

Mixed-Mode Oscillations in coupled multiple time scale piecewise linear oscillators. Application to a neuroendocrine system.

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inria

INVENTEURS DU MONDE NUMÉRIQUE
INNOVATEURS DU MONDE VIRTUEL

Mycenae

Multiscale dYnamiCs in neuroENdocrine AxEs

Summary

- 1) Introduction: GnRH pulsatility and the smooth model.
- 2) The piecewise linear (PWL) model.
 - a) Dynamical behavior.
 - b) Quantitative aspects.
 - c) Application to GnRH secretion patterns.
- 3) Mixed mode oscillations due to canard phenomena.

1) Introduction: GnRH pulsatility and the smooth model

MYCENAE Project-Team: thematics

Biological background: neuro-endocrinology

Understanding complex hormonal oscillations

1) Introduction: GnRH pulsatility and the smooth model

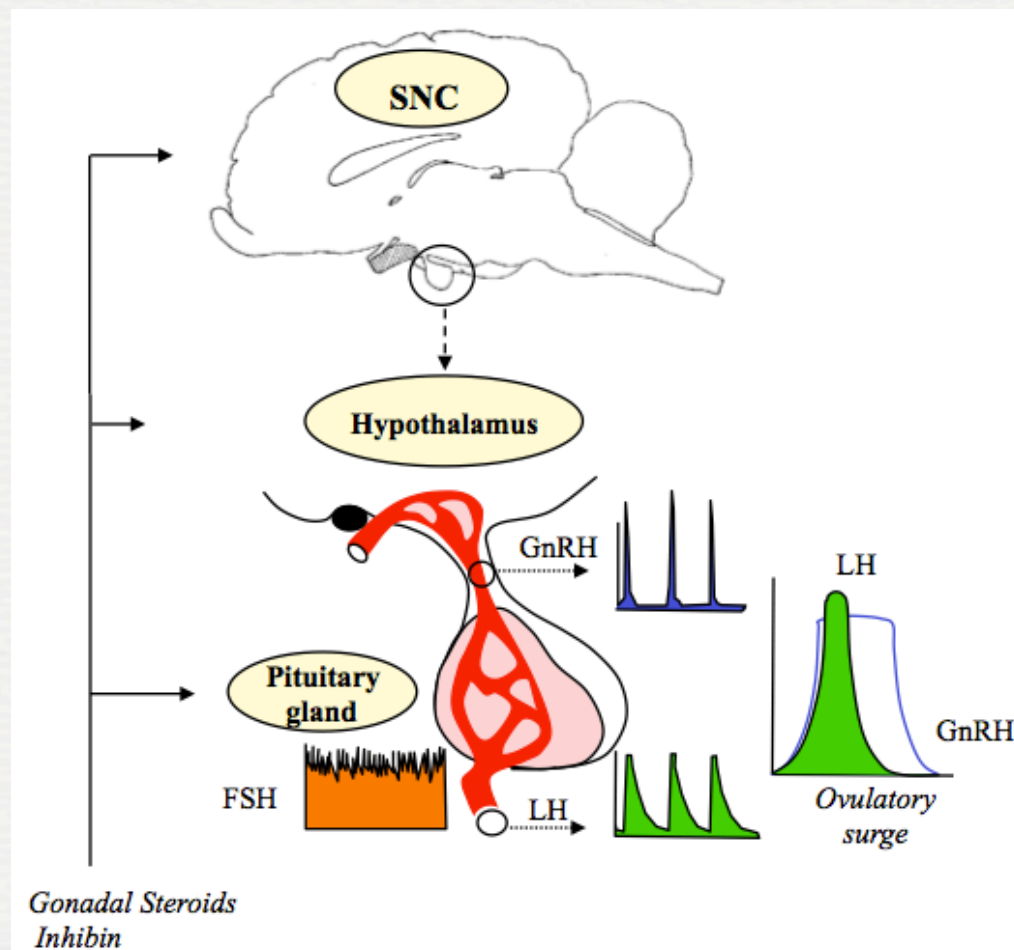
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Understanding complex hormonal oscillations

GnRH (gonadotropin releasing neurohormone)

- Prominent role in the control of reproductive processes in mammals.
- Secreted by the synchronous activity of neurons located in the hypothalamus.
- GnRH is released in the blood in an oscillatory manner.



Herbison, Endocr. Rev., 1998

A **neurohormone** is any hormone produced and released by neuroendocrine cells (also called neurosecretory cells) into the blood.

1) Introduction: GnRH pulsatility and the smooth model

Mechanisms behind the pulsatility are poorly understood

- 📌 Significant challenge to experimental studies.
- 📌 GnRH neurons are scarce, sparsely located in the hypothalamus and interspersed with other neuronal and glial cells.

Model design and mathematical analysis: Infer the underlying mechanisms

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Model design and mathematical analysis: Infer the underlying mechanisms

Core model: GnRH pulse & surge generator

$$\varepsilon\delta\frac{dx}{dt} = -y + f(x)$$

$$\varepsilon\frac{dy}{dt} = a_0x + a_1y + a_2 + cX$$

$$\varepsilon\frac{dX}{dt} = -Y + g(X)$$

$$\frac{dY}{dt} = X + b_1Y + b_2$$

$$f(x) = -x^3 + 3\lambda x \quad g(X) = -X^3 + 3\mu X$$

3 time scales : $O(1)$, $O(\varepsilon)$, $O(\delta\varepsilon)$

SIAM J. Appl. Dyn. Syst. 2007

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Model design and mathematical analysis: Infer the underlying mechanisms

Core model: GnRH pulse & surge generator

Two coupled
FitzHugh-Nagumo

(Two-dimensional simplification
of the **Hodgkin-Huxley** model of
spike generation)

$$\varepsilon\delta\frac{dx}{dt} = -y + f(x)$$

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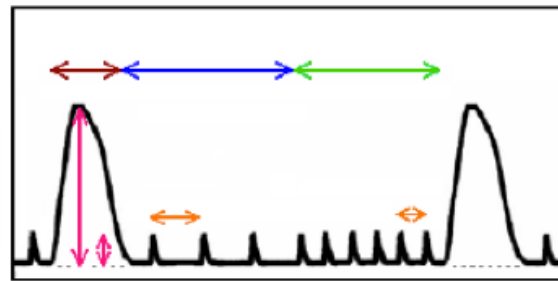
Quasi-stationary regime,
quasi-periodic regime

Periodic regime

1) Introduction: GnRH pulsatility and the smooth model

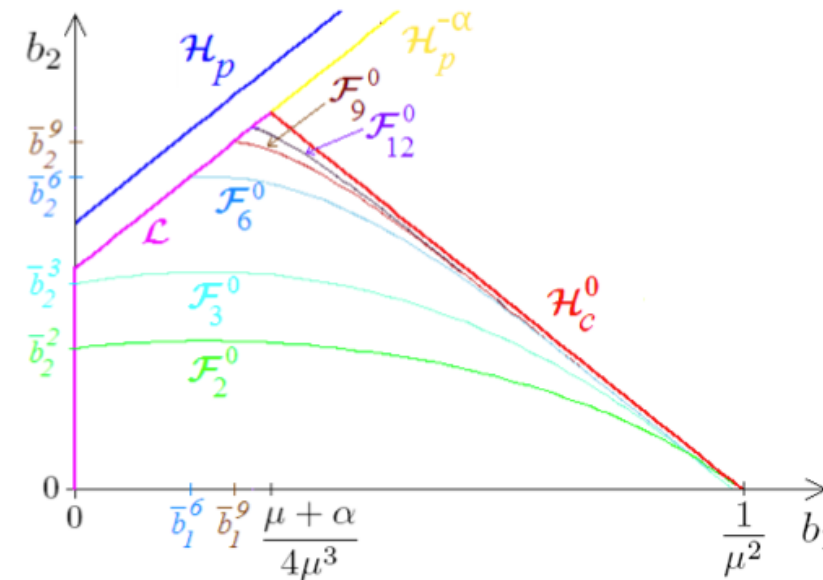
Phenomenological model with both qualitative & quantitative aspects

Qualitative and quantitative specifications

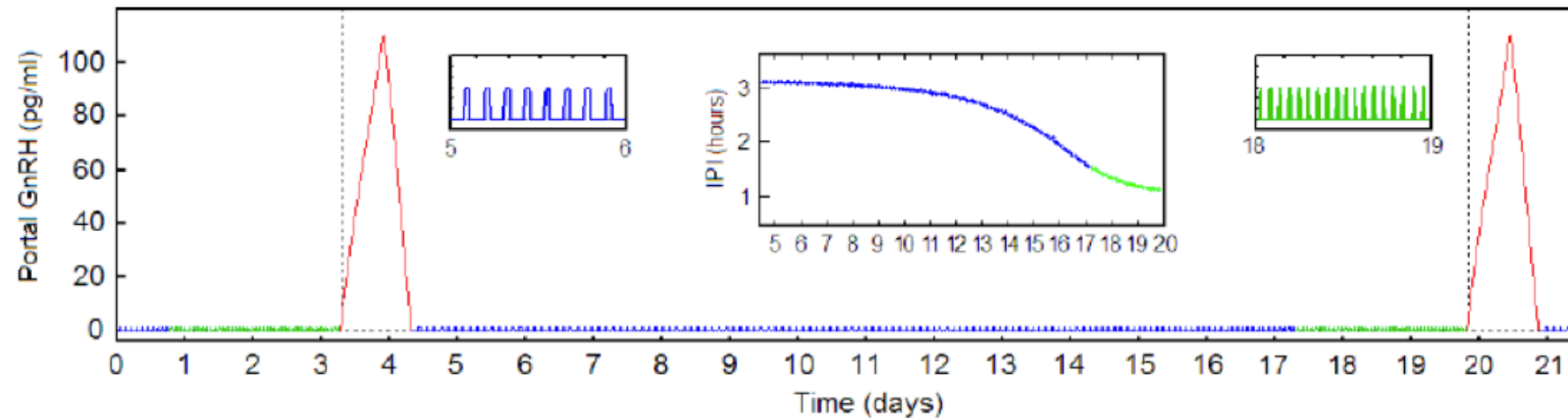


Dynamics-based parameter calibration

- ⊙ Parameter space restriction
- ⊙ Parameter space foliation (meta-parameter)
- ⊙ Semi-automated procedure



SIAM J. Appl. Dyn. Sys. 2009



J. Neuroendocrinol. 2010

1) Introduction: GnRH pulsatility and the smooth model

Phenomenological model with both qualitative & quantitative aspects

Foliation-Based Parameter Tuning in a Model of the GnRH Pulse and Surge Generator, SIADS, F. Clément and A. Vidal, 2009

Quantitative specifications for GnRH secretion pattern along the ovarian cycle in the ewe.

Feature	Specification	Unit
whole cycle duration	16.5	days
follicular phase duration (surge excepted)	2.5	days
surge duration	1	days
luteal phase duration	13	days
pulse to surge amplitude ratio	1 to 60	—
frequency increase ratio	1 to 4	—

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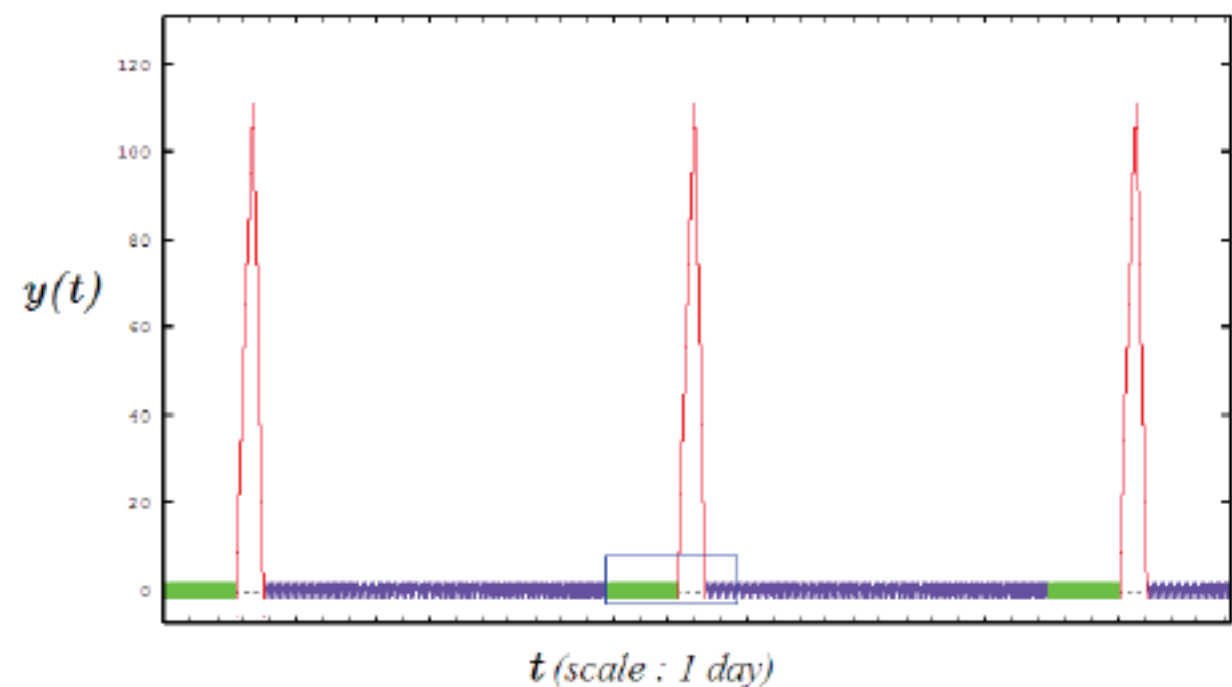
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Parameter values for the ovarian cycle in the ewe.

ε	0.02	δ	0.0125
a_0	0.52	a_1	0.011
a_2	1.14	c	0.70
b_1	0.246	b_2	1.5103



1) Introduction: GnRH pulsatility and the smooth model

Phenomenological model with both qualitative & quantitative aspects

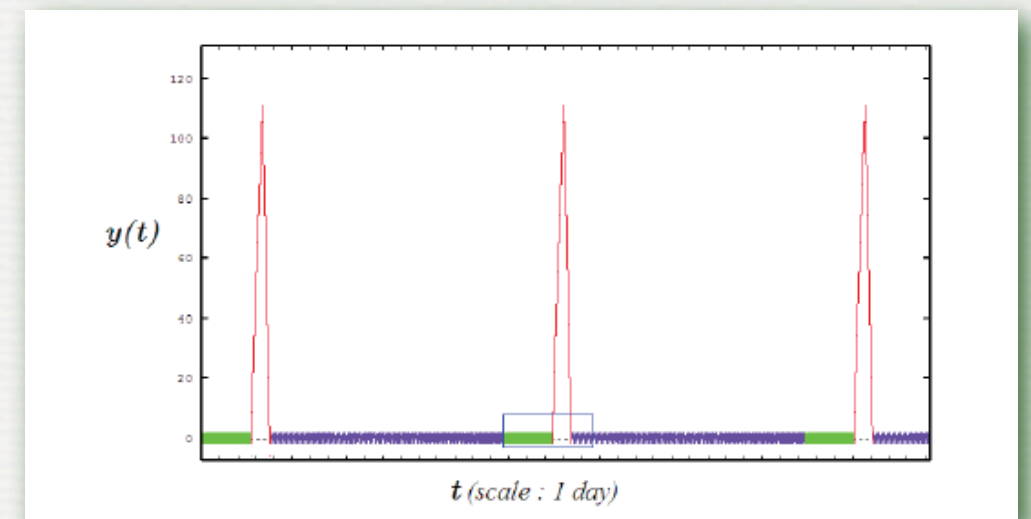
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Aspects that remained unclear or not fully controlled:

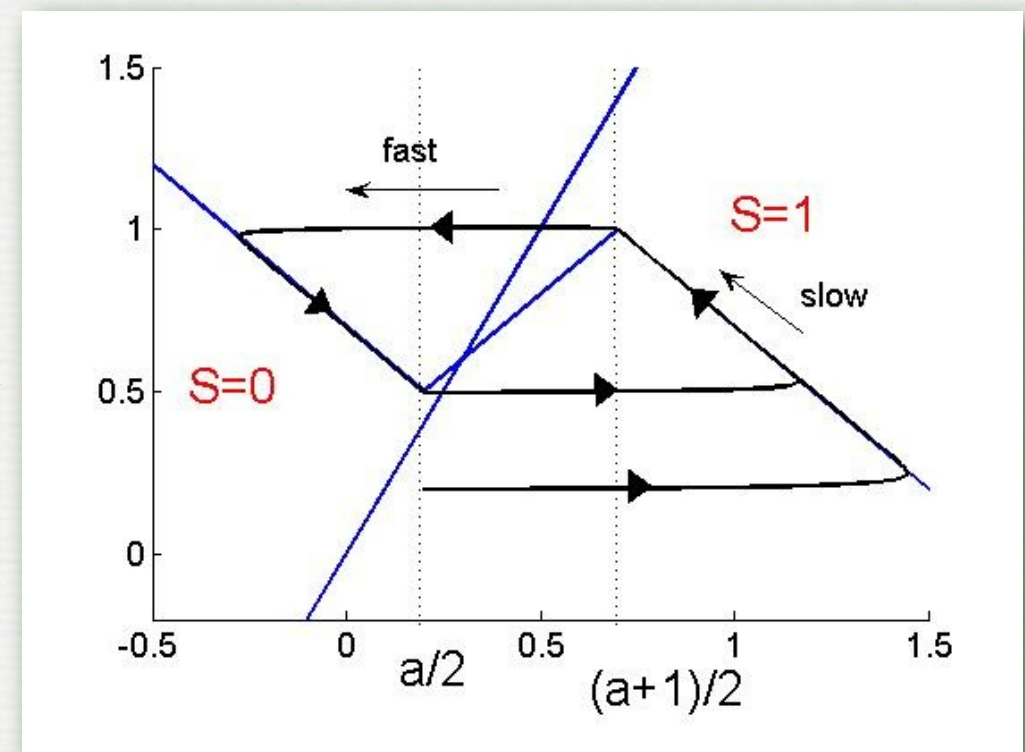
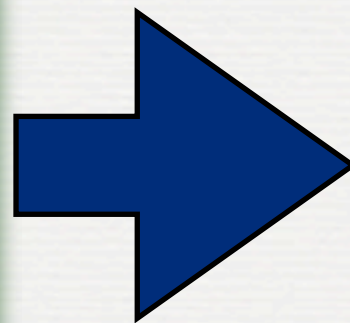
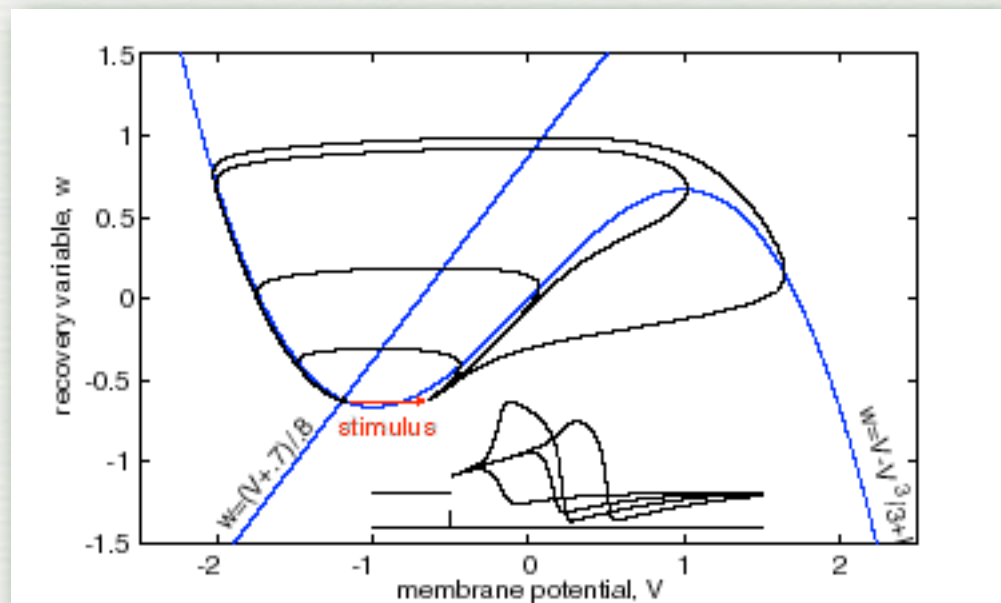
- Pulse to surge amplitude ratio.
- Frequency related:
 - Follicular-luteal phases duration.
 - Frequency increase ratio.



1) Introduction: GnRH pulsatility and the smooth model

Can we propose a PWL version of the model to go beyond?

FitzHugh-Nagumo

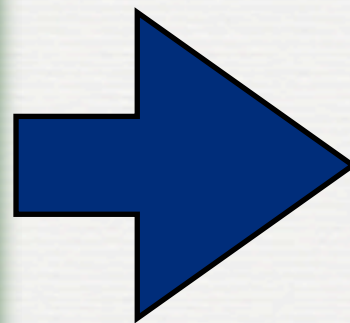
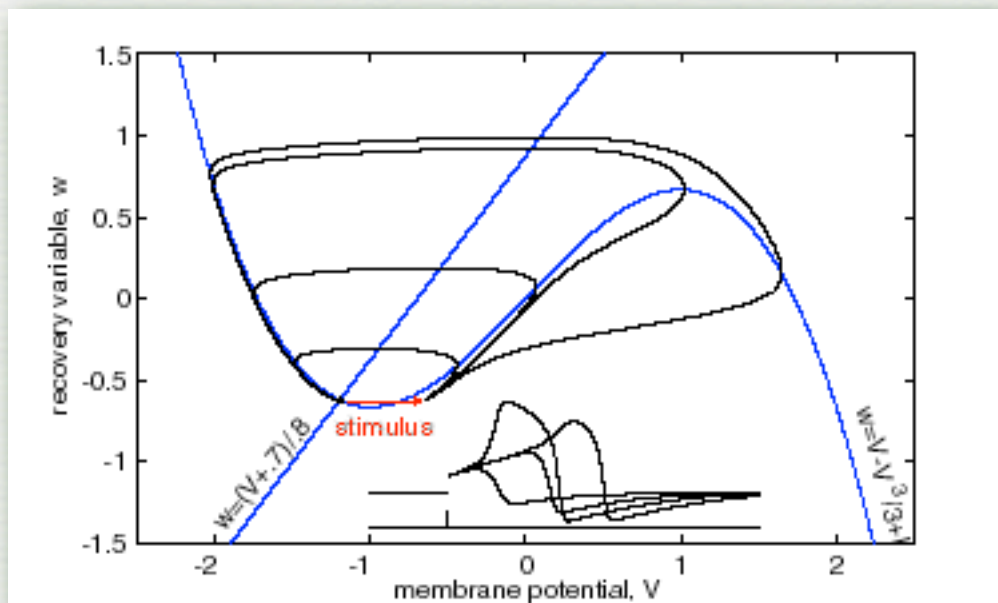


(source: *scholarpedia*)

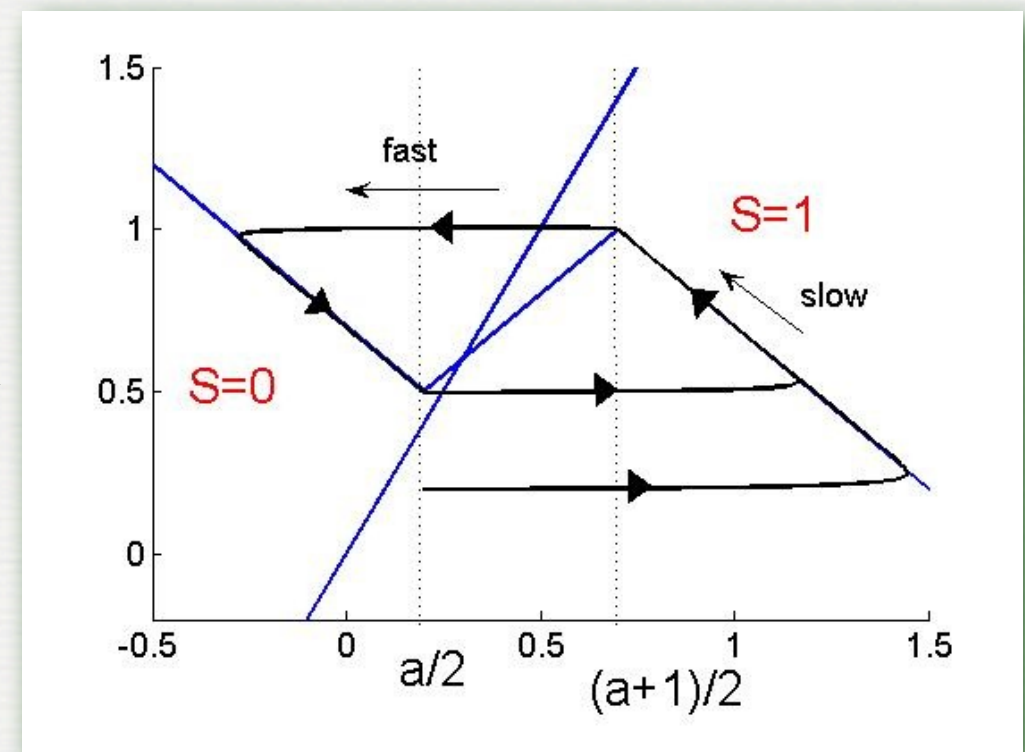
1) Introduction: GnRH pulsatility and the smooth model

Can we propose a PWL version of the model to go beyond?

