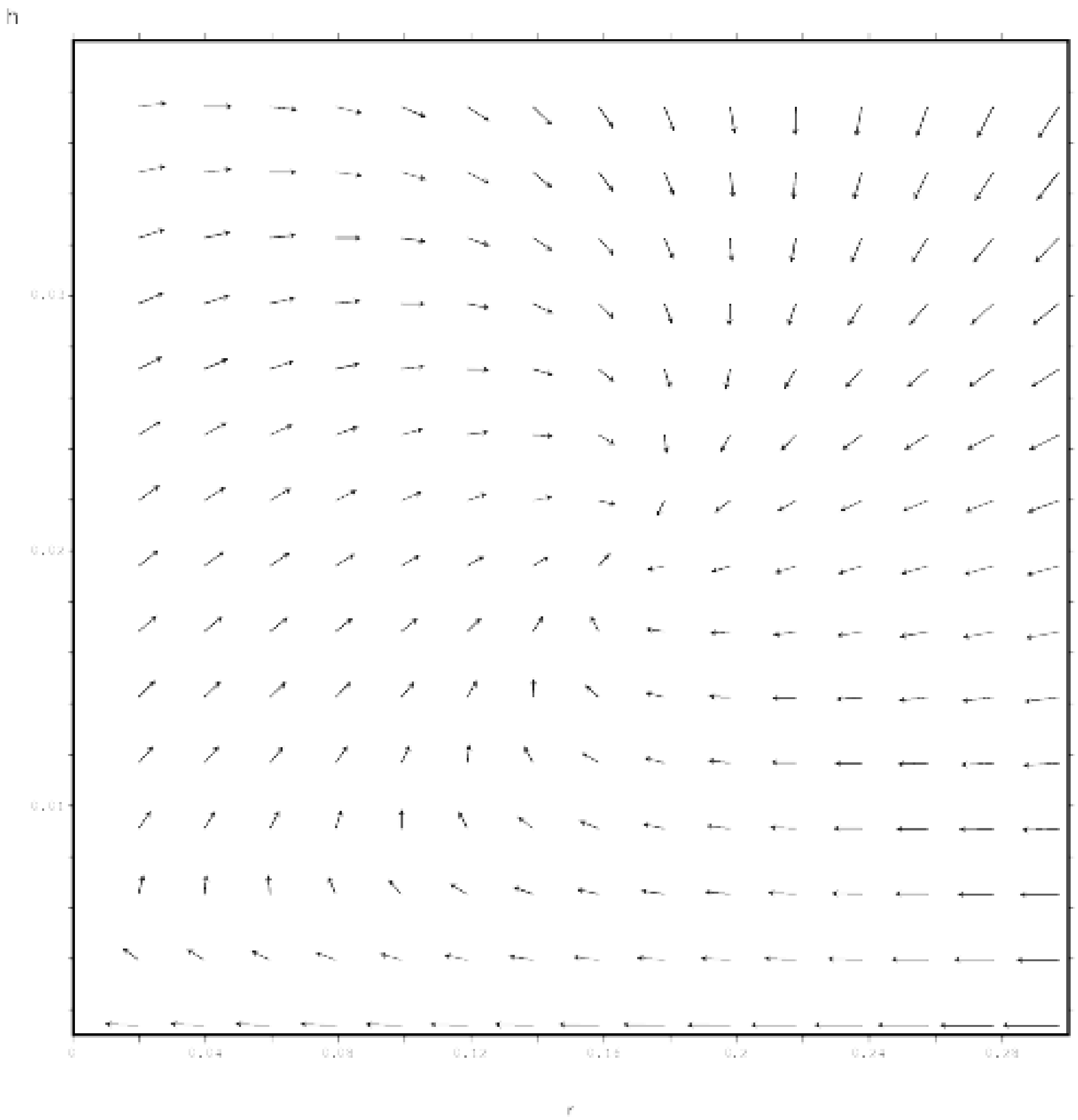
$$
\begin{cases}
\dfrac{dH}{dt} = -\alpha H\{(N_1 + N_3)H - (N_4 + N_6)\dfrac{e^{-\beta L}}{H^{\beta/\alpha}} + r - c^*\}, \\
\dfrac{dr}{dt} = -N_5 \dfrac{e^{-\beta L}}{H^{\beta/\alpha}} + N_2 H + K(r)
\end{cases}
$$