FitzHugh-Nagumo



McKean's caricature



Goal: keep the richness of the dynamics with better access to quantitative outputs.

(source: *scholarpedia*)

2) The piecewise linear model

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(a_0x + a_1y + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - k_1 - 1, & \text{if } x \leq -1, \\ k_1x, & \text{if } |x| \leq 1, \\ -x + k_1 + 1, & \text{if } x \geq 1, \end{cases}$$
$$\begin{cases} \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases} \quad g(X) = \begin{cases} -X - k_2 - 1, & \text{if } X \leq -1, \\ k_2X, & \text{if } |X| \leq 1, \\ -X + k_2 + 1, & \text{if } X \geq 1, \end{cases}$$

$$(x, y, X, Y)^T \in \mathbb{R}^4, \quad 0 < \varepsilon, \delta \ll 1, \quad b_1 \geq 0, \quad a_0, a_1, a_2, b_2, c, k_1, k_2 > 0$$

2) The piecewise linear model

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🔧 System in X, Y is independent, so we call it the **forcing system**. As it runs in a slower timescale, is also called the **slow system**. It models the **average activity of regulatory neurons**.

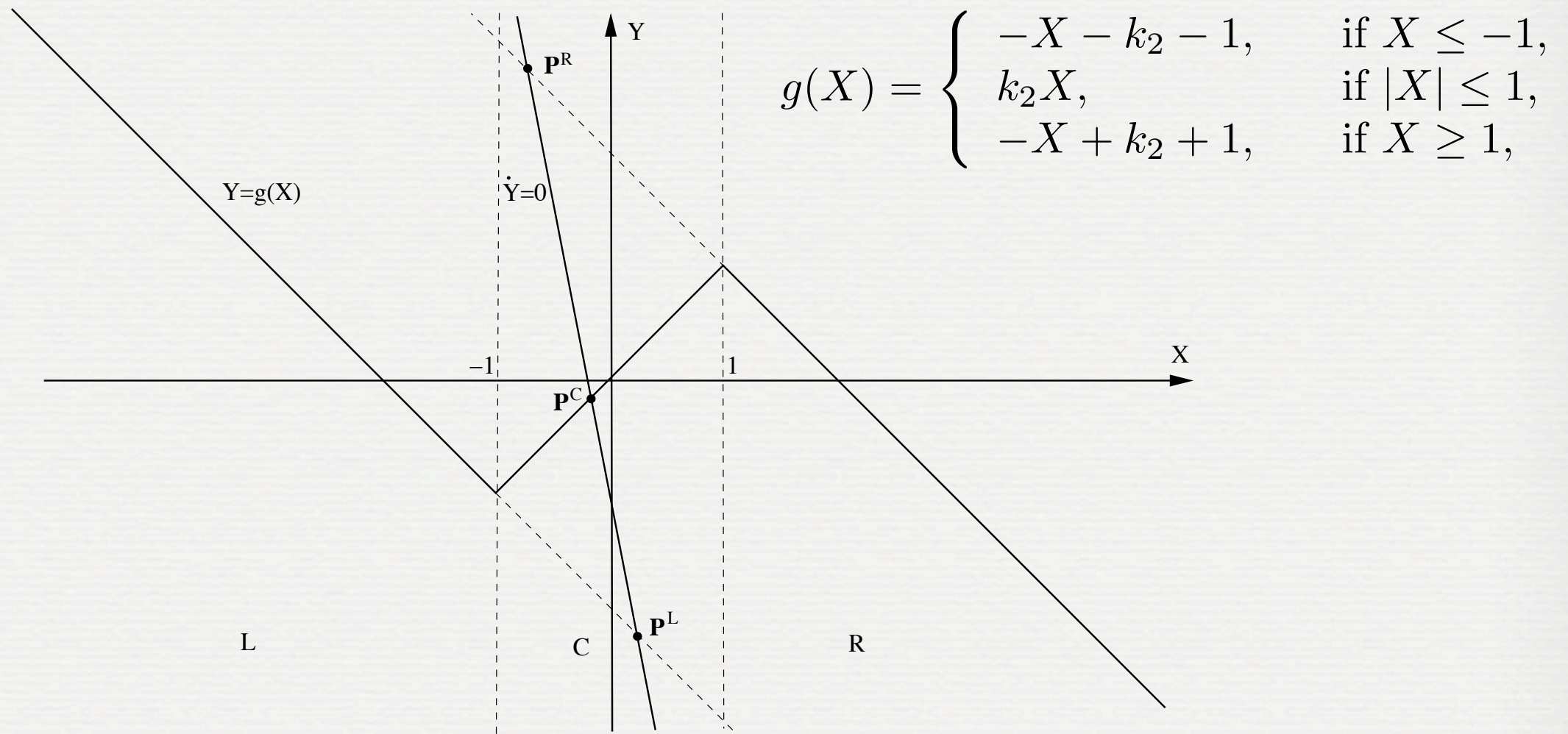
🔧 System in x, y is driven by X variable of the forcing system, so we call it the **forced system**. As it runs in the fast timescale, also is called the **fast system**. It models the **average activity of GnRH neurohormones**.

2) The piecewise linear model

a) Dynamical behavior.

Forcing (or slow) system: PWL with 3 zones

$$\begin{cases} \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases} \quad s = t\delta, \quad \longrightarrow \quad \begin{cases} X' = -Y + g(X), \\ Y' = \varepsilon(X + b_1Y + b_2), \end{cases}$$



Difference between this system and the original FitzHugh-Nagumo model is the choice of a negative slope of the Y -nullcline.

2) The piecewise linear model

a) Dynamical behavior.

Forcing (or slow) system: PWL with 3 zones

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Forcing (or slow) system: PWL with 3 zones

$$\begin{cases} X' = -Y + g(X), \\ Y' = \varepsilon(X + b_1 Y + b_2), \end{cases}$$

$b_2 = 0$ The vector field is **symmetric** with respect to the origin.

Llibre and Sotomayor, 1996 and Freire, Ponce, Rodrigo and Torres, 2002.

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Llibre and Sotomayor, 1996 and Freire, Ponce, Rodrigo and Torres, 2002.

$b_2 \neq 0$ The system is **quasi-symmetrical** (coefficient matrices of left and right zones coincide).

$b_1 = 0$ PWL equivalent to **Van der Pol**.

$b_1 \leq 1$ It possesses one equilibrium point. Llibre, Núñez and Teruel 2002 and Llibre, Ordóñez and Ponce, 2013.

$b_1 > 1$ It can have three equilibria.

2) The piecewise linear model

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Forcing (or slow) system: PWL with 3 zones

$$\begin{cases} X' = -Y + g(X), \\ Y' = \varepsilon(X + b_1 Y + b_2), \end{cases}$$

(H1) $b_2 < 1 + b_1 k_2$. Always possesses a real equilibrium in the central zone.

Theorem

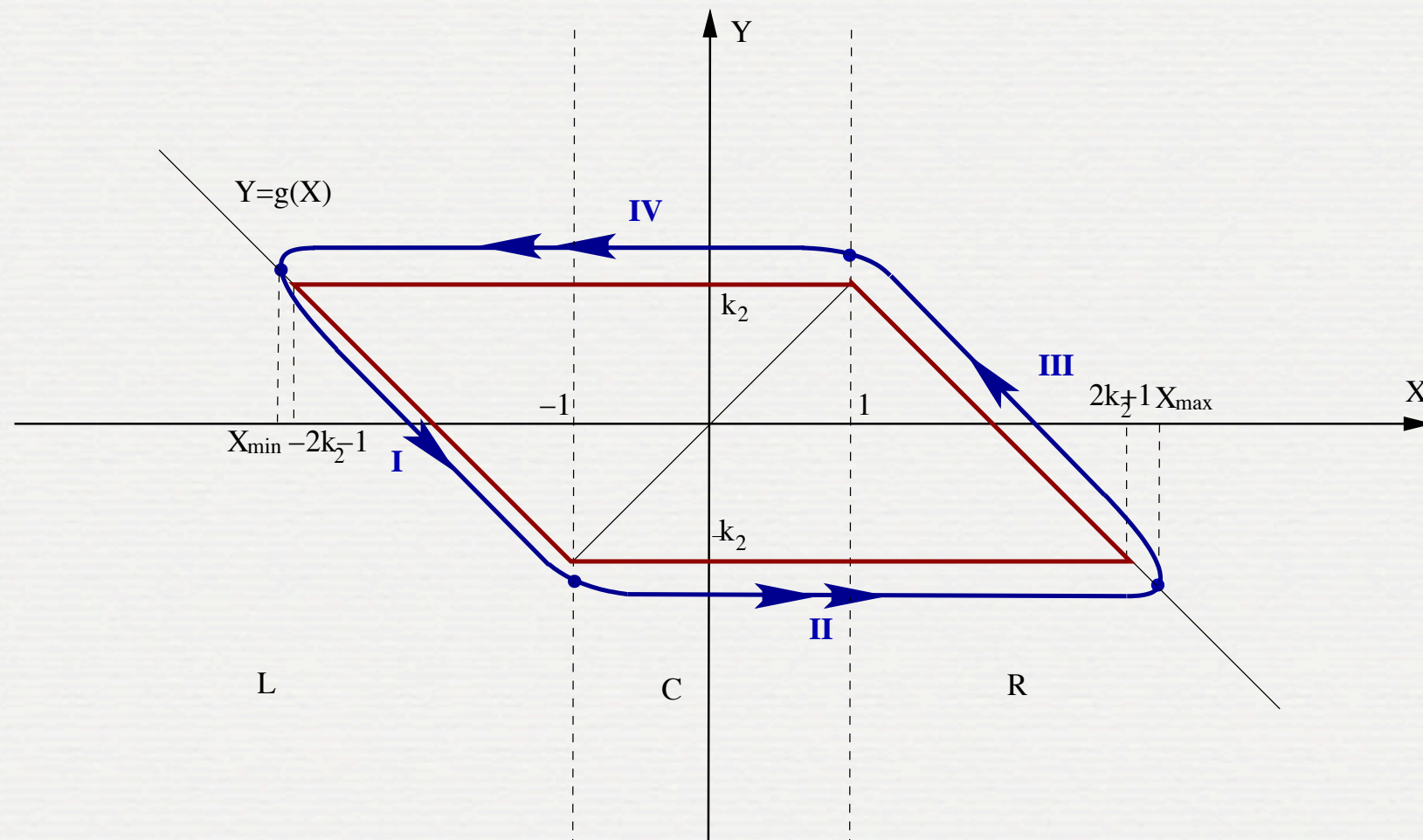
Consider $b_1 \geq 0$, $b_2, k_2 > 0$ and $0 < \varepsilon \ll 1$ and assume that (H1) holds. Then,

1. If $b_1 \in [0, 1]$ the system possesses a unique relaxation oscillation cycle $\gamma_X(\eta)$ overlapping the three zones for ε small enough.
2. If $b_1 > 1$, assume that $Y^L > k_2 + (1 + b_2 + b_1 k_2)\varepsilon$ and $Y^R < -k_2 - (1 + b_1 k_2 - b_2)\varepsilon$. Then, the system possesses a unique relaxation oscillation cycle $\gamma_X(\eta)$ overlapping the three zones for ε small enough.

2) The piecewise linear model

a) Dynamical behavior.

Forcing (or slow) system: PWL with 3 zones



1. If $b_1 \in [0, 1)$ the velocity of the flow along phases I and III of the limit cycle $\gamma_X(\eta)$ is decreasing.
2. If $b_1 = 1$ the velocity of the flow along phases I and III of the limit cycle $\gamma_X(\eta)$ is almost constant.
3. If $b_1 > 1$ the velocity of the flow along phases I and III of the limit cycle $\gamma_X(\eta)$ is increasing.

2) The piecewise linear model

a) Dynamical behavior.

Forced (or fast) system: PWL with 3 zones

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(a_0x + a_1y + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - k_1 - 1, & \text{if } x \leq -1, \\ k_1x, & \text{if } |x| \leq 1, \\ -x + k_1 + 1, & \text{if } x \geq 1, \end{cases}$$

(H2) $a_0 - a_1 > 0$. The system possesses only one equilibrium point.

2) The piecewise linear model

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Forced (or fast) system: PWL with 3 zones

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(a_0x + a_1y + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - k_1 - 1, & \text{if } x \leq -1, \\ k_1x, & \text{if } |x| \leq 1, \\ -x + k_1 + 1, & \text{if } x \geq 1, \end{cases}$$

(H2) $a_0 - a_1 > 0$. The system possesses only one equilibrium point.

X change the location of the y-nullcline

$$y = -\frac{(a_0x + a_2 + cX)}{a_1}.$$

2) The piecewise linear model

a) Dynamical behavior.

Forced (or fast) system: PWL with 3 zones

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(a_0x + a_1y + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - k_1 - 1, & \text{if } x \leq -1, \\ k_1x, & \text{if } |x| \leq 1, \\ -x + k_1 + 1, & \text{if } x \geq 1, \end{cases}$$

(H2) $a_0 - a_1 > 0$. The system possesses only one equilibrium point.

X change the location of the y-nullcline

$$y = -\frac{(a_0x + a_2 + cX)}{a_1}.$$

When X moves to the right, the nullcline is translated to the left.

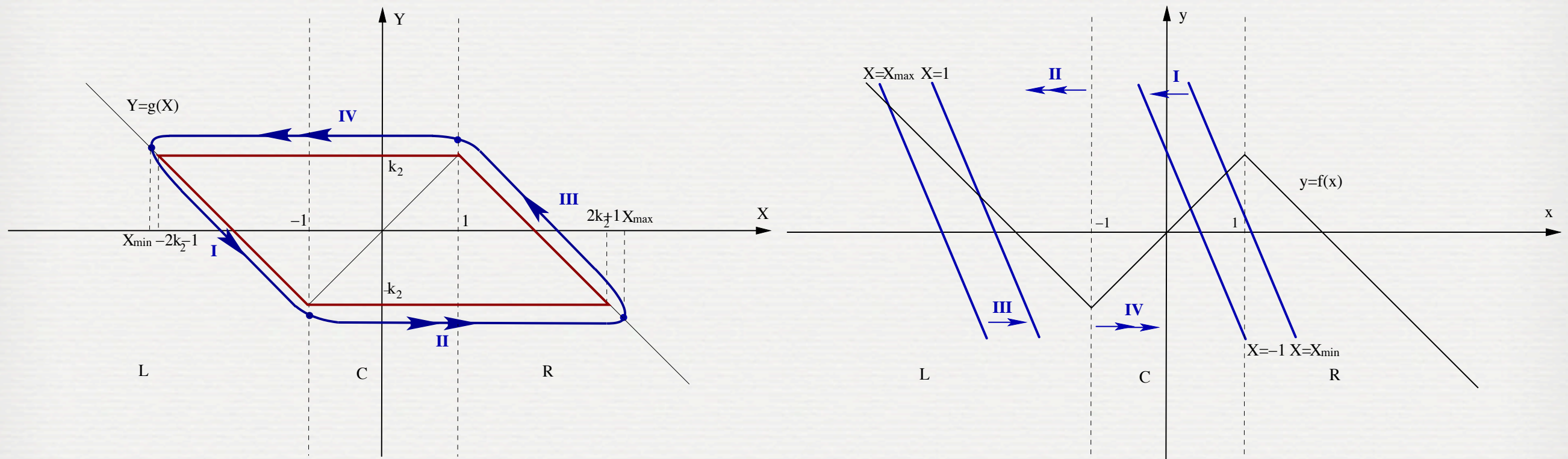
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2) The piecewise linear model

a) Dynamical behavior.

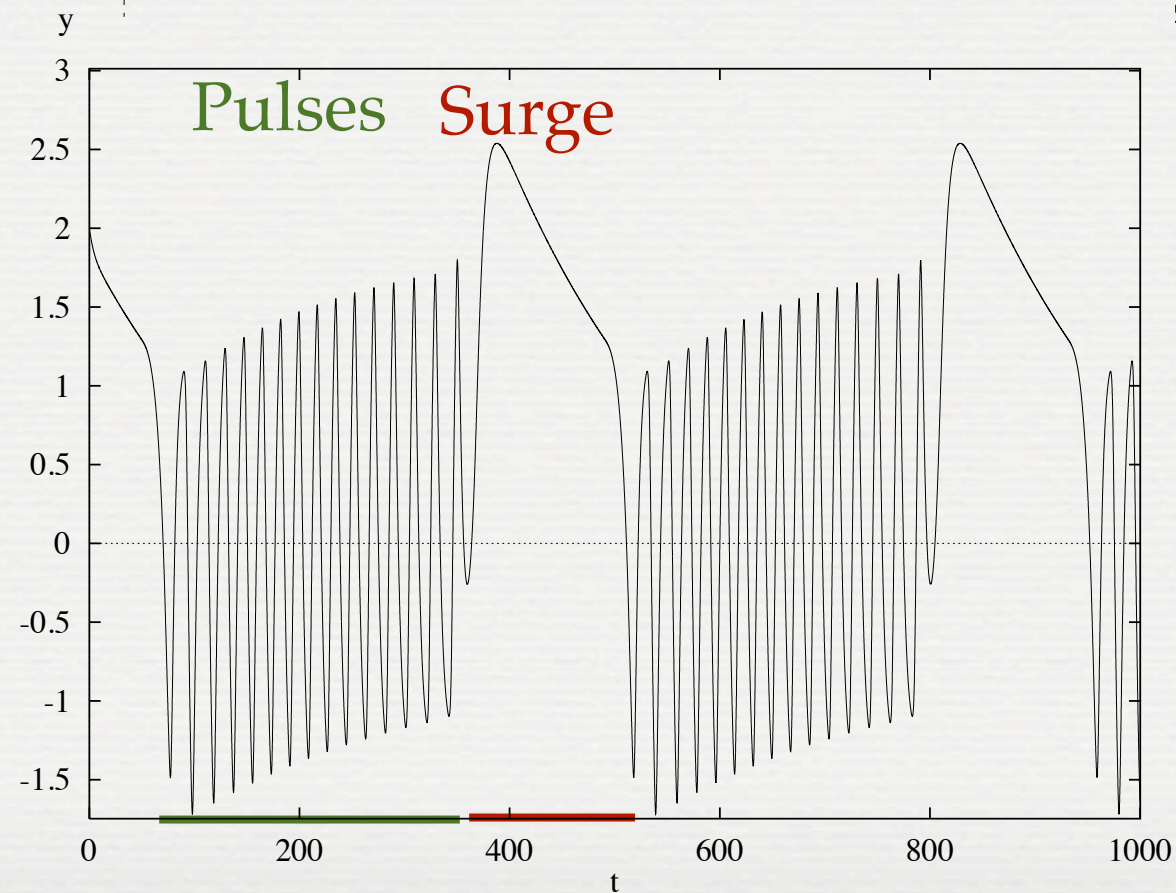
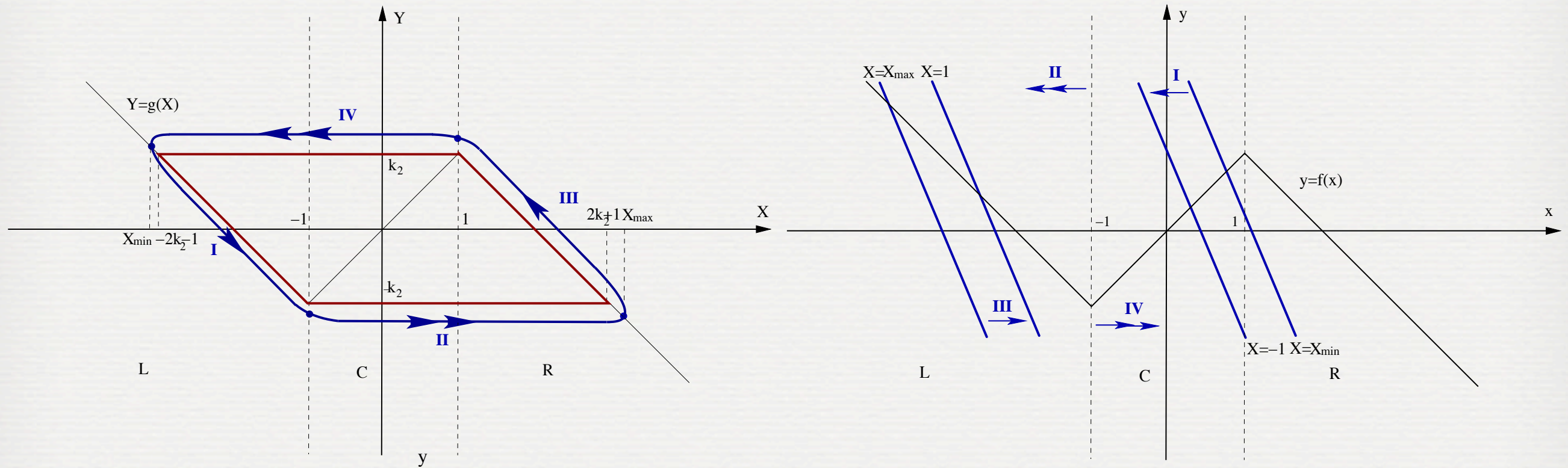
$$(H3) \quad |a_0 + a_1 k_1 - a_2| < c < \frac{a_0 + a_1 k_1 + a_2}{2k_2 + 1}.$$

- The left canard super-explosion bifurcation takes place when $|X| < 1$.
- The right canard super-explosion cannot occur.



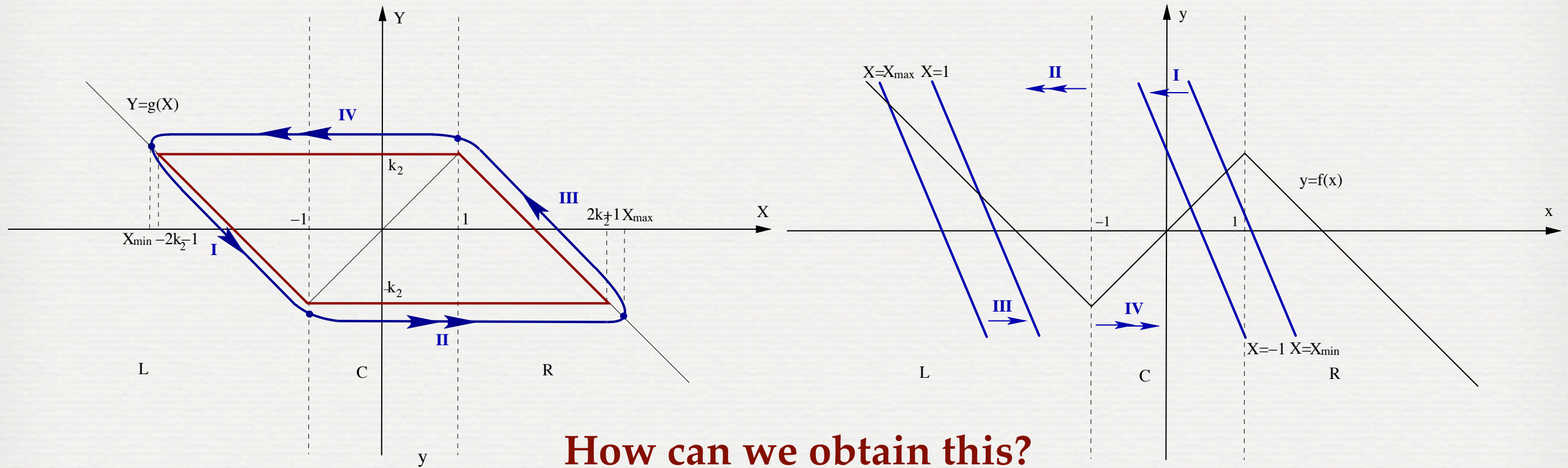
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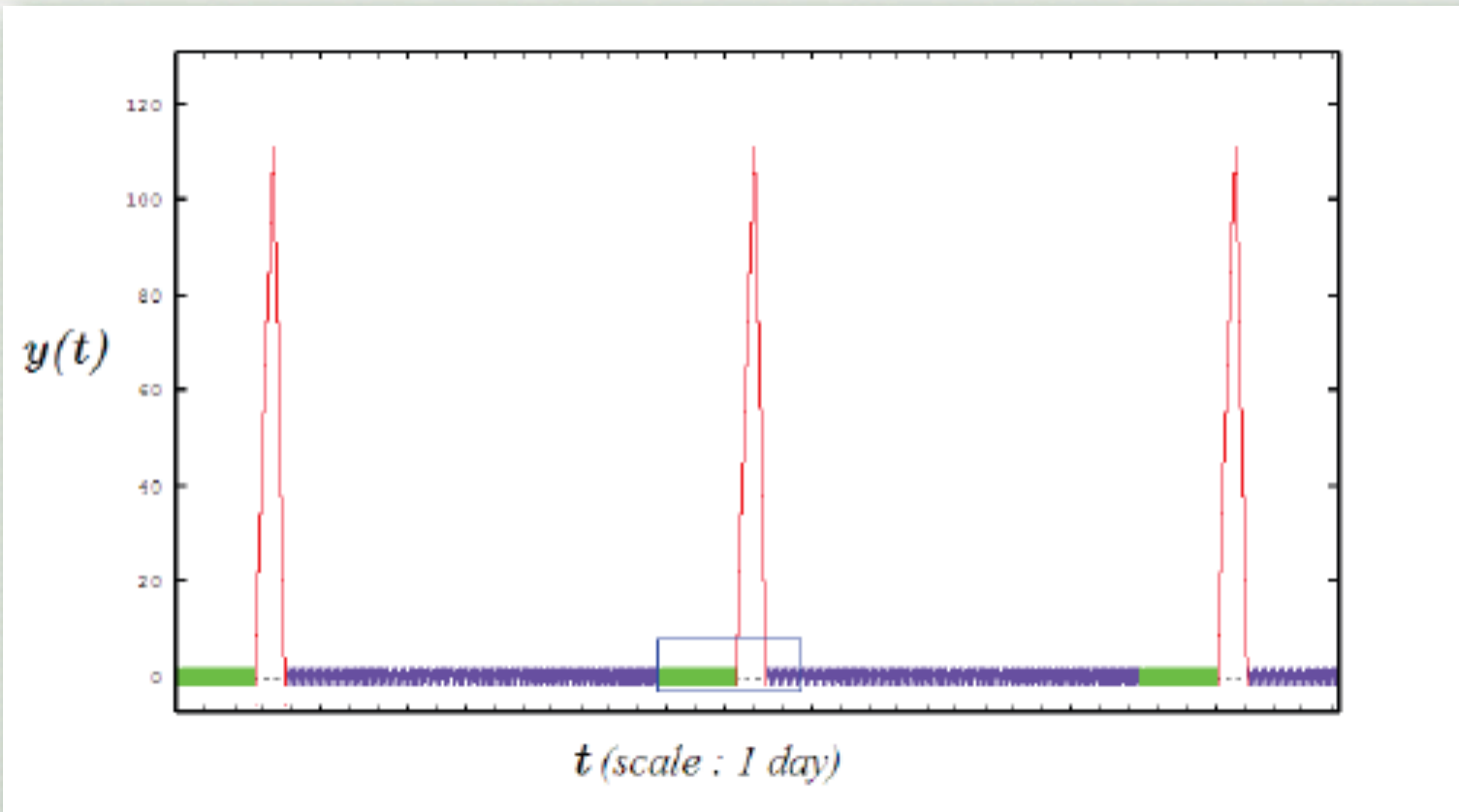


2) The piecewise linear model

a) Dynamical behavior.



How can we obtain this?



2) The piecewise linear model

b) Quantitative aspects.

Feature	Specification	Unit
whole cycle duration	16.5	days
high frequency duration	2.5	days
surge duration	1	days
low frequency duration	13	days
pulse to surge amplitude ratio	1 to 60	-
frequency increase ratio	1 to 4	-

TABLE 4.1

Quantitative specifications for the GnRH secretion pattern along the ovarian cycle in the ewe

2) The piecewise linear model

b) Quantitative aspects.

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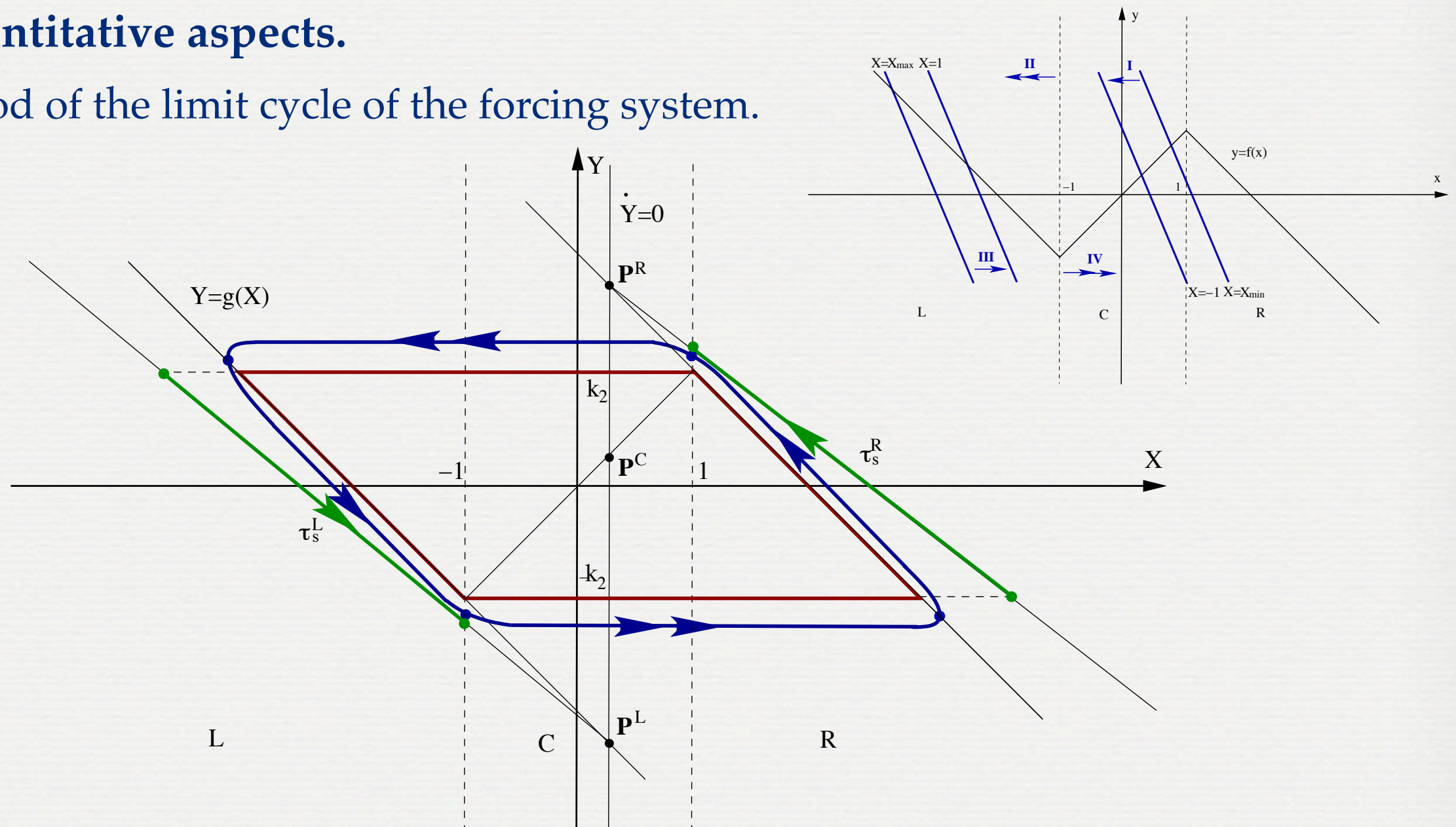
Quantitative specifications for the GnRH secretion pattern along the ovarian cycle in the ewe

- 🔊 Period of the limit cycle of the forcing system.
- 🔊 Period (and frequency) of the oscillations in the pulsatile phase.
- 🔊 Approximation of the maximum of the surge.

2) The piecewise linear model

b) Quantitative aspects.

Period of the limit cycle of the forcing system.



Time $t_s^L = \tau_s^L / \delta$ approximates the time that the system spends during pulses.

Time $t_s^R = \tau_s^R / \delta$ approximates the time that the system spends during surge.

2) The piecewise linear model

b) Quantitative aspects.

Period of the limit cycle of the forcing system.

Ratio between the durations of the pulsatile phase and the surge regime.

$$\rho_s(b_1, b_2, k_2, \varepsilon) = \frac{t_s^L}{t_s^R} = \begin{cases} \frac{\log \left[\frac{\varepsilon(X^L + 1)}{(\lambda_s^L - \varepsilon b_1)(Y^L - k_2)} \right]}{\log \left[\frac{\varepsilon(X^R - 1)}{(\lambda_s^L - \varepsilon b_1)(Y^R + k_2)} \right]} = \frac{\beta^L}{\beta^R} + \frac{(b_1 - 1)(\beta^L - \beta^R)}{(\beta^R)^2} \varepsilon + O(\varepsilon^2), & \text{if } b_1 \neq 1, \\ \frac{(1 + b_2 + k_2)(-2k_2 + \varepsilon(k_2 + b_2 - 1))}{(b_2 - k_2 - 1)(2k_2 + \varepsilon(1 + b_2 - k_2))} = \frac{1 + b_2 + k_2}{1 - b_2 + k_2} \left(1 - \frac{b_2 \varepsilon}{k_2} \right) + O(\varepsilon^2), & \text{if } b_1 = 1. \end{cases}$$

$$\text{with } \lambda_s^L = \frac{-1 + \varepsilon b_1 + \sqrt{1 + 2(b_1 - 2)\varepsilon + b_1^2 \varepsilon^2}}{2},$$

$$\beta^L = \log \left[\frac{b_2 - 1 - b_1 k_2}{b_2 - 1 + (b_1 - 2)k_2} \right], \quad \beta^R = \log \left[\frac{b_2 + 1 + b_1 k_2}{b_2 + 1 - (b_1 - 2)k_2} \right].$$

2) The piecewise linear model

b) Quantitative aspects.

Period of the limit cycle of the forced system (pulses). Depends on X .

We can proceed in the same way to compute the period...

Moreover, we can prove the following result.

Theorem

For each point $p \in (-1, 1)$, consider the function $X(p) = -(p(a_0 + a_1 k_1) + a_2)/c$. For $X = X(p)$, under hypothesis (H1), (H2) and (H3), the function $\tau_f(X(p))$ is continuous in $(-1, 1)$, possesses two vertical asymptotes at $p = -1$ and $p = 1$, is strictly decreasing for $p \in (-1, 0)$, strictly increasing for $p \in (0, 1)$ and has a minimum at $p = 0$.

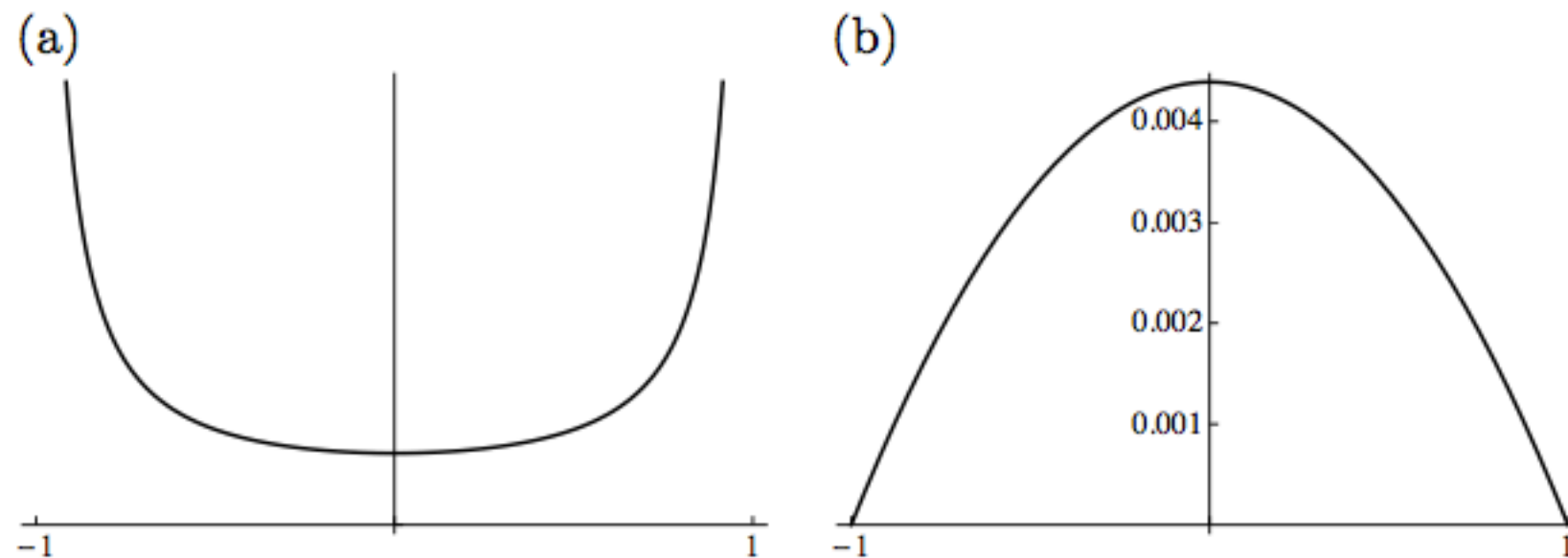


FIG. 3.2. Representation of the period $\tau_f(X(p))$ (a) and frequency $\omega(X(p))$ (b) with $p \in (-1, 1)$ for the values $\delta = 0.0125$, $k_1 = 3$, $a_0 = 1$, $a_1 = 0.9999$, $a_2 = 1.9998$ and $c = 2.4891$.

2) The piecewise linear model

b) Quantitative aspects.

Following the neuroendocrine knowledge, we need increasing frequency during the whole pulsatile regime.

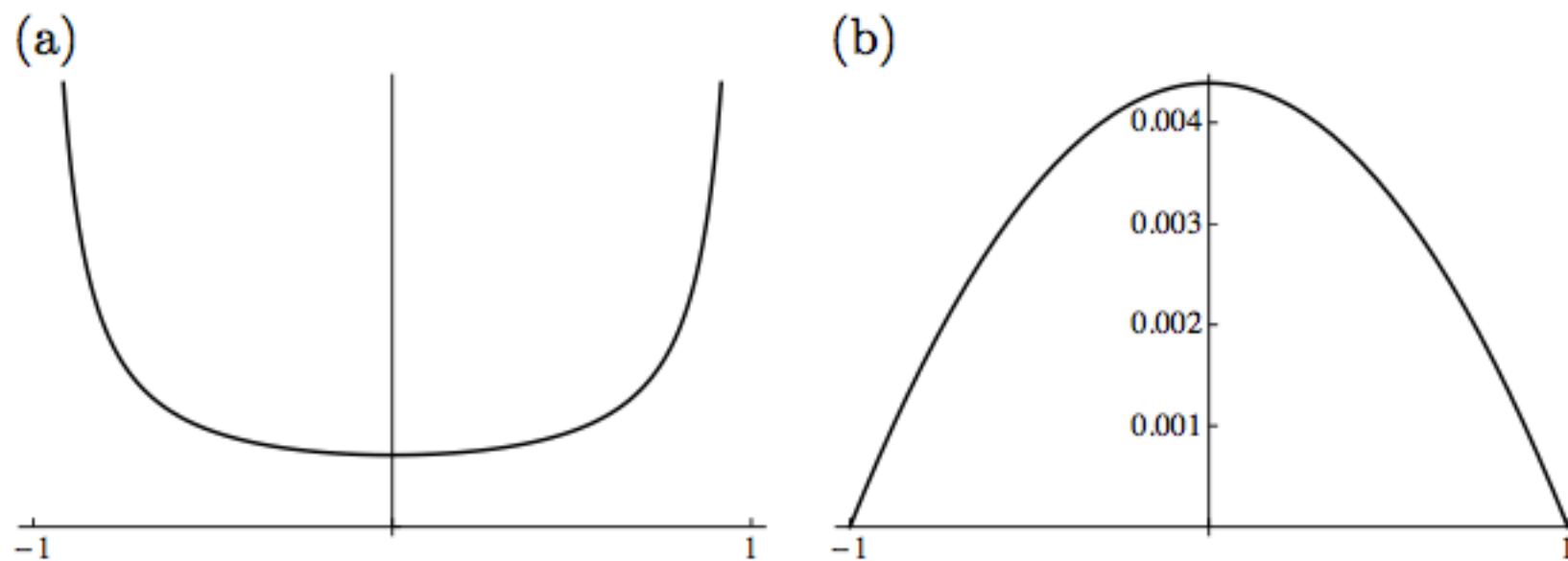
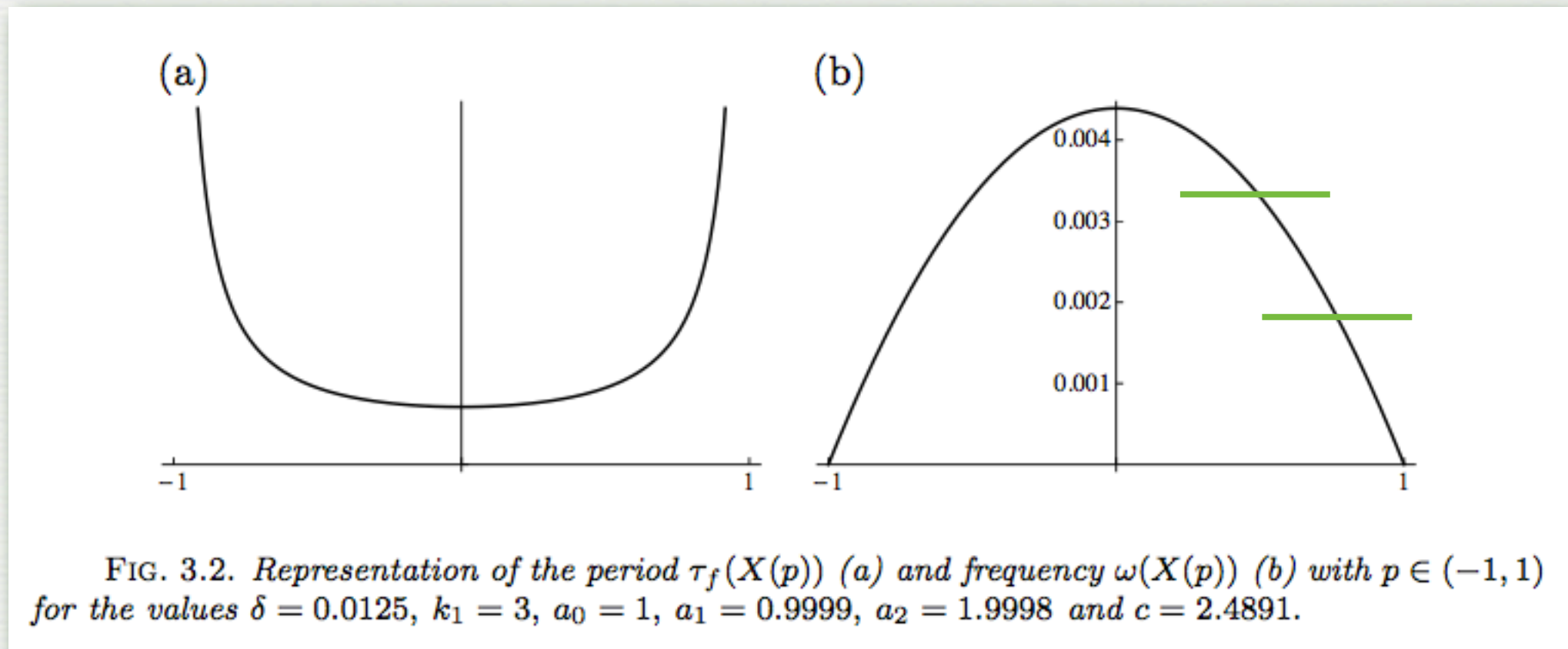


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b) Quantitative aspects.

Following the neuroendocrine knowledge, we need increasing frequency during the whole pulsatile regime.



(H4) $a_2 < c$. Increasing frequency during the whole pulsatile regime.

Ratio of frequency increase

$$\rho_f(a_0, a_1, a_2, c, k_1, \delta) = \frac{\omega(-1)}{\omega(-2k_2 - 1)}.$$

2) The piecewise linear model

b) Quantitative aspects.

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Low-high frequency durations rate.

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TABLE 4.1

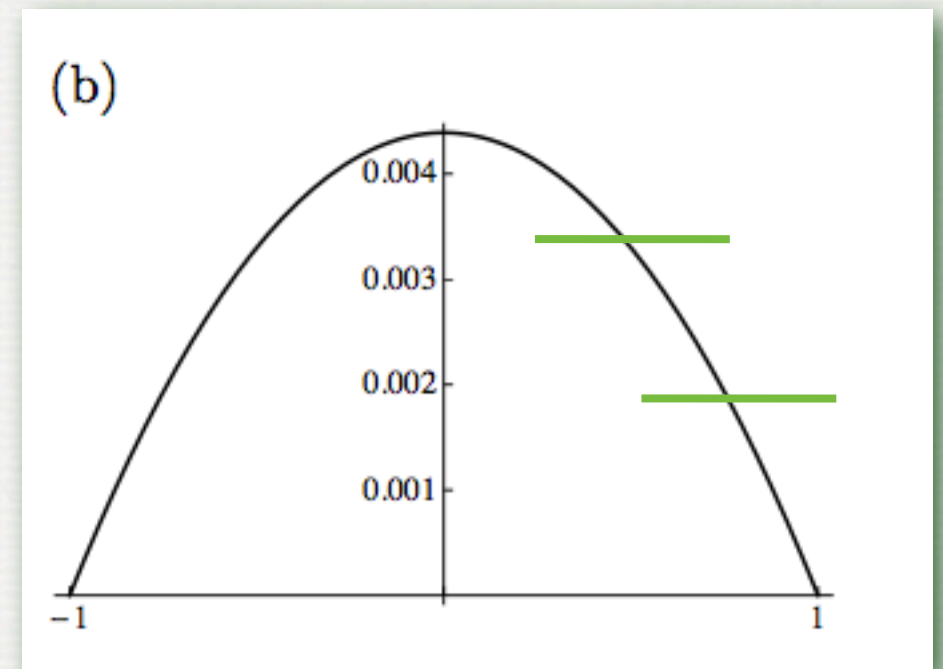
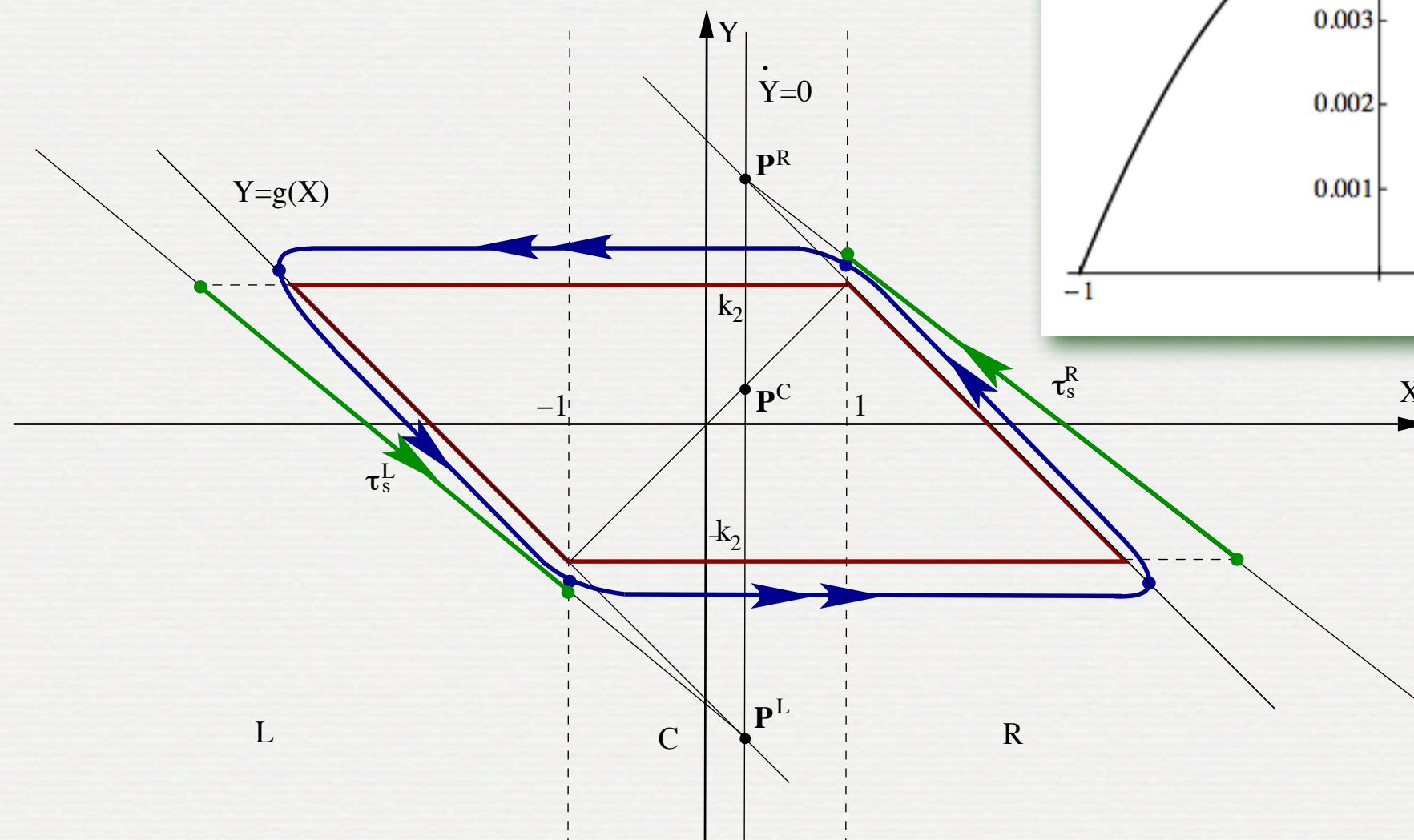
Quantitative specifications for the GnRH secretion pattern along the ovarian cycle in the ewe

1. If $b_1 \in [0, 1)$ the velocity of the flow along phase I of the limit cycle $\gamma_X(\eta)$ is decreasing and then, the system remains a larger amount of time in the high frequency regime.
2. If $b_1 = 1$ the velocity of the flow along phase I of the limit cycle $\gamma_X(\eta)$ is almost constant and the system remains the same amount of time in both the low and high frequency regimes.
3. If $b_1 > 1$ the velocity of the flow along phase I of the limit cycle $\gamma_X(\eta)$ is increasing and then, the system remains a larger amount of time in the low frequency regime.