Oscillatory behavior appears



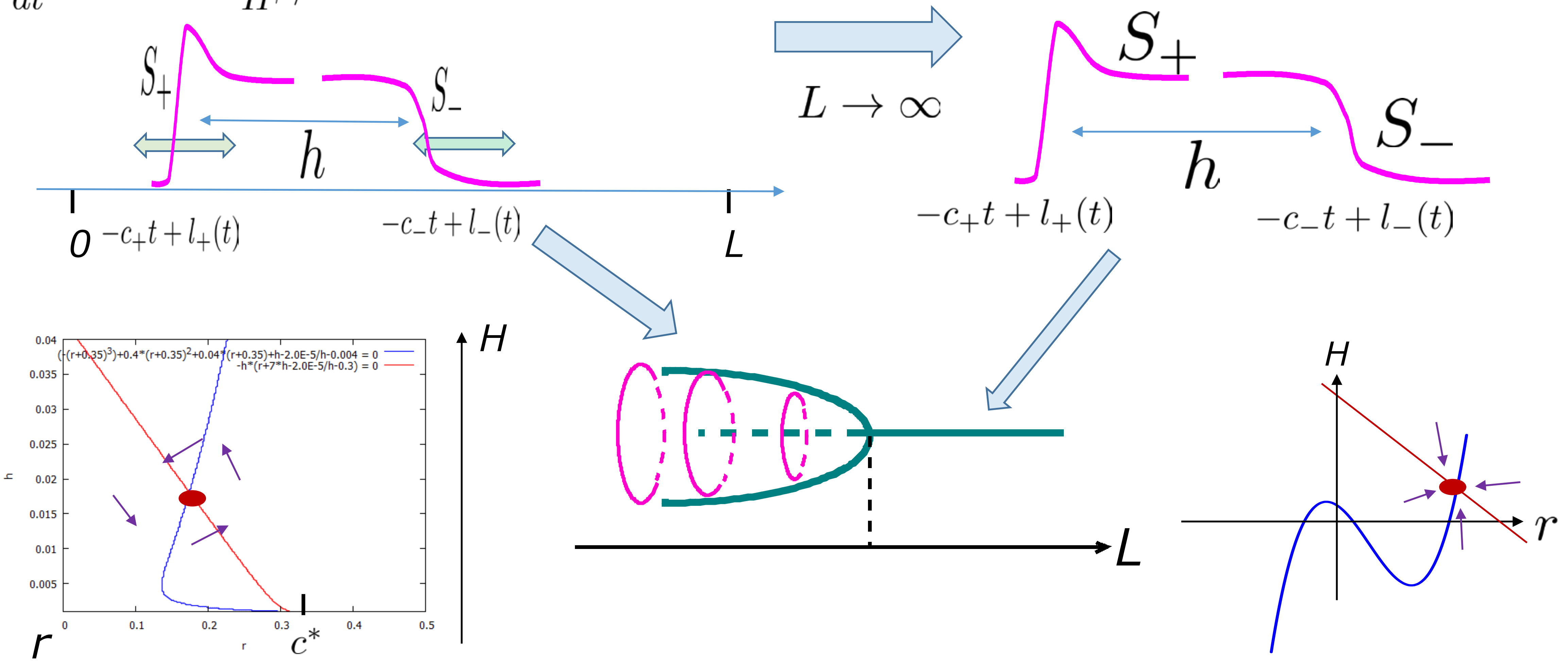
Enlargement



Dependence on L

$$\begin{cases} \dfrac{dH}{dt} &= -\alpha H\{(N_1+N_3)H - (N_4+N_6)\dfrac{e^{-\beta L}}{H^{\beta/\alpha}} + r - c^*\}, \\ \dfrac{dr}{dt} &= -N_5\dfrac{e^{-\beta L}}{H^{\beta/\alpha}} + N_2 H + K(r) \end{cases}$$

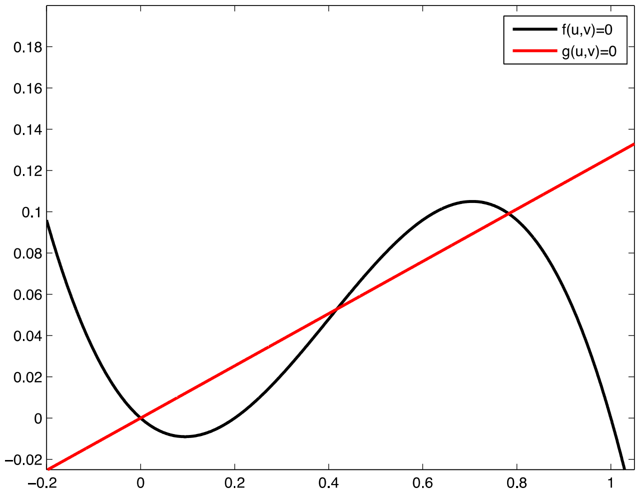
$$\begin{cases} \dfrac{dH}{dt} &= -\alpha H\{(N_1+N_3)H + r - c^*\}, \\ \dfrac{dr}{dt} &= N_2 H + K(r) \end{cases}$$