2) The piecewise linear model

b) Quantitative aspects.

Low-high frequency durations rate.

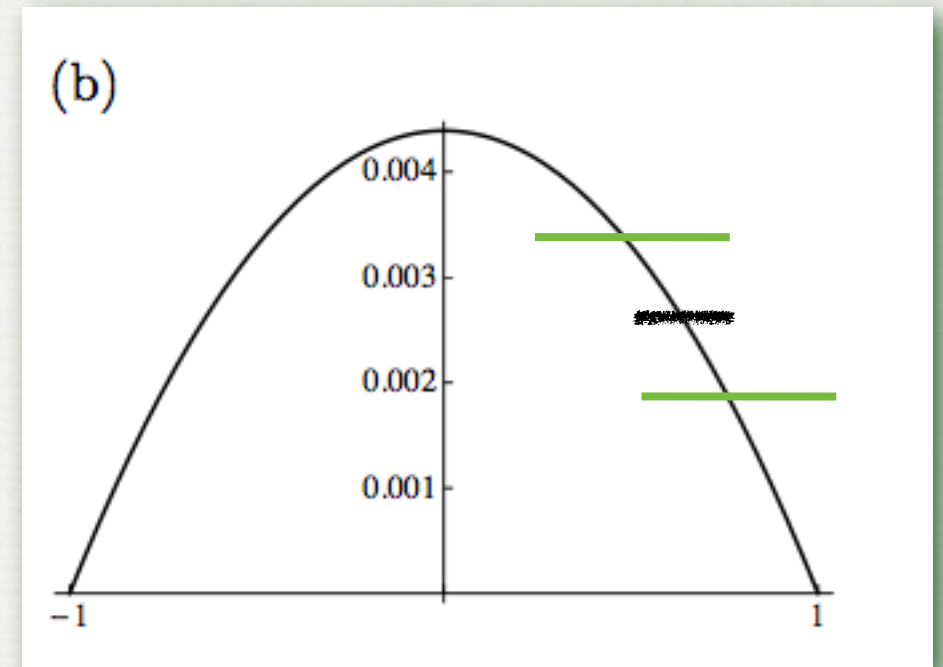
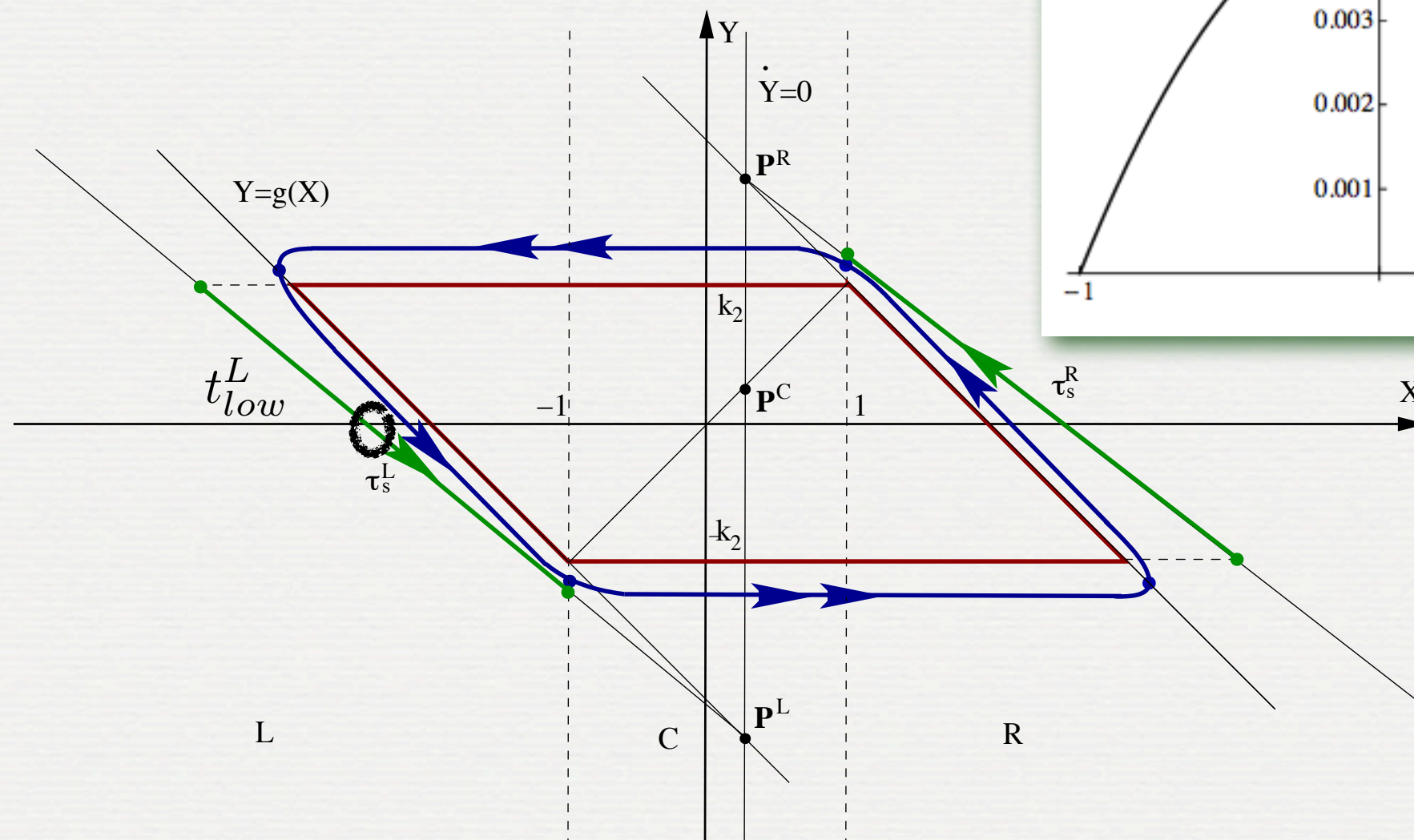


We consider by convention that the change between both regimes takes place when the flow on the relaxation cycle passes through $Y = 0$ during phase I.

2) The piecewise linear model

b) Quantitative aspects.

Low-high frequency durations rate.



We consider by convention that the change between both regimes takes place when the flow on the relaxation cycle passes through $Y = 0$ during phase I.

2) The piecewise linear model

b) Quantitative aspects.

Low frequency duration rate.

$$t_{low}^L = \frac{\beta_{low}}{\delta \lambda_s^L} = \frac{\beta_{low}}{\delta} \left(\frac{1}{\varepsilon(b_1 - 1)} + \frac{1}{b_1 - 1} + \varepsilon + O(\varepsilon^2) \right),$$

$$\text{where } \beta_{low} = \log \left[\frac{b_2 - k_2 - 1}{b_2 - 1 + (b_1 - 2)k_2} \right].$$

Duration ratio between the low and high frequency parts.

$$b_1 \neq 1$$

$$\phi(b_1, b_2, k_2, \varepsilon) = \frac{t_{low}^L}{t_s^L} = \frac{\beta_{low}}{\beta^L} \left(1 + \frac{(1 - b_1)\varepsilon}{\beta^L} \right) + O(\varepsilon^2)$$

$$b_1 = 1$$

$$\phi_1 = \frac{(\varepsilon - 1)k_2}{\varepsilon(b_2 + k_2 - 1) - 2k_2} = \frac{1}{2} + O(\varepsilon)$$

2) The piecewise linear model

b) Quantitative aspects.

Feature	Specification	Unit
whole cycle duration ✓	16.5	days
high frequency duration ✓	2.5	days
surge duration ✓	1	days
low frequency duration ✓	13	days
pulse to surge amplitude ratio	1 to 60	-
frequency increase ratio ✓	1 to 4	-

TABLE 4.1

Quantitative specifications for the GnRH secretion pattern along the ovarian cycle in the ewe,

2) The piecewise linear model

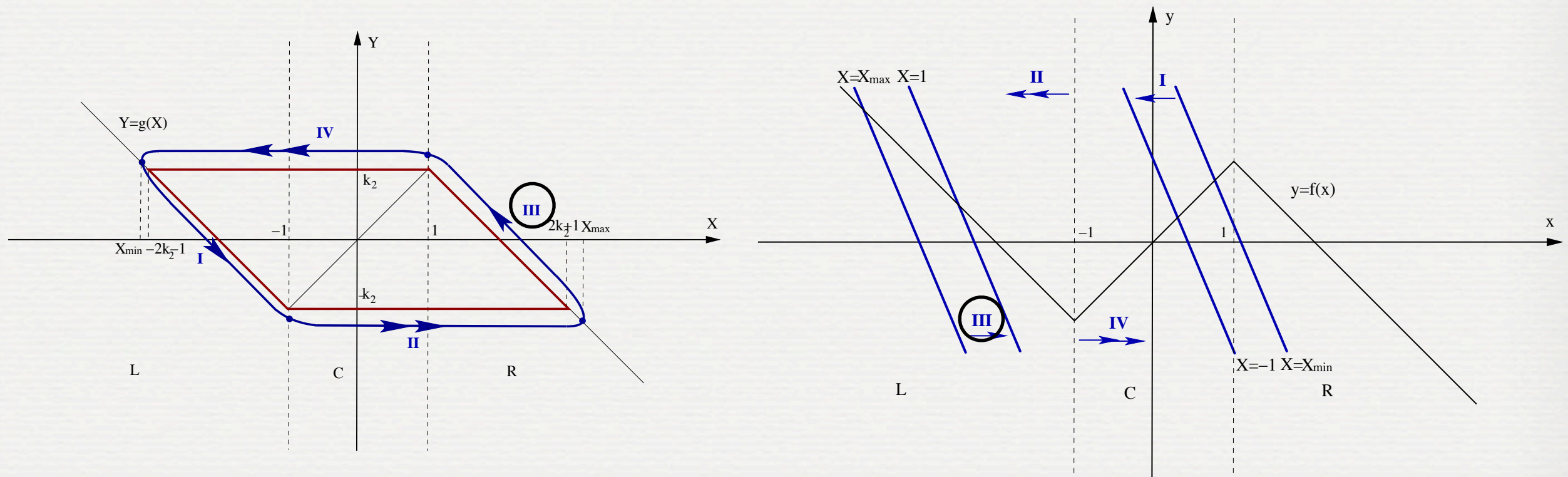
b) Quantitative aspects.

Approximation of the maximum of the surge.

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TABLE 4.1

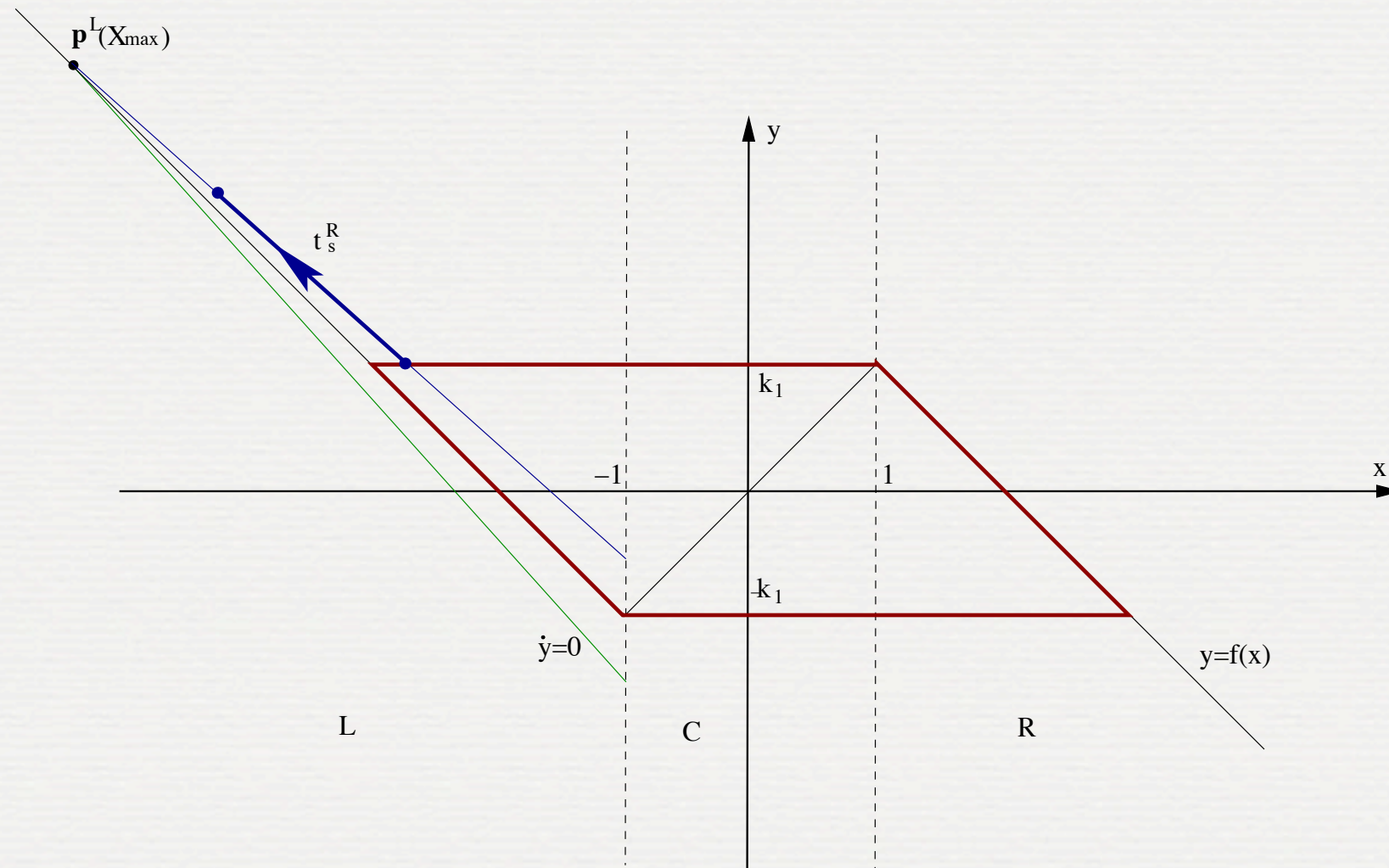
Quantitative specifications for the GnRH secretion pattern along the ovarian cycle in the ewe,



2) The piecewise linear model

b) Quantitative aspects.

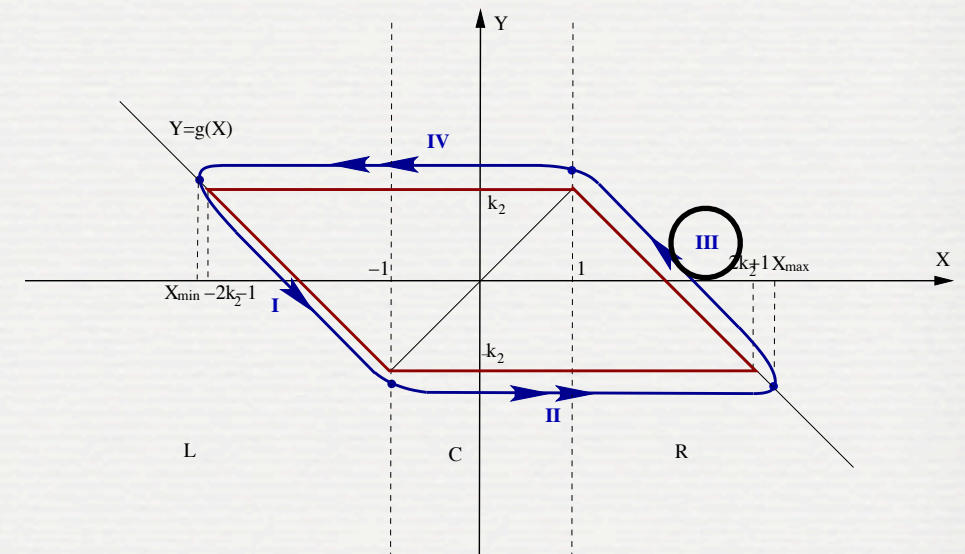
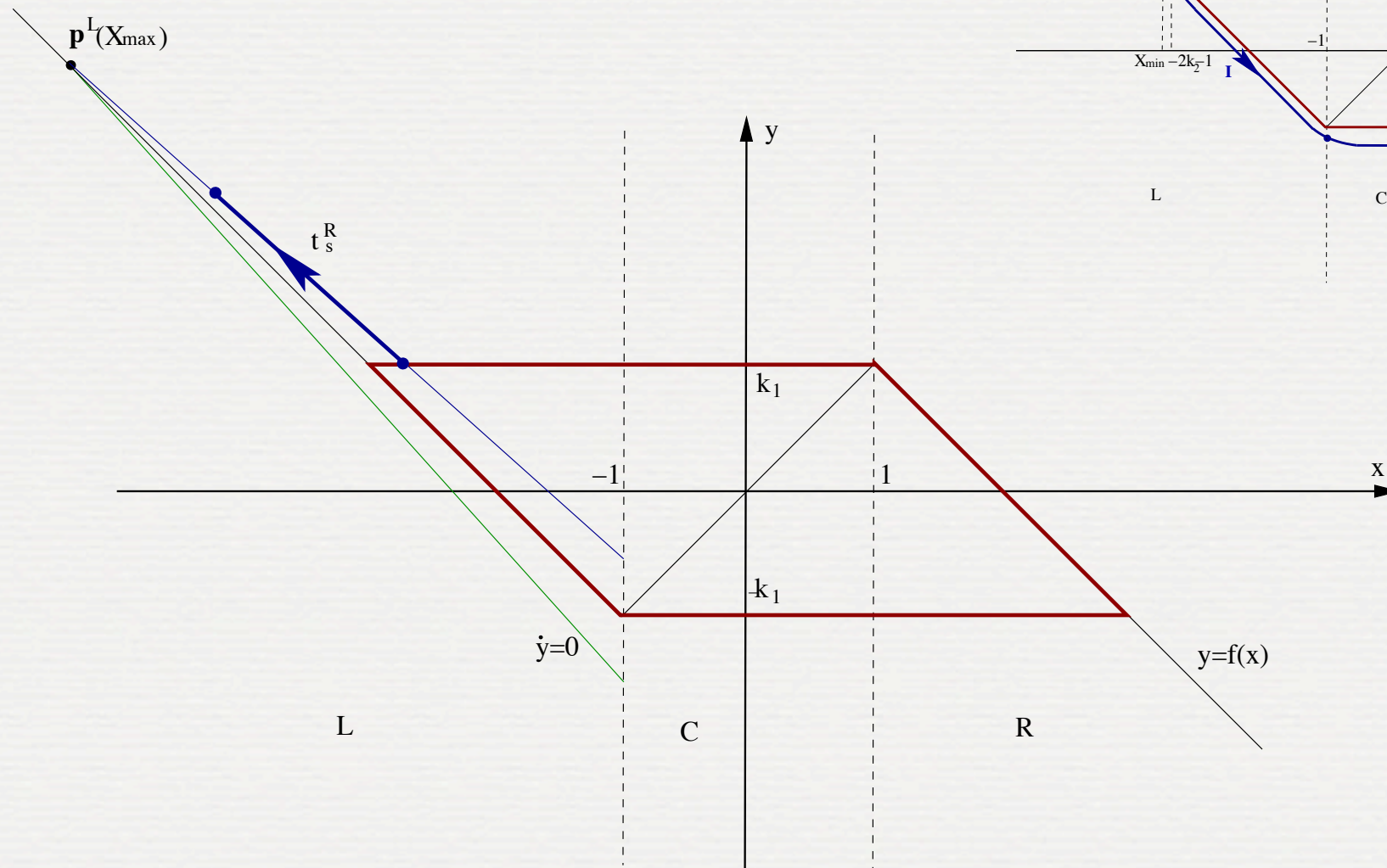
Approximation of the maximum of the surge.



2) The piecewise linear model

b) Quantitative aspects.

Approximation of the maximum of the surge.



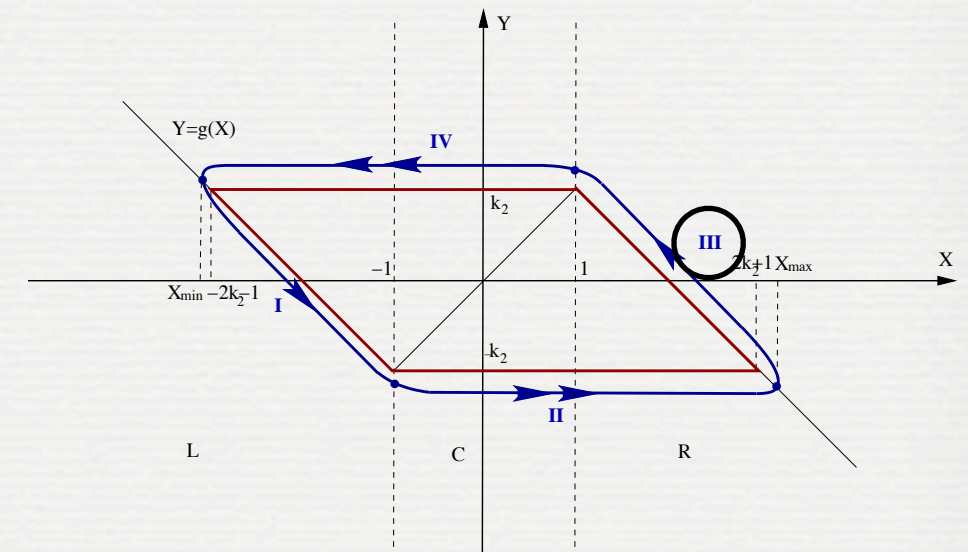
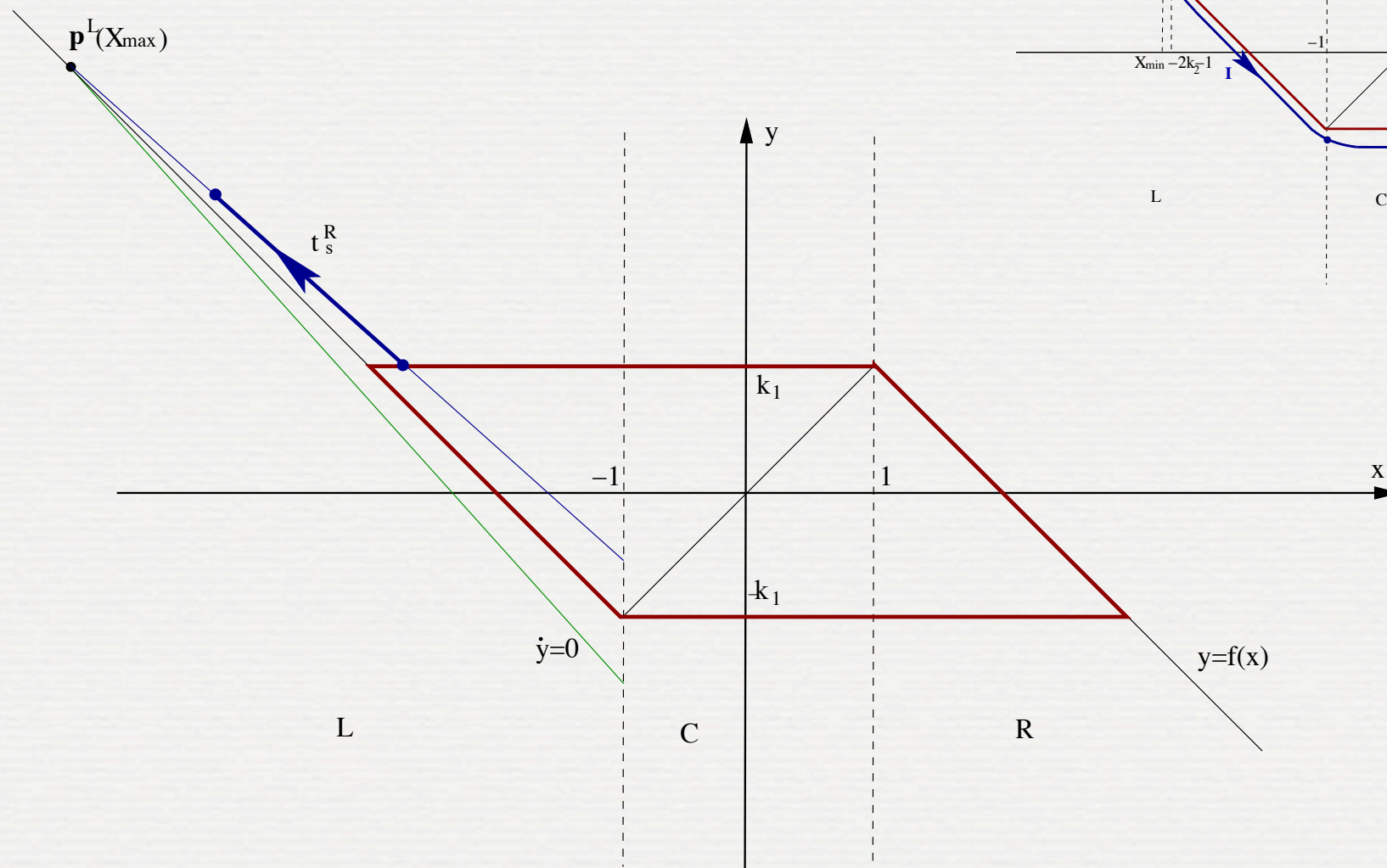
$$y = f(x), Y = g(X) \text{ and } s = t\delta$$

$$\begin{cases} x' = \frac{a_0 x + a_1 f(x) + a_2 + cX}{df(x)/dx}, \\ X' = \varepsilon \frac{X + b_1 g(X) + b_2}{dg(X)/dX}, \end{cases}$$

2) The piecewise linear model

b) Quantitative aspects.

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$$X > 1 \implies g(X) = -X + k_2 + 1,$$

$$x < -1 \implies f(x) = -x - k_1 - 1.$$

$$\begin{cases} x' = -(a_0 x + a_1 (-x - k_1 - 1) + a_2 + cX), \\ X' = -\varepsilon (X + b_1 (-X + k_2 + 1) + b_2). \end{cases}$$

Linear system during the surge

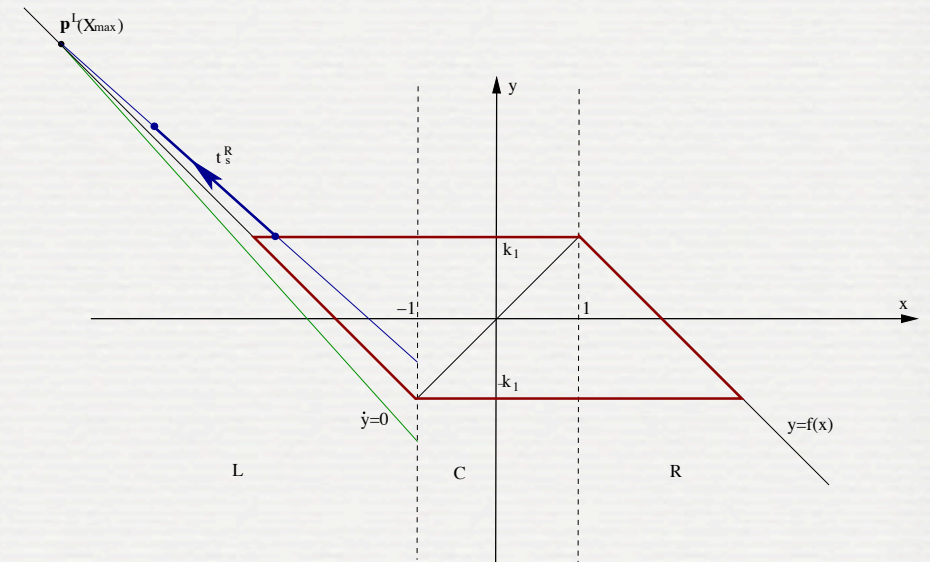
2) The piecewise linear model

b) Quantitative aspects.

Approximation of the maximum of the surge.

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$$(x(0), X(0)) = (-2k_1 - 1, 2k_2 + 1)$$



2) The piecewise linear model

b) Quantitative aspects.

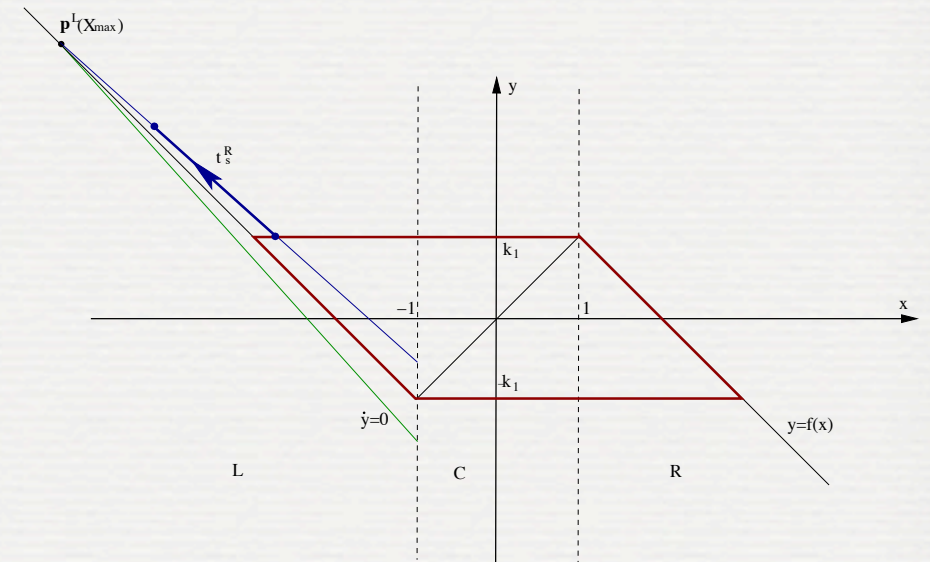
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$$(x(0), X(0)) = (-2k_1 - 1, 2k_2 + 1)$$

$$X(s) = \frac{b_1(1 + k_2) + b_2 - \exp[(b_1 - 1)\varepsilon s] (1 + b_2 - k_2(b_1 - 2))}{b_1 - 1}$$

$$X(s_{end}) = 1 \quad \longrightarrow \quad s_{end} = \frac{\beta^R}{(b_1 - 1)\varepsilon}$$



2) The piecewise linear model

b) Quantitative aspects.

Approximation of the maximum of the surge.

$$\begin{cases} x' = -(a_0x + a_1(-x - k_1 - 1) + a_2 + cX), \\ X' = -\varepsilon(X + b_1(-X + k_2 + 1) + b_2). \end{cases}$$

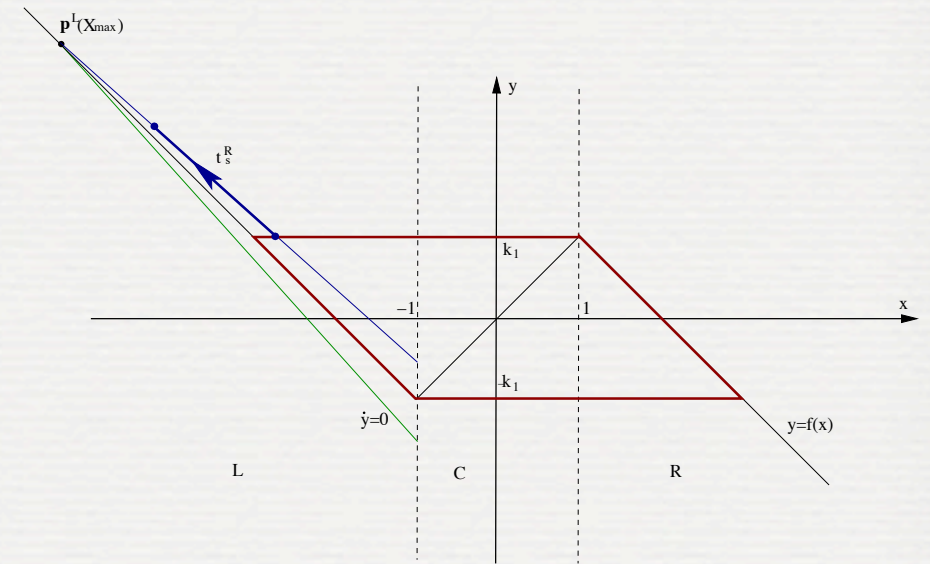
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$$(H5) \quad a_0k_1 + a_1 - a_2 > 0, |(a_1 - a_0)/c| \ll 1 \quad \longrightarrow \quad x \text{ decreases on the entire time interval}$$

$x(s_{end})$ approximation of the minimum reached by x during the surge



2) The piecewise linear model

b) Quantitative aspects.

Approximation of the maximum of the surge.

$$\begin{cases} x' = -(a_0x + a_1(-x - k_1 - 1) + a_2 + cX), \\ X' = -\varepsilon(X + b_1(-X + k_2 + 1) + b_2). \end{cases}$$

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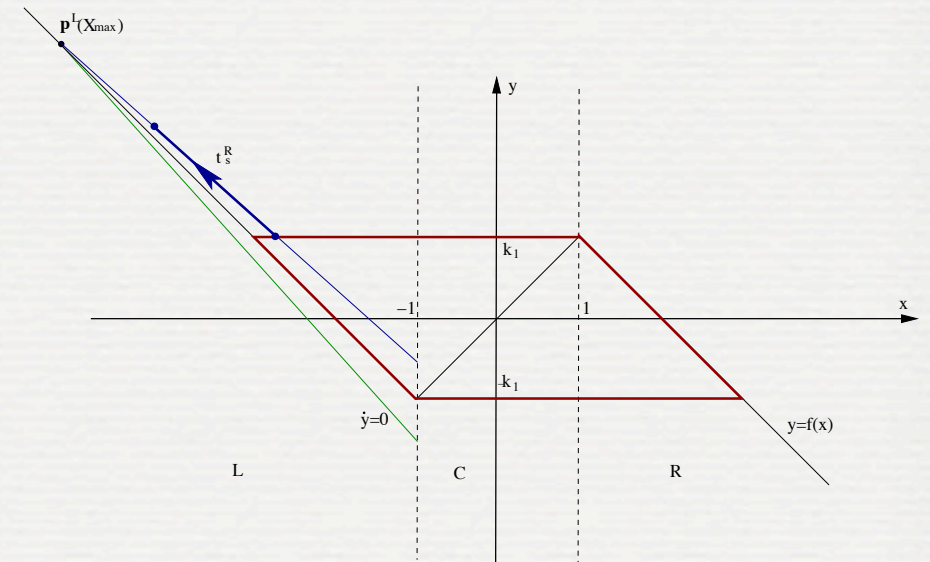
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$x(s_{end})$ approximation of the minimum reached by x during the surge



$$y_{\max}(a_0, a_1, a_2, b_1, b_2, c, k_1, k_2, \varepsilon) = -x(s_{end}) - k_1 - 1$$

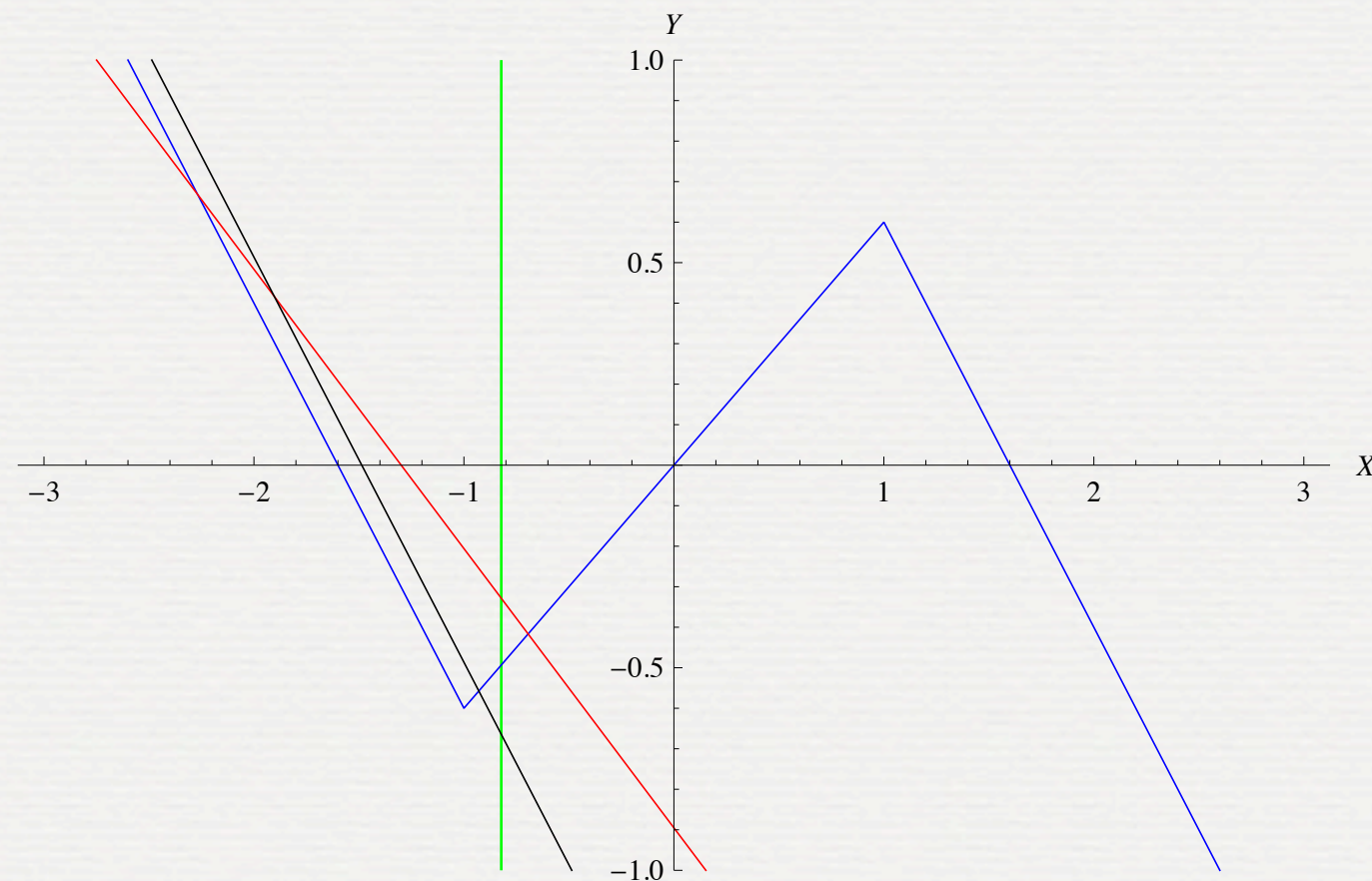
approximation of the maximum of the surge



2) The piecewise linear model

c) Application to GnRH secretion patterns.

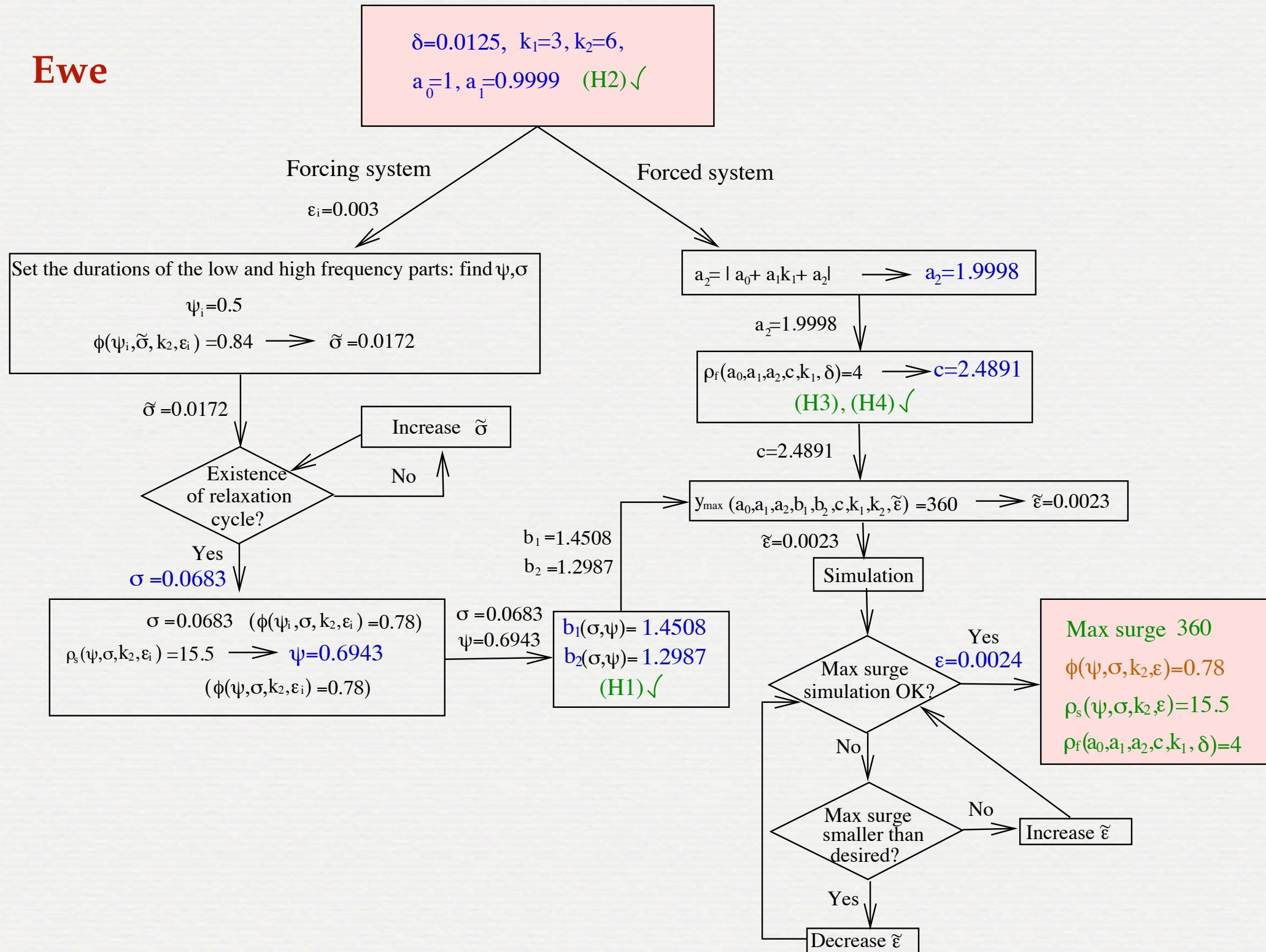
	Ewe	Monkey	Rat
Feature	Specification	Specification	Specification
whole cycle duration	16.5	28	5
high frequency duration	2.5	13	3
surge duration	1	1	1
low frequency duration	13	14	1
pulse to surge amplitude ratio	1 to 60	1 to 25	1 to 20
frequency increase ratio	1 to 4	1 to 4	1 to 4



2) The piecewise linear model

c) Application to GnRH secretion patterns.

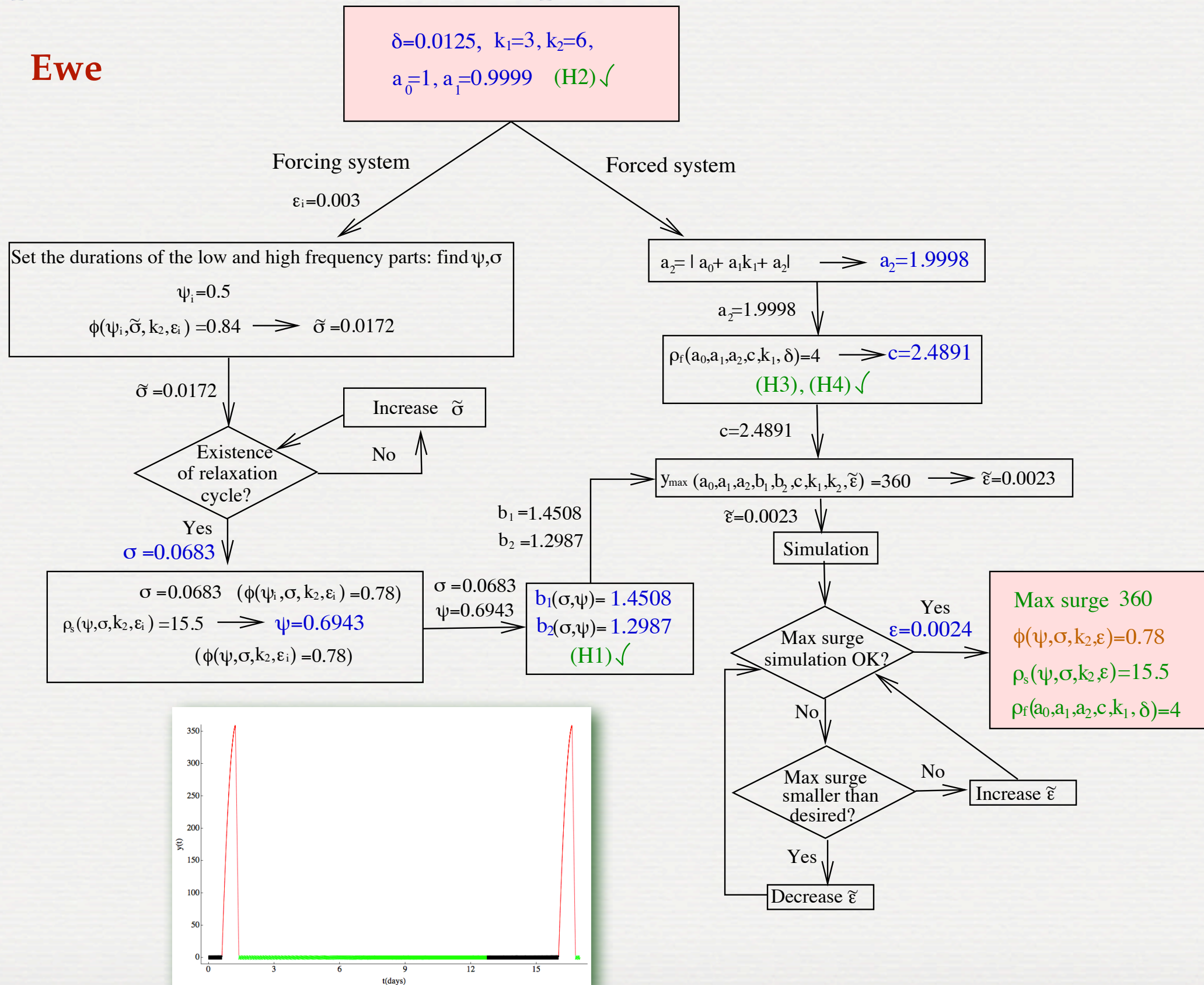
Ewe



2) The piecewise linear model

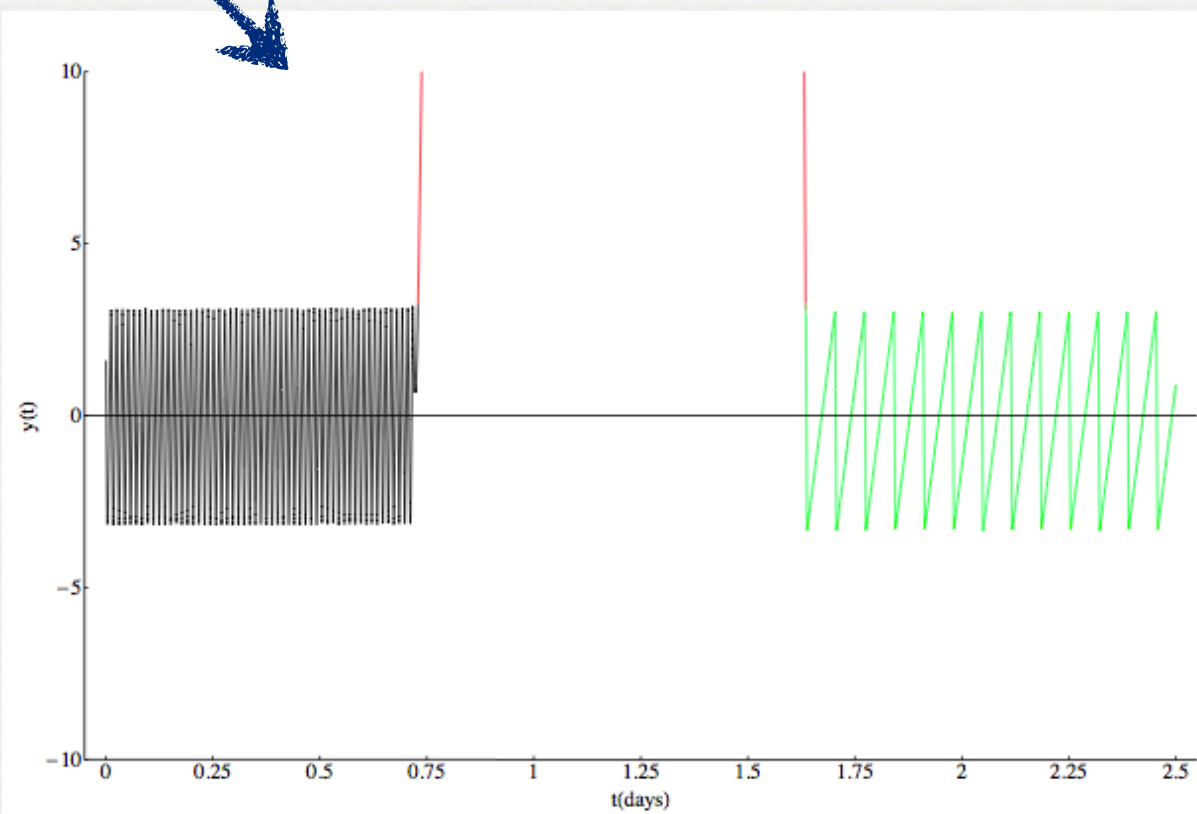
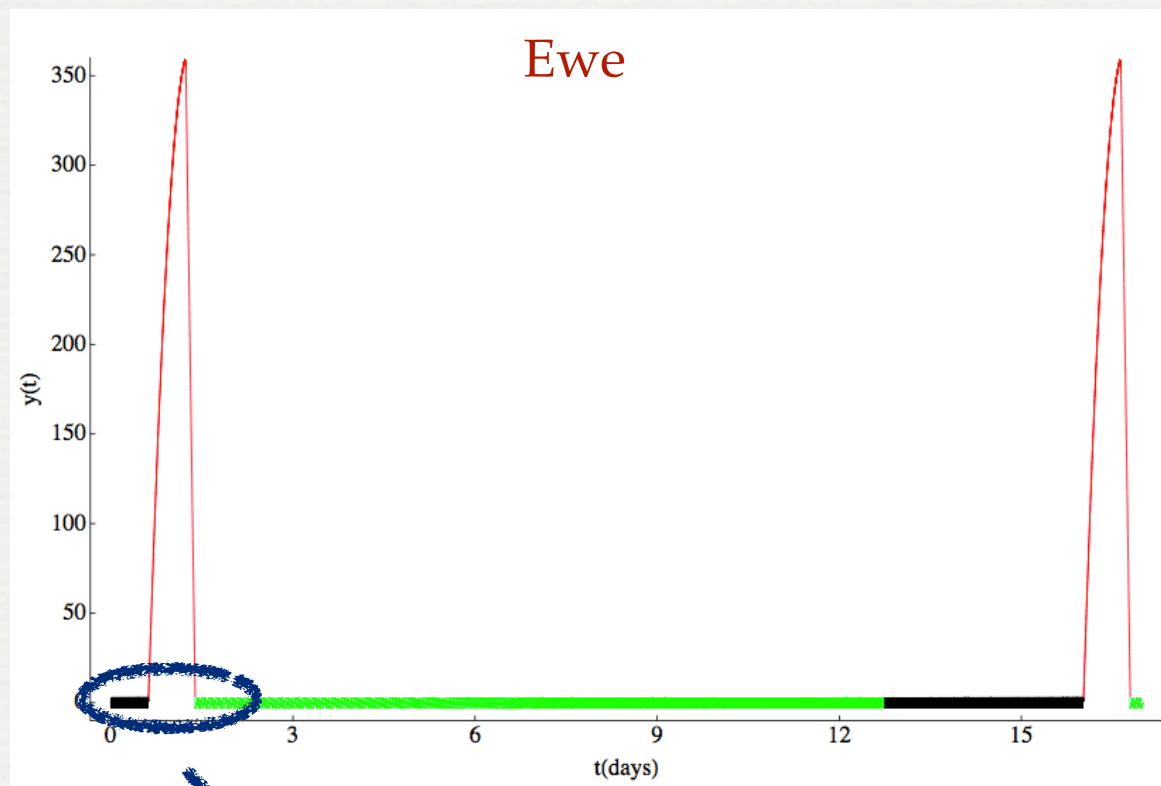
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Ewe