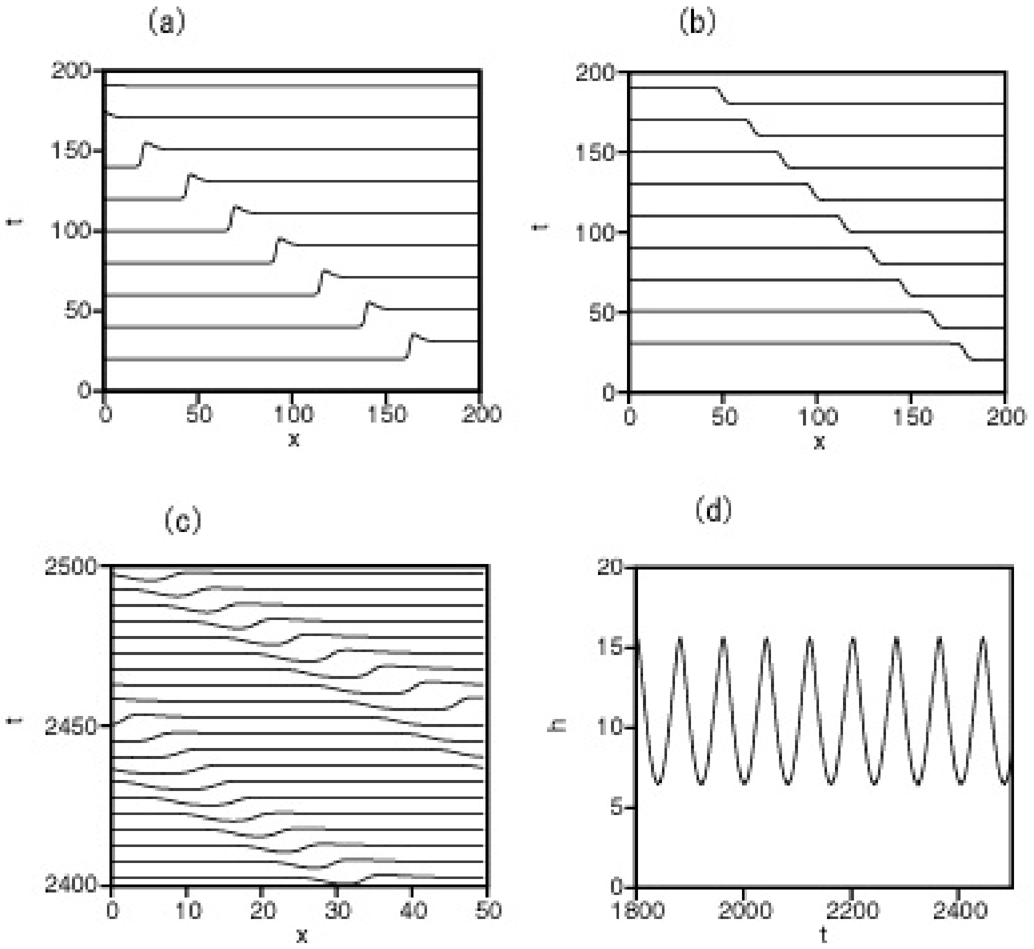


フロント解の運動

$$u_t = d_u u_{xx} + u(1-u)(u-a) - v$$

$$v_t = d_v v_{xx} + \varepsilon\left(\frac{(u-\gamma v)e^{-b(u-\gamma v)}}{e^{b(u-\gamma v)} + e^{-b(u-\gamma v)}}\right)$$