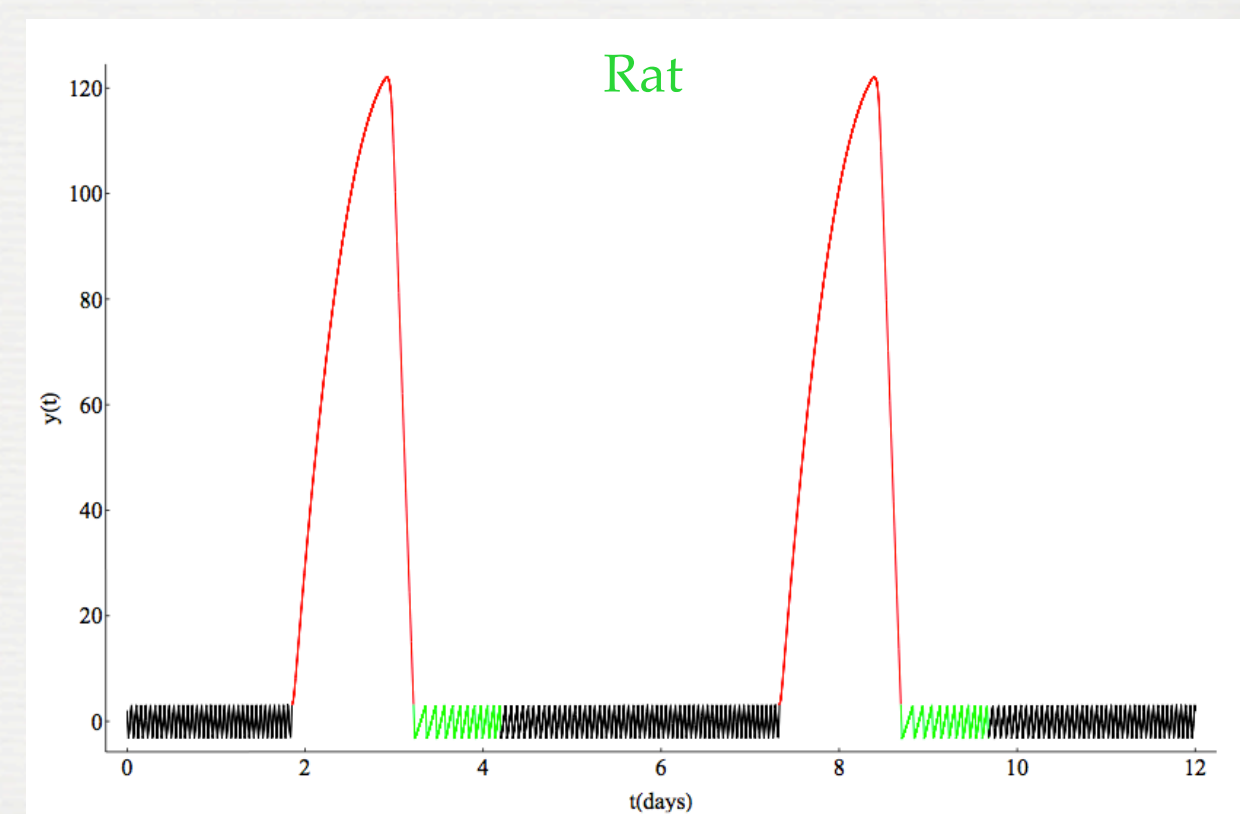
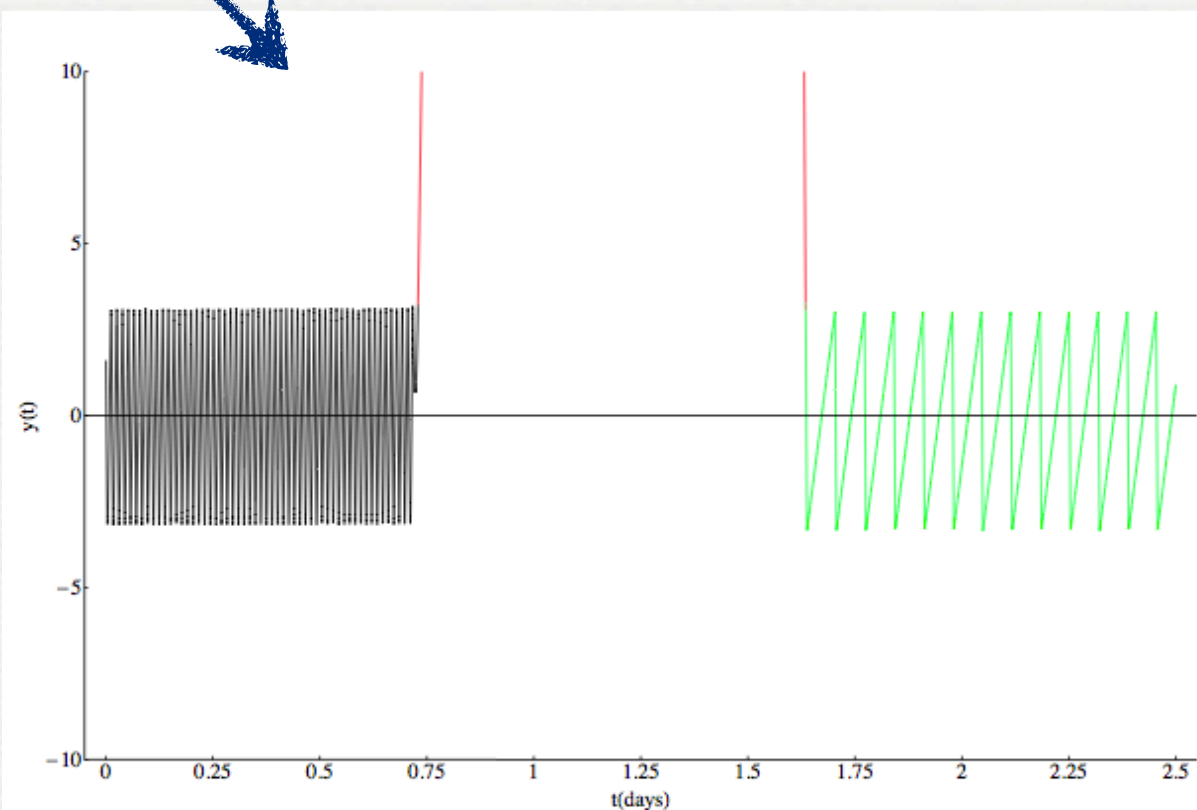
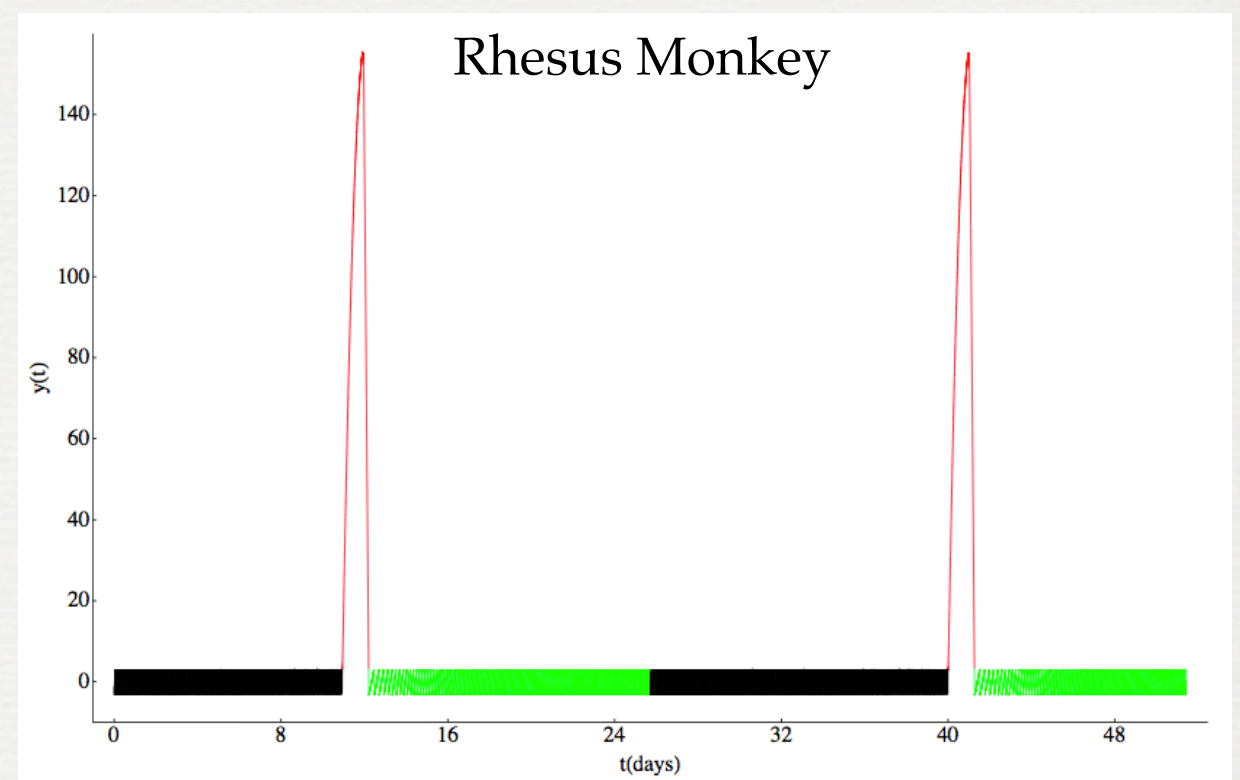
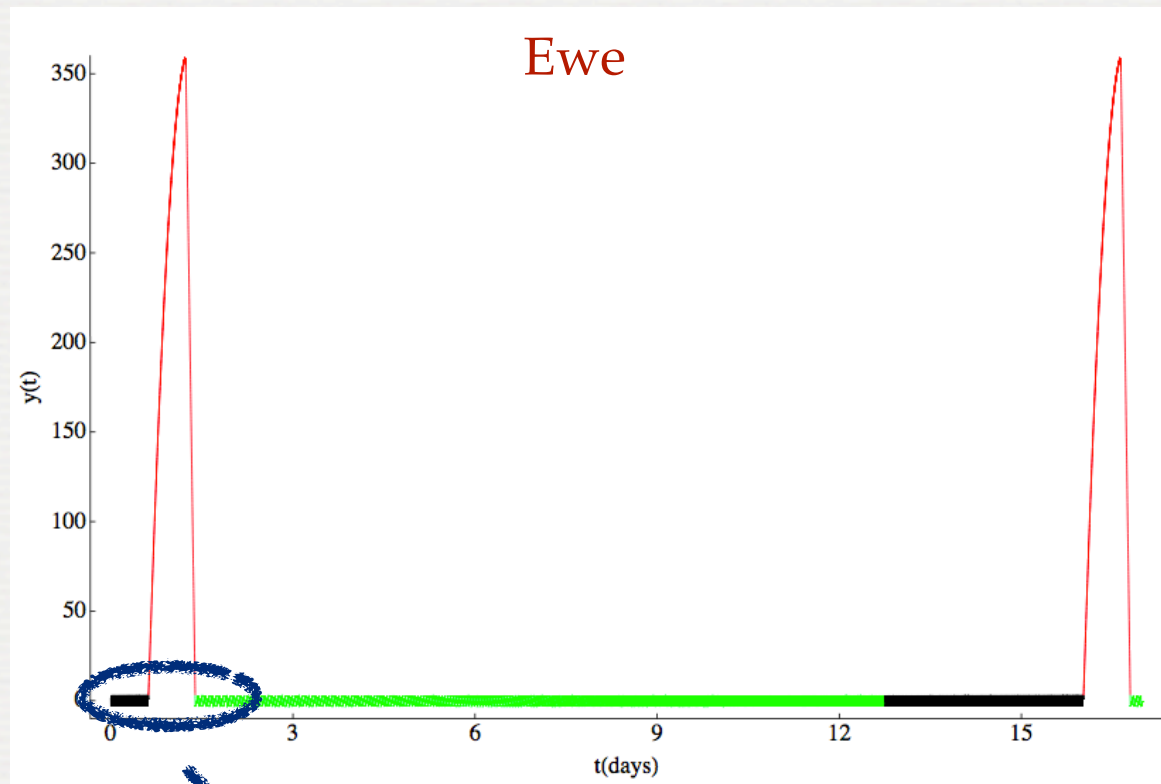
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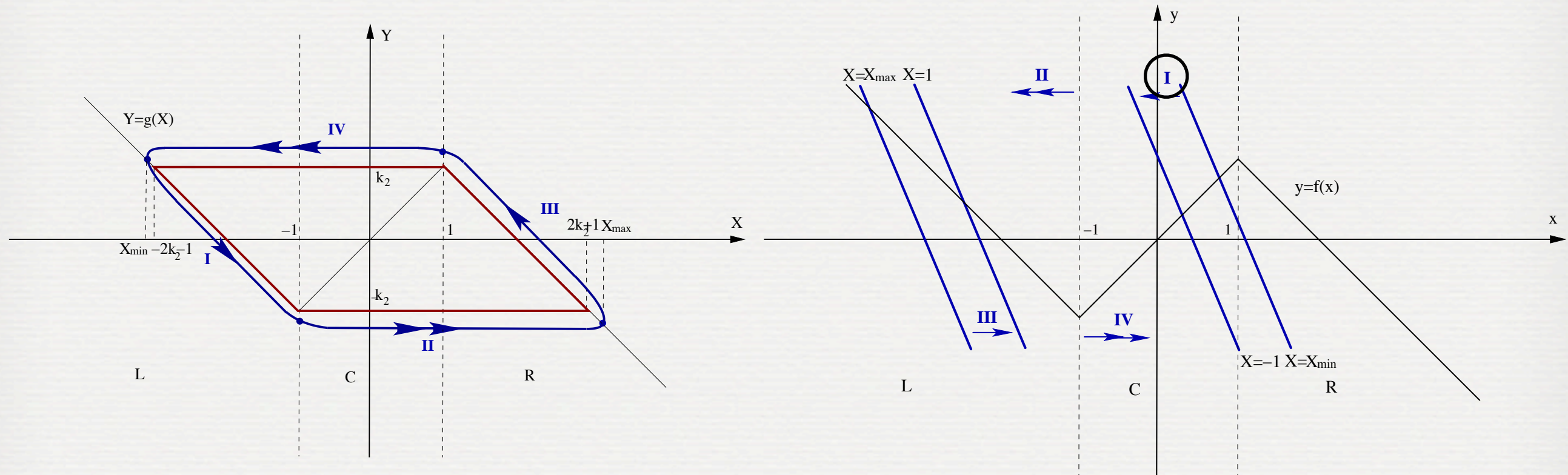


3) Mixed mode oscillations due to canard phenomena

For *biological convenience*, we have forbidden the nullcline to cross the upper corner.

3) Mixed mode oscillations due to canard phenomena

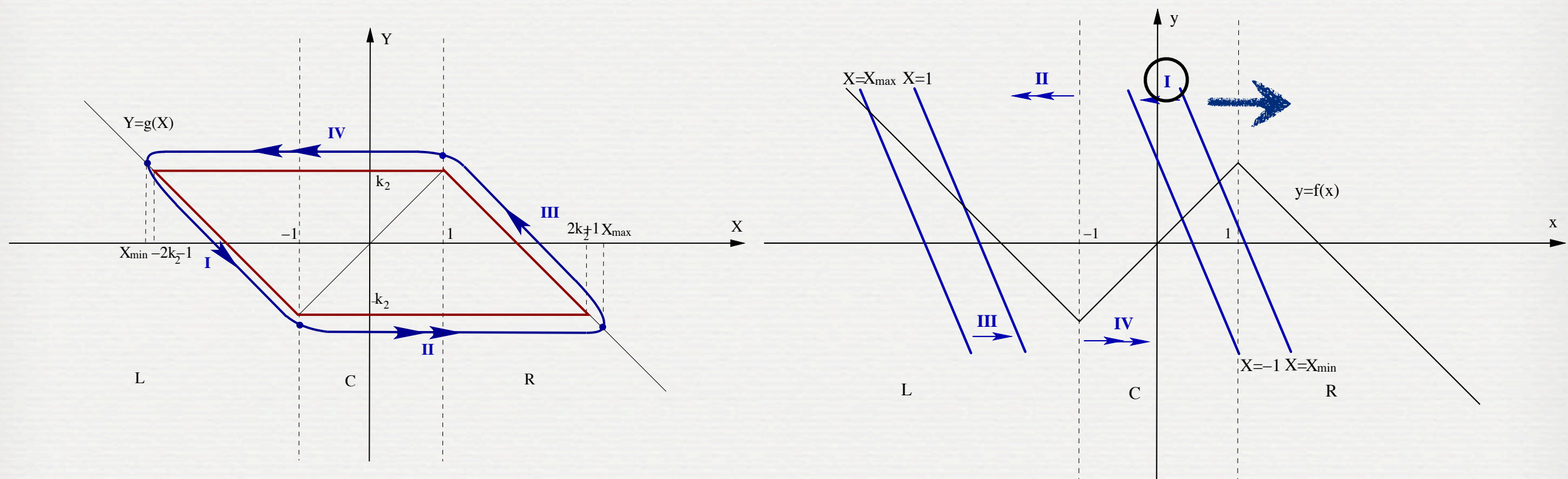
For *biological convenience*, we have forbidden the nullcline to cross the upper corner.



3) Mixed mode oscillations due to canard phenomena

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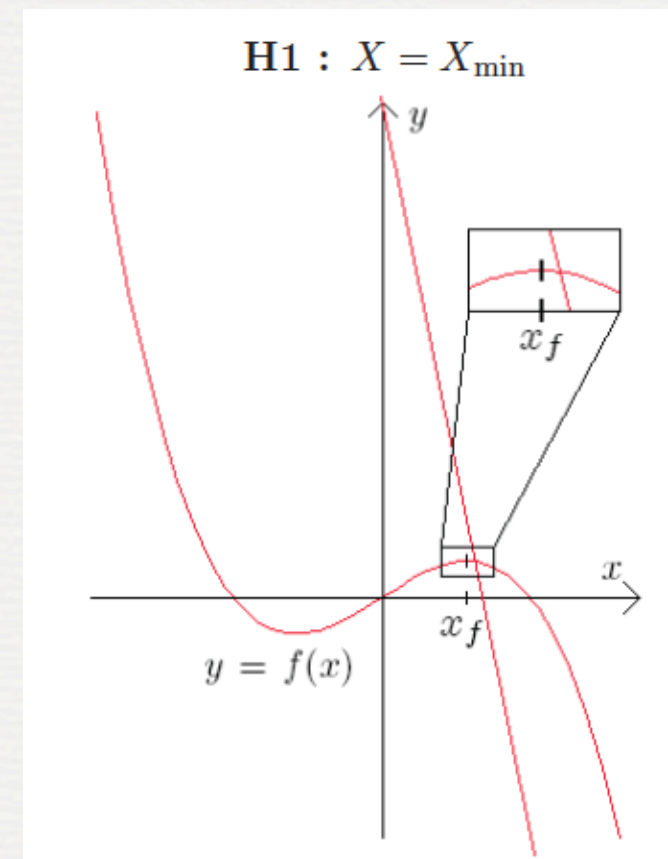
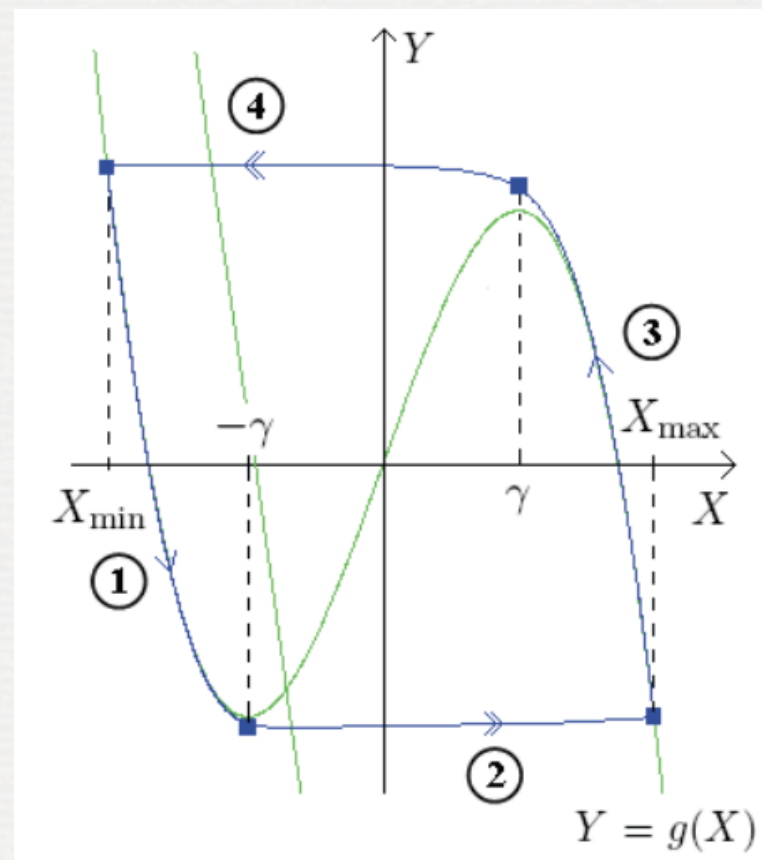
What does it happen if we let the nullcline cross the upper corner?