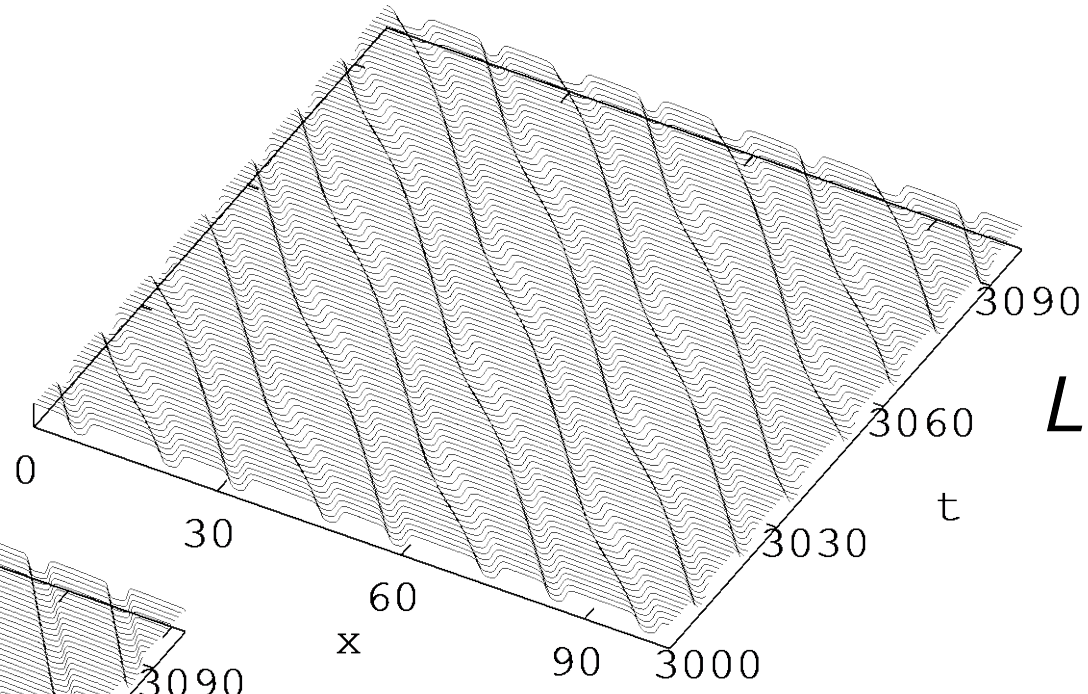
PDE simulation Modified FHN2 (non-monotone)

b=1.5

$a=0.2, \varepsilon=0.0025, \gamma=7.9, b=1.5, d_u=0.05, d_v=0.005$

$$u_t = d_u u_{xx} + u(1-u)(u-a) - v$$

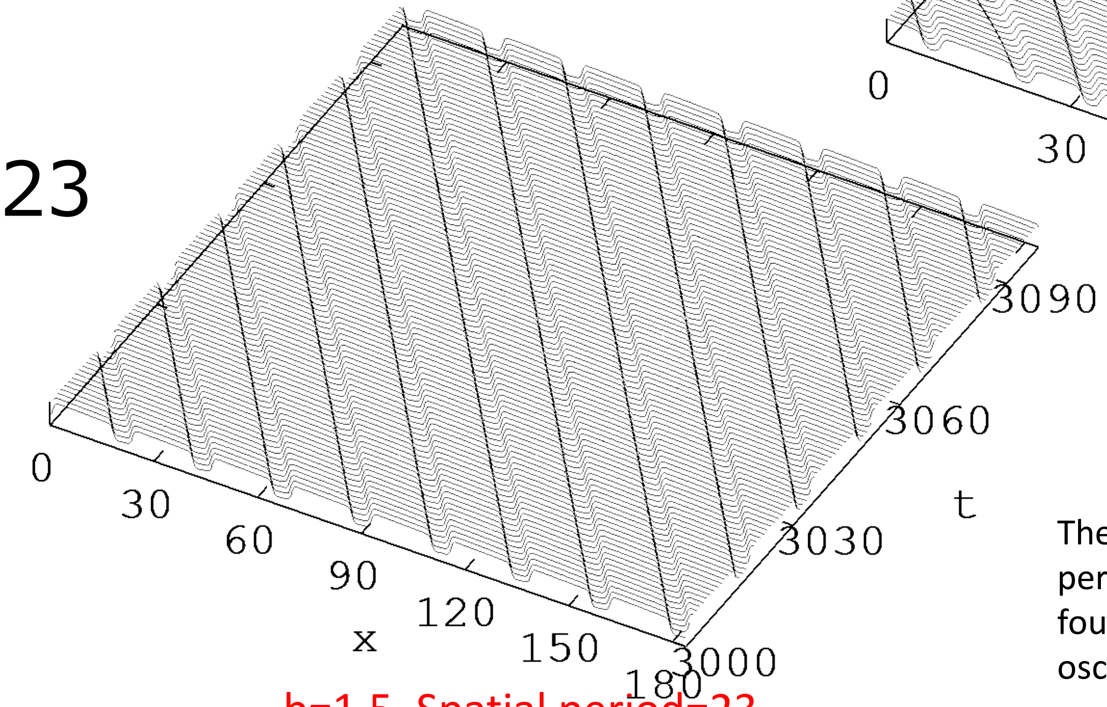
$$v_t = d_v v_{xx} + \varepsilon\left(\frac{(u-\gamma v)e^{-b(u-\gamma v)}}{e^{b(u-\gamma v)} + e^{-b(u-\gamma v)}}\right)$$



$L = 13$

b=1.5, Spatial period=13

$L = 23$



b=1.5, Spatial period=23

The bifurcation diagram shows that the minimum stable period is =22.88, when b=1.5. In the PDE simulation we found stable PTW when spatial period=23 and oscillatory pattern of solutions when spatial period=13.