In the smooth original version of the system:
Krupa, Vidal, Desroches and Clément, SIADS 2012

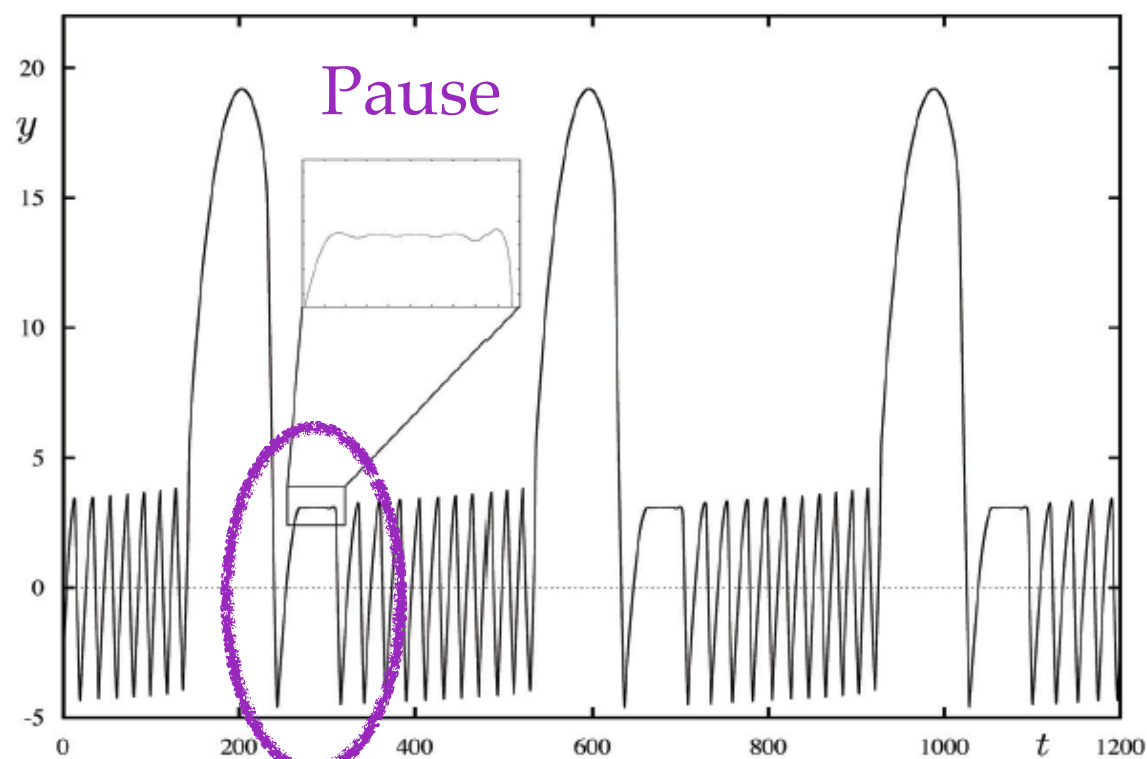
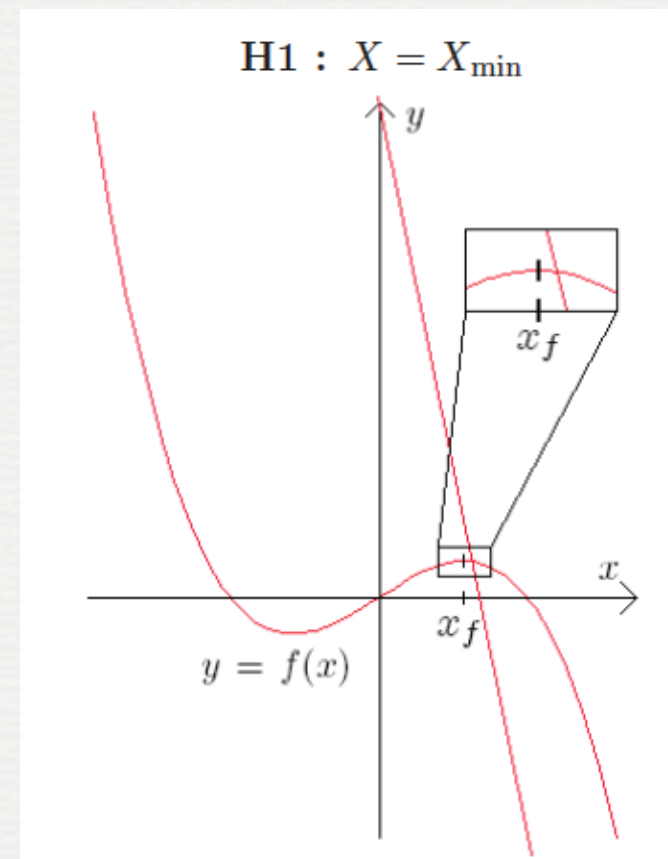
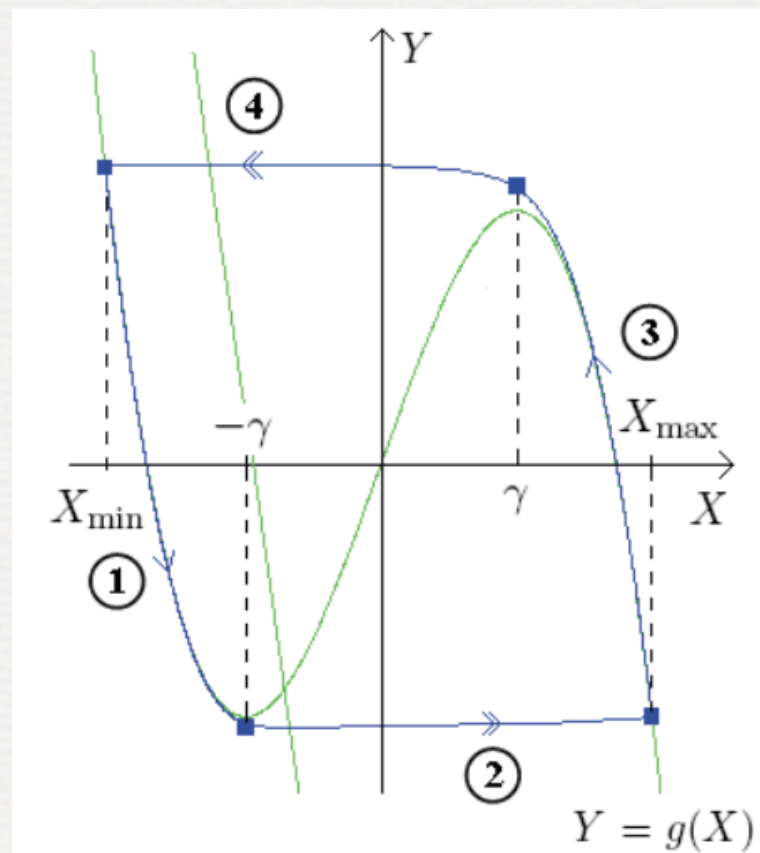
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Krupa, Vidal, Desroches and Clément, SIADS 2012



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Krupa, Vidal, Desroches and Clément, SIADS 2012

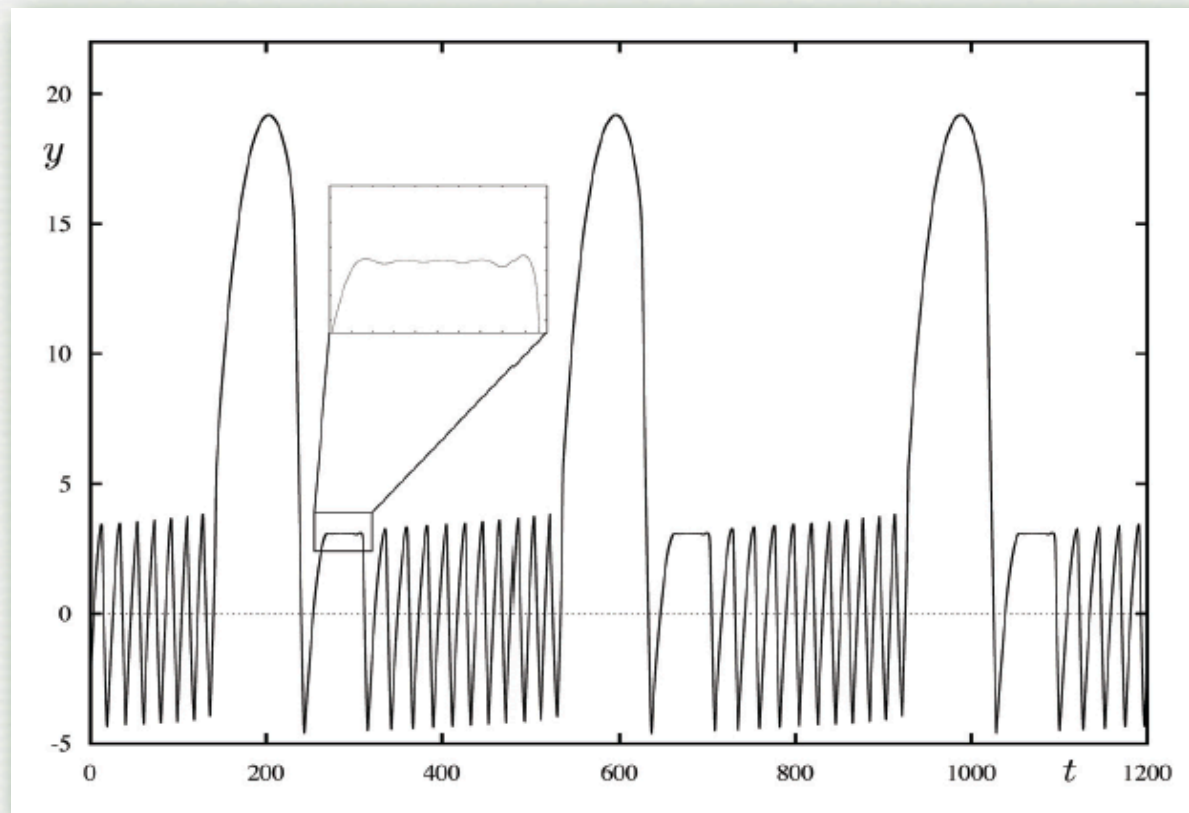


We observe two novelties:

1. There exists a **pause** between the surge and the pulses
2. In this pause, there are small oscillations

3) Mixed mode oscillations due to canard phenomena

Krupa, Vidal, Desroches and Clément, SIADS 2012



Under certain conditions, they prove the existence of an attractive and unique limit cycle of this type

They numerically observe a one to one compensation mechanism between the number of small oscillations and pulses

They explain this compensation as the interaction between two canard-mediated phenomena

3) Mixed mode oscillations due to canard phenomena

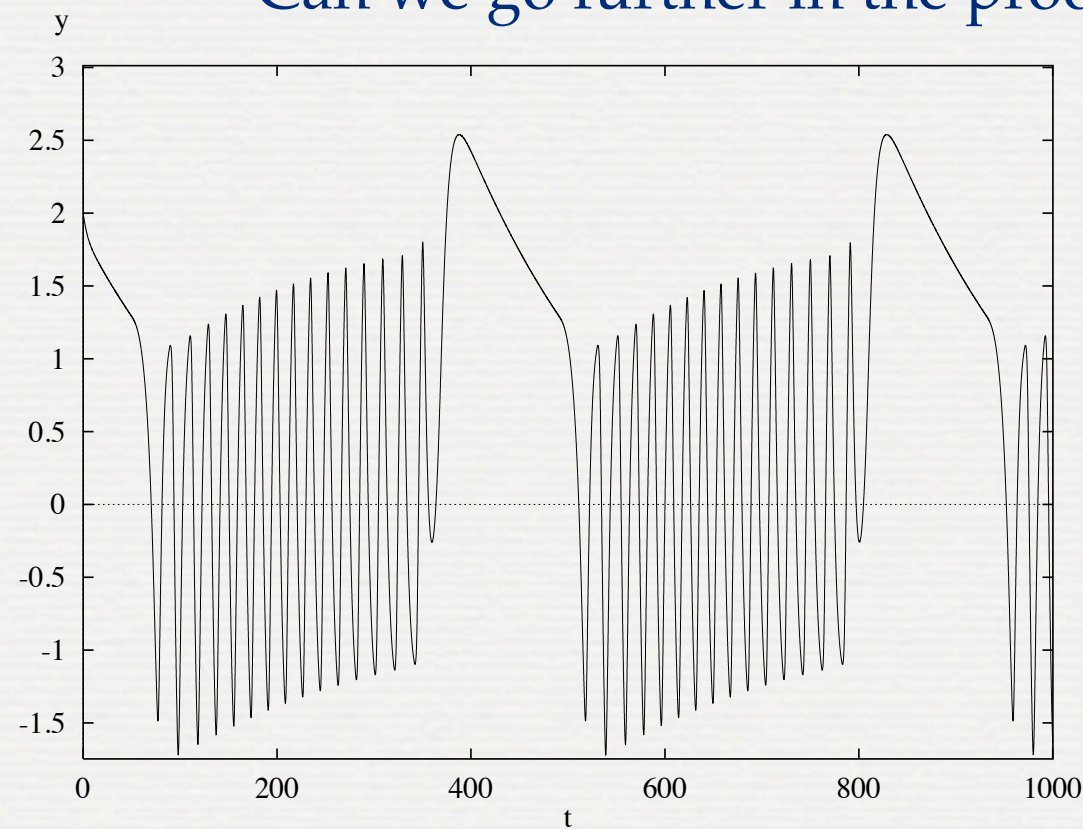
Can the PWL version of the model produce Mixed Mode Oscillations?

Can we go further in the proofs of the canard interactions?

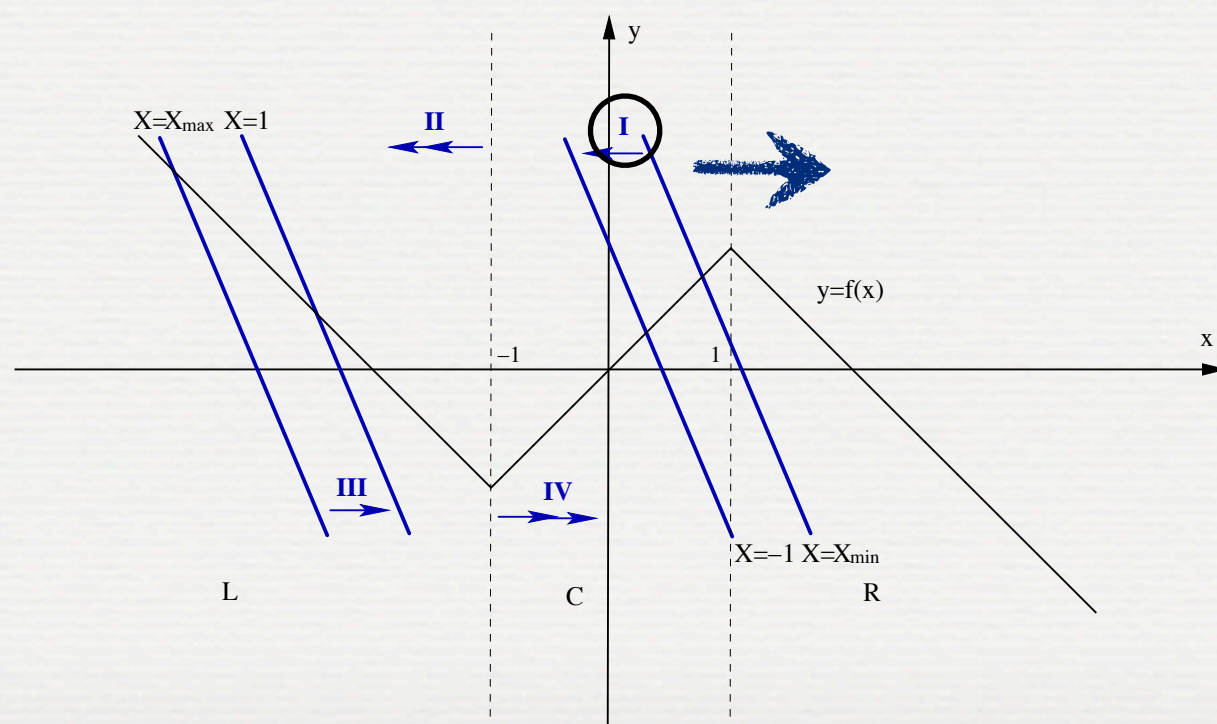
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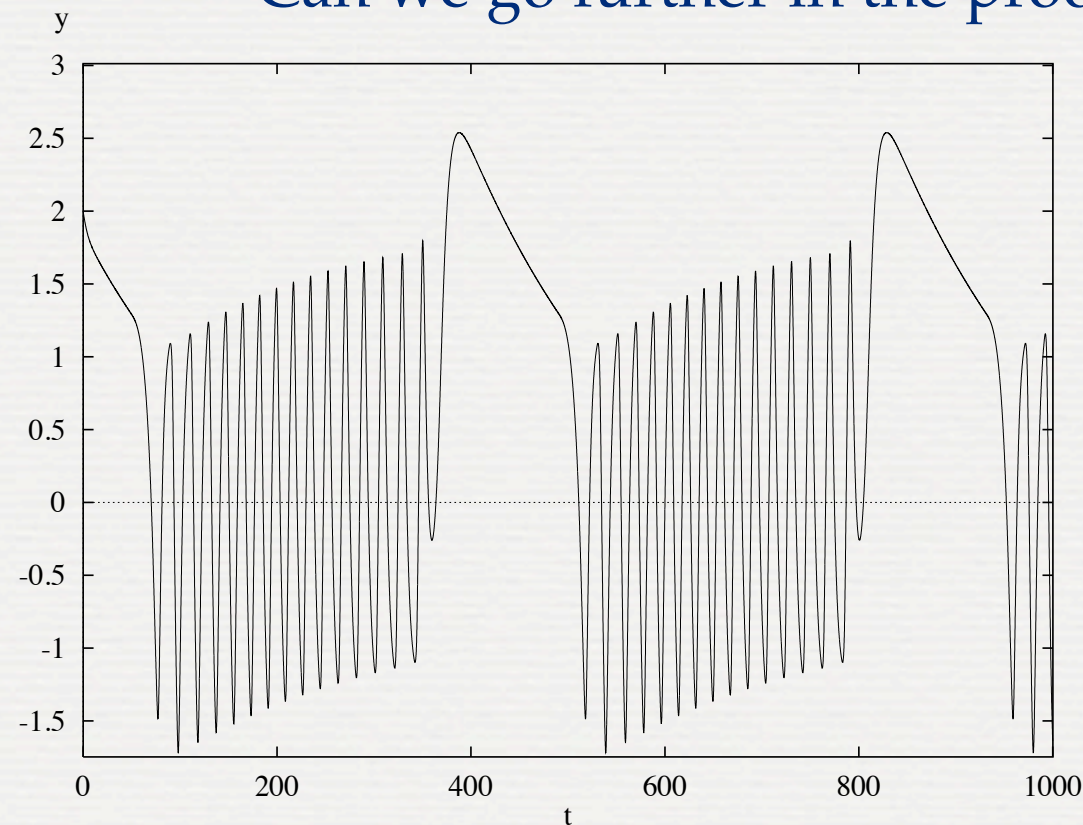
In the current formulation, the PWL system does not display small oscillations... **Why??**



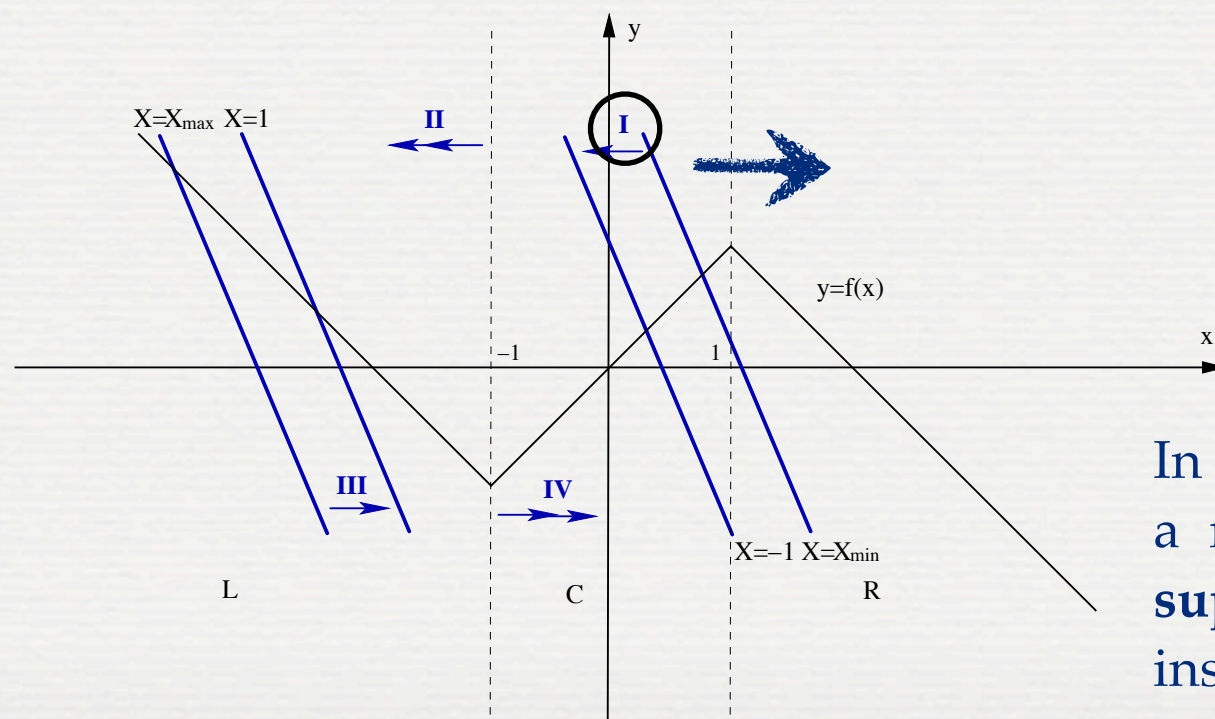
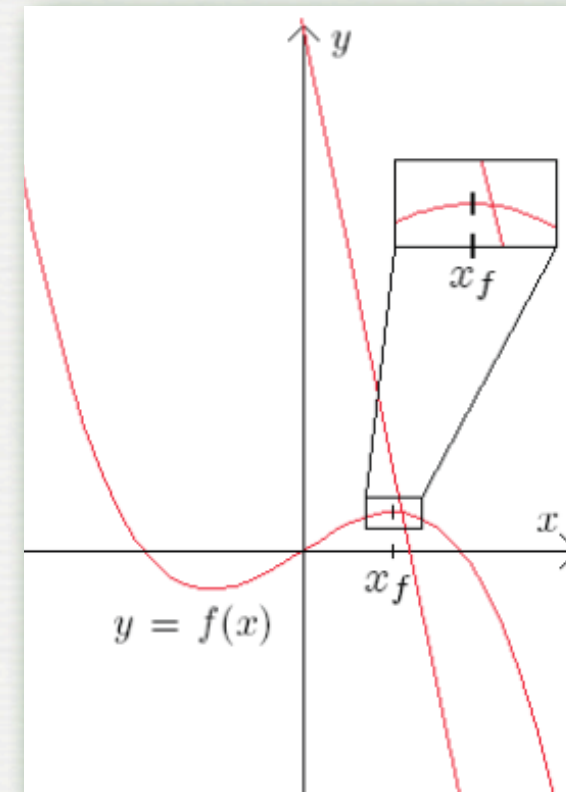
3) Mixed mode oscillations due to canard phenomena

Can the PWL version of the model produce Mixed Mode Oscillations?

Can we go further in the proofs of the canard interactions?