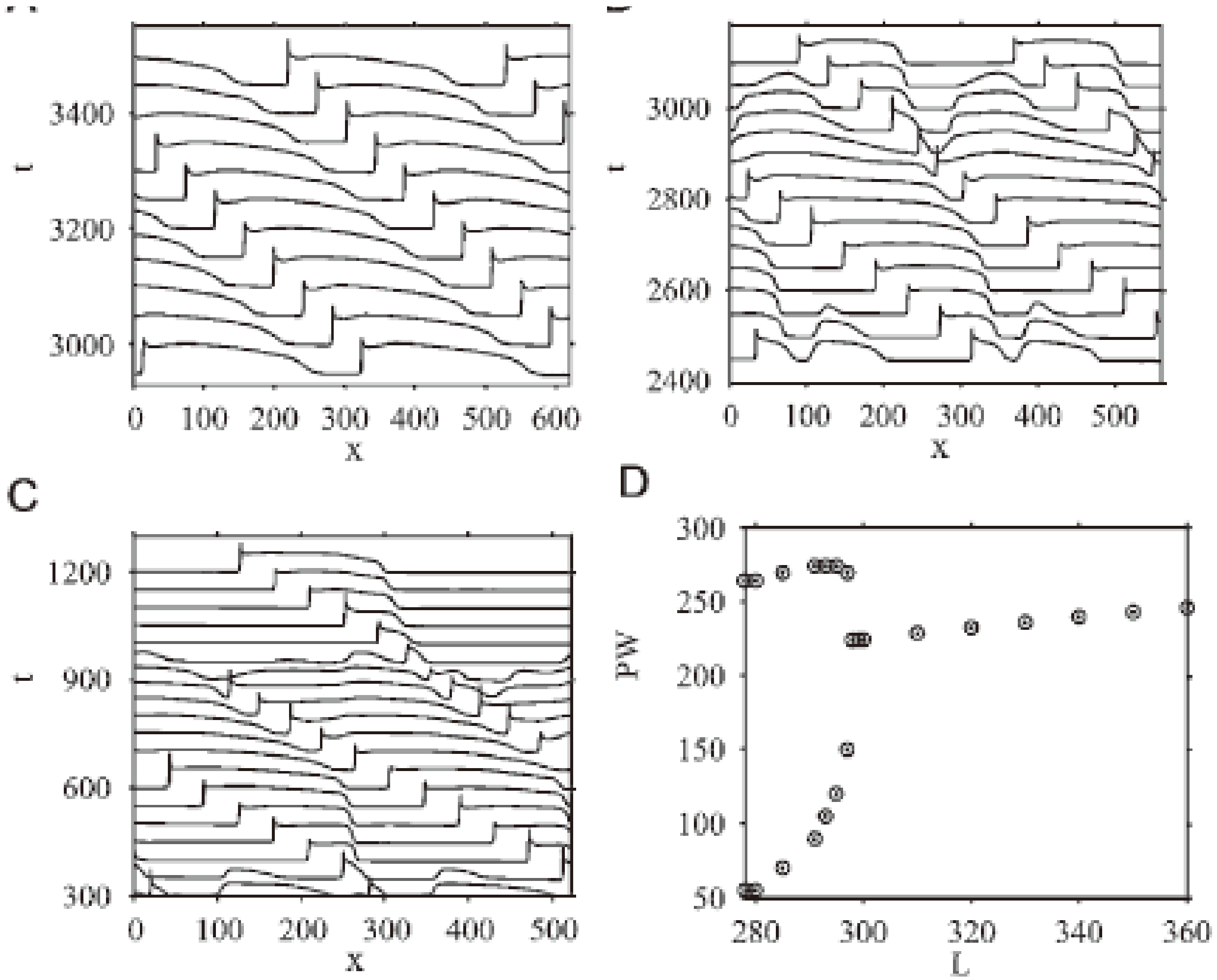
However, the onset of oscillation is at about period=20.

Ludy-Ruo model

Mathematical model describing heart muscle excitation (Hodgkin-Huxley type) with 8 variables

Qualitative comparison is possible with real experiment

L is increasing



Summary

・Construction of oscillatory traveling pulse train consisting with stable traveling pulses.

Thank you for your attention.