In the current formulation, the PWL system does not display small oscillations... **Why??**



In the smooth system, the vertical nullcline crosses a real canard explosion, in our case is a **canard super-explosion**, that is, the relaxation cycle is born instantaneously

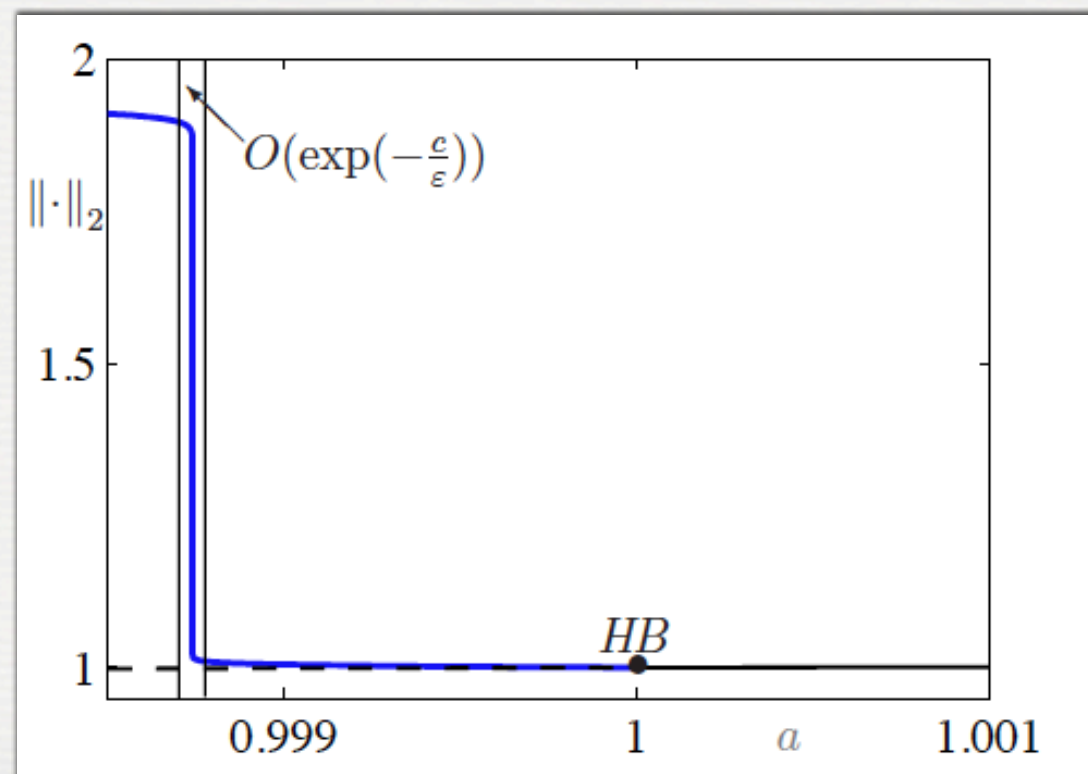
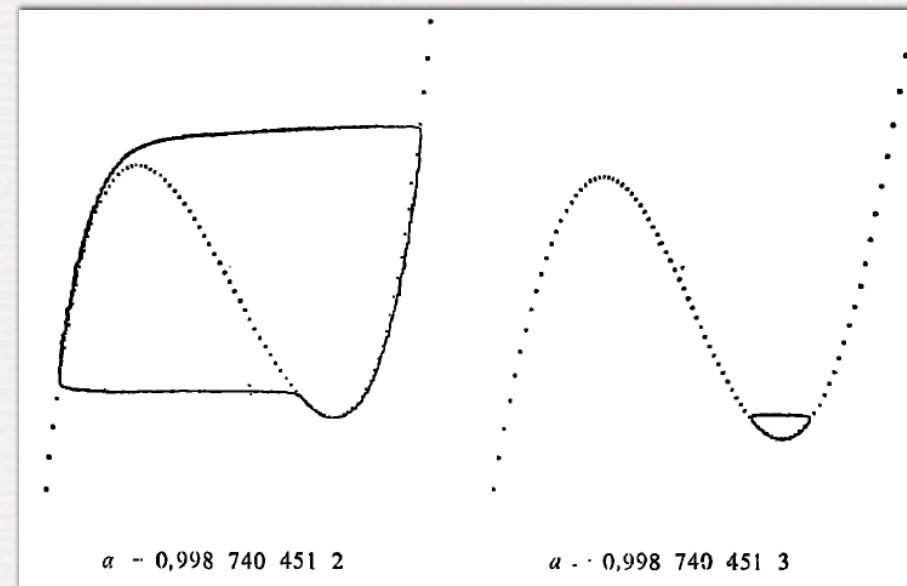
3) Mixed mode oscillations due to canard phenomena

- *Chasse au Canard*, E. Benoît, J. Callot, F. Diener and M. Diener, CM 1981

Van der Pol oscillator

$$\begin{cases} \varepsilon \dot{x} = y - x^3/3 + x, \\ \dot{y} = a - x. \end{cases}$$

$$a \in \mathbb{R}, 0 < \varepsilon \ll 1$$



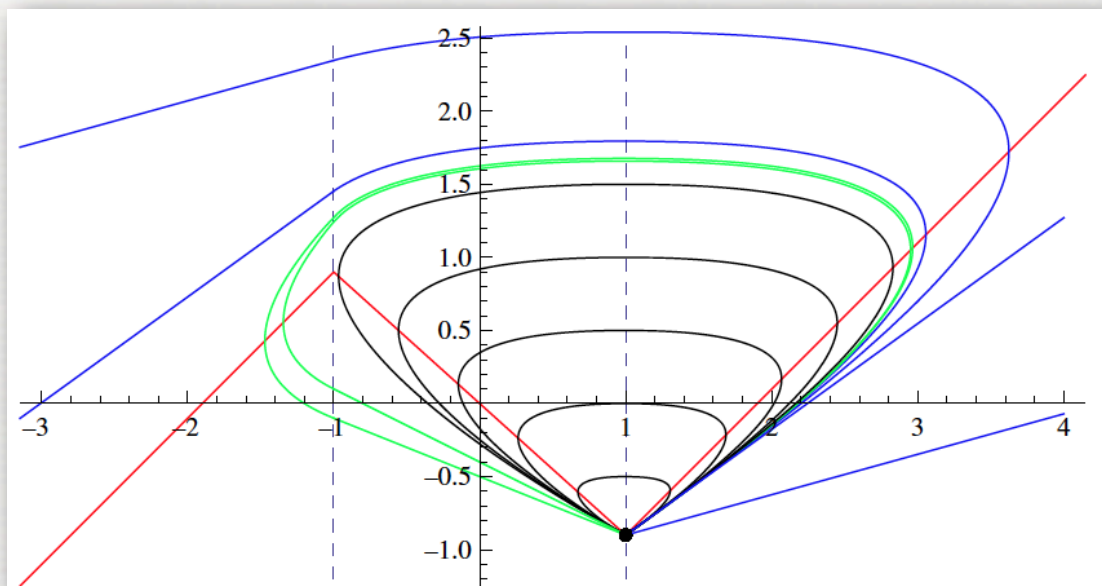
3) Mixed mode oscillations due to canard phenomena

- *Canards in PWL systems: explosions and super-explosions*, M. Desroches, E. Freire, S.J. Hogan, E. Ponce and P. Thota, Proceedings of the Royal S. 2013

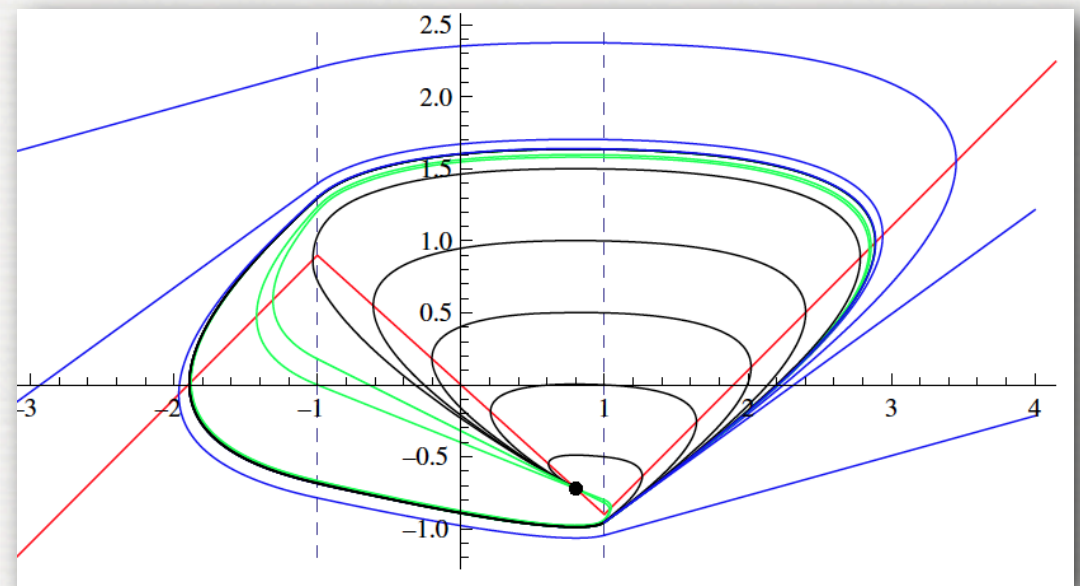
$$\begin{cases} \dot{x} = y - f(x), \\ \dot{y} = \varepsilon(a - x), \end{cases} \quad f(x) = \begin{cases} x + k + 1, & \text{if } x < -1, \\ -kx, & \text{if } -1 \leq x \leq 1, \\ x - k - 1, & \text{if } x > 1, \end{cases}$$

$4\varepsilon - k^2 < 0$ Node case: **canard super-explosion**

$$k = 0.9, \varepsilon = 0.2$$



$$a = 1$$



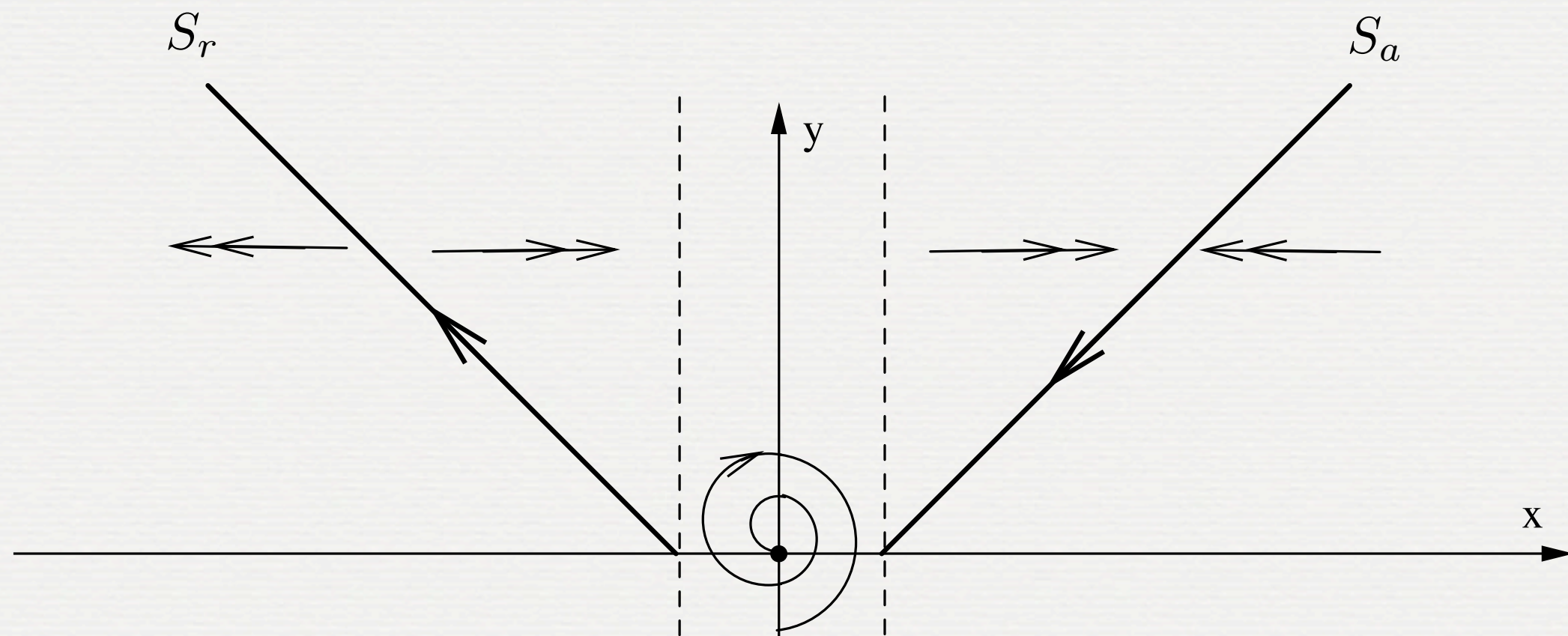
$$a = 0.8$$

3) Mixed mode oscillations due to canard phenomena

- *A generation Mechanism of Canards in a PWL system*, N. Arima, H. Okazaki, H. Nakano, IEICE 1997

Add an extra 'small' piece in the corner to generate a canard cycle

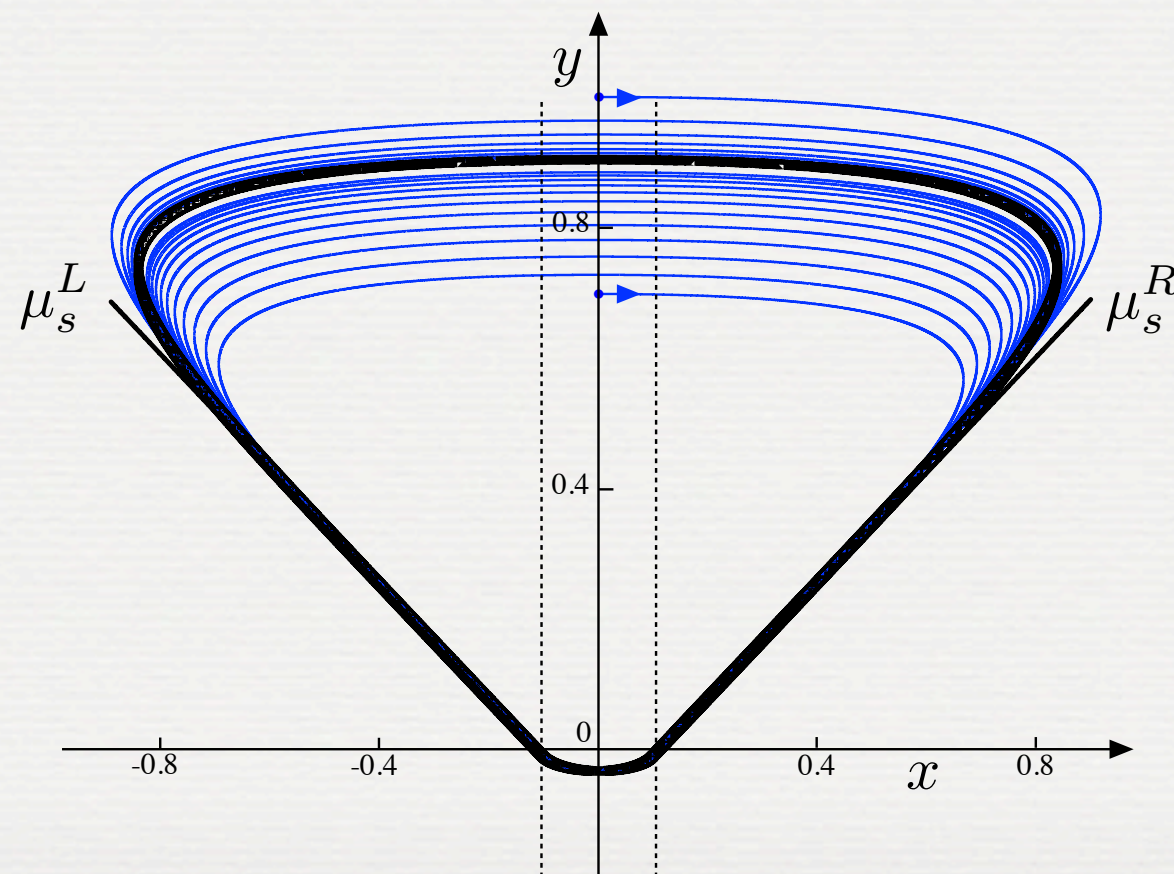
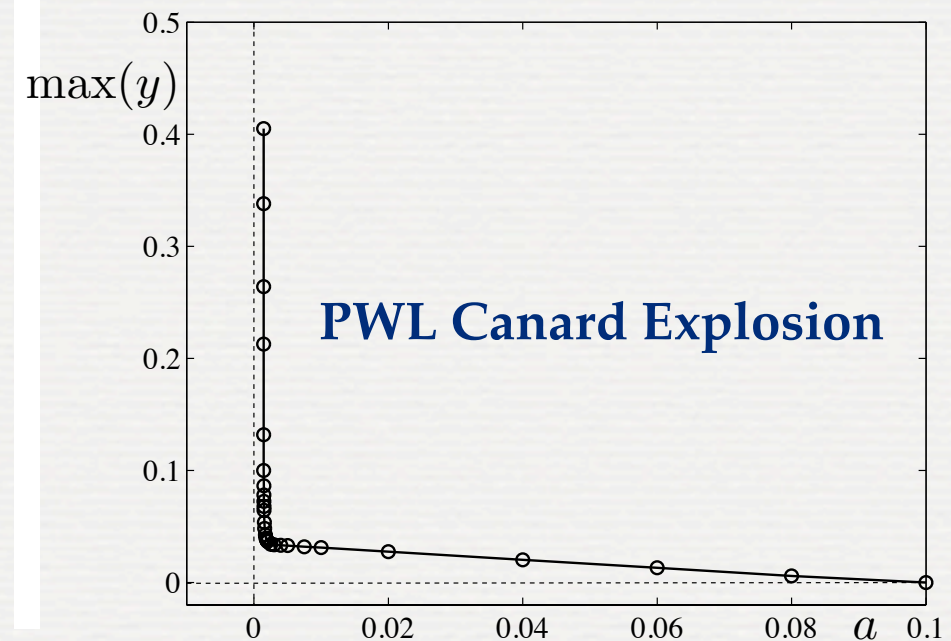
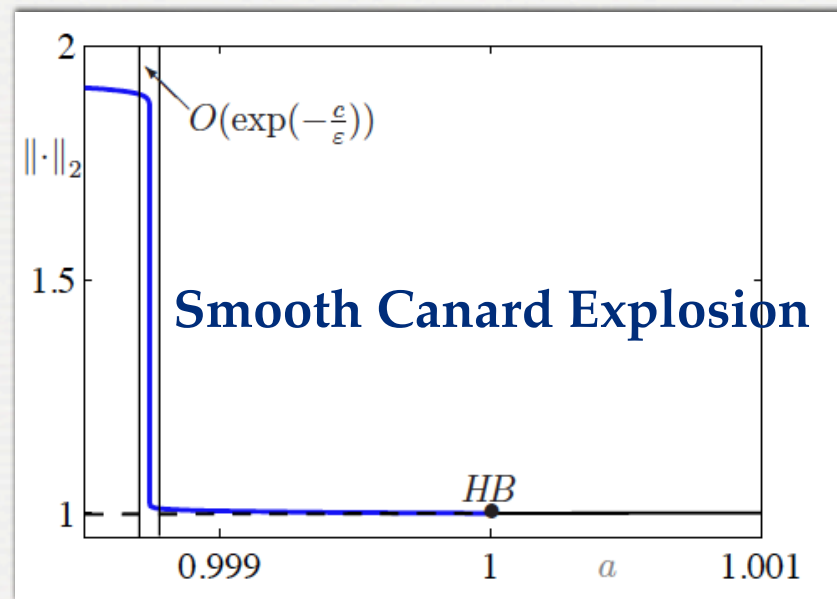
The equilibrium point of the extra piece should be a focus to let the flow pass through



- *Canard-like explosion of limit cycles in twodimensional PWL models of FitzHugh–Nagumo type*, H. G. Rotstein, S. Coombes, A. M. Gheorghe, SIADS. 2012

3) Mixed mode oscillations due to canard phenomena

F-G, Desroches, Krupa and Teruel, Dyn. Sys. 2016

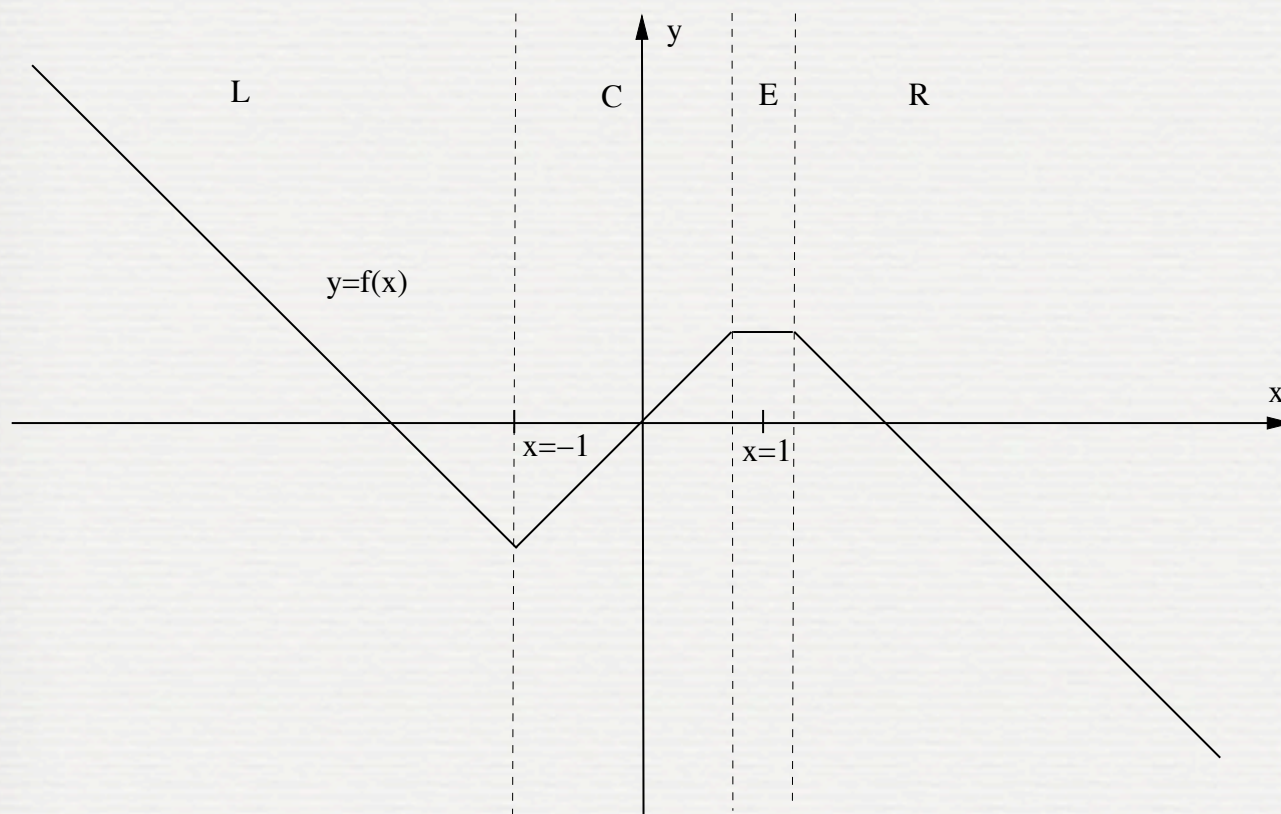


3) Mixed mode oscillations due to canard phenomena

To obtain the analogous to a canard explosion in the PWL case, **we need to add one extra zone**

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - 2, & \text{if } x \leq -1, \\ x, & \text{if } x \in [-1, 1 - \sqrt{\delta}), \\ 1 - \sqrt{\delta}, & \text{if } x \in [1 - \sqrt{\delta}, 1 + \sqrt{\delta}), \\ -x + 2, & \text{if } x \geq 1 + \sqrt{\delta}, \end{cases}$$

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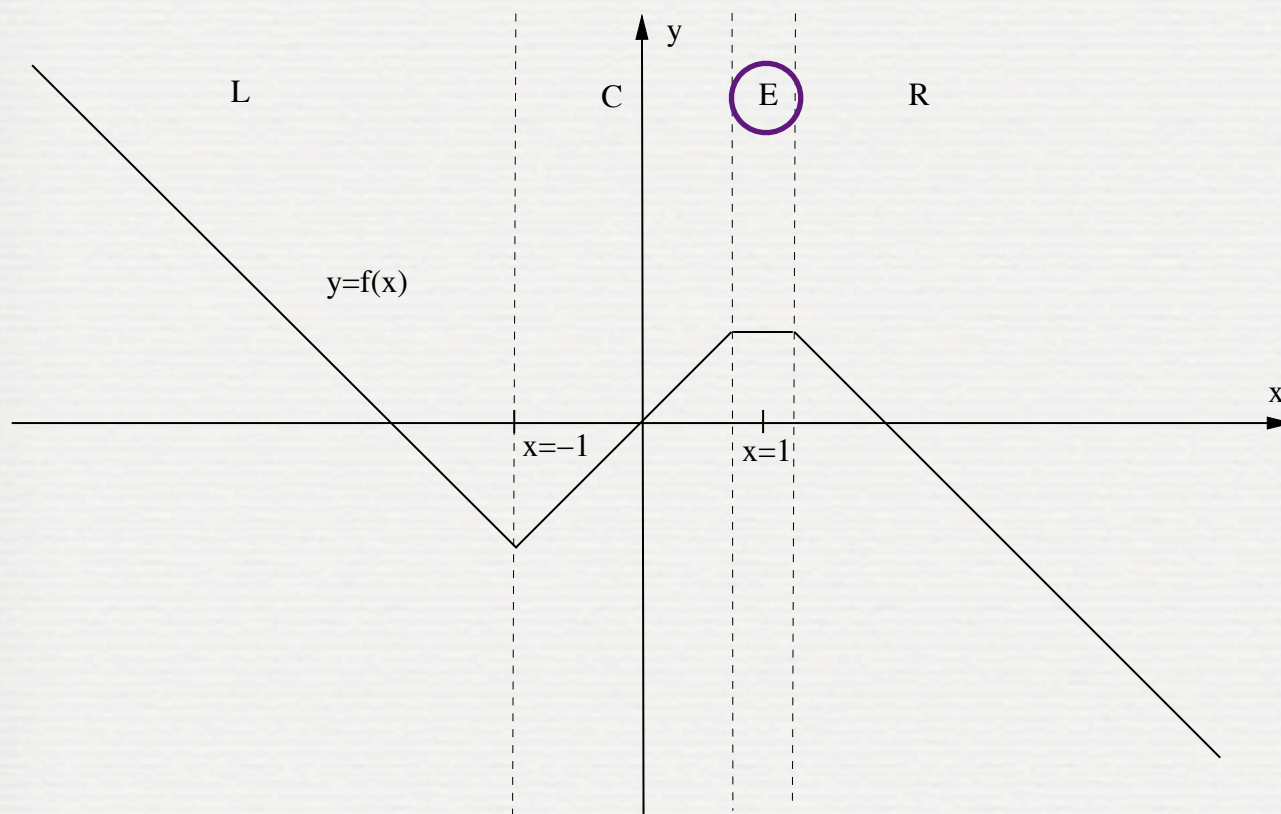


3) Mixed mode oscillations due to canard phenomena

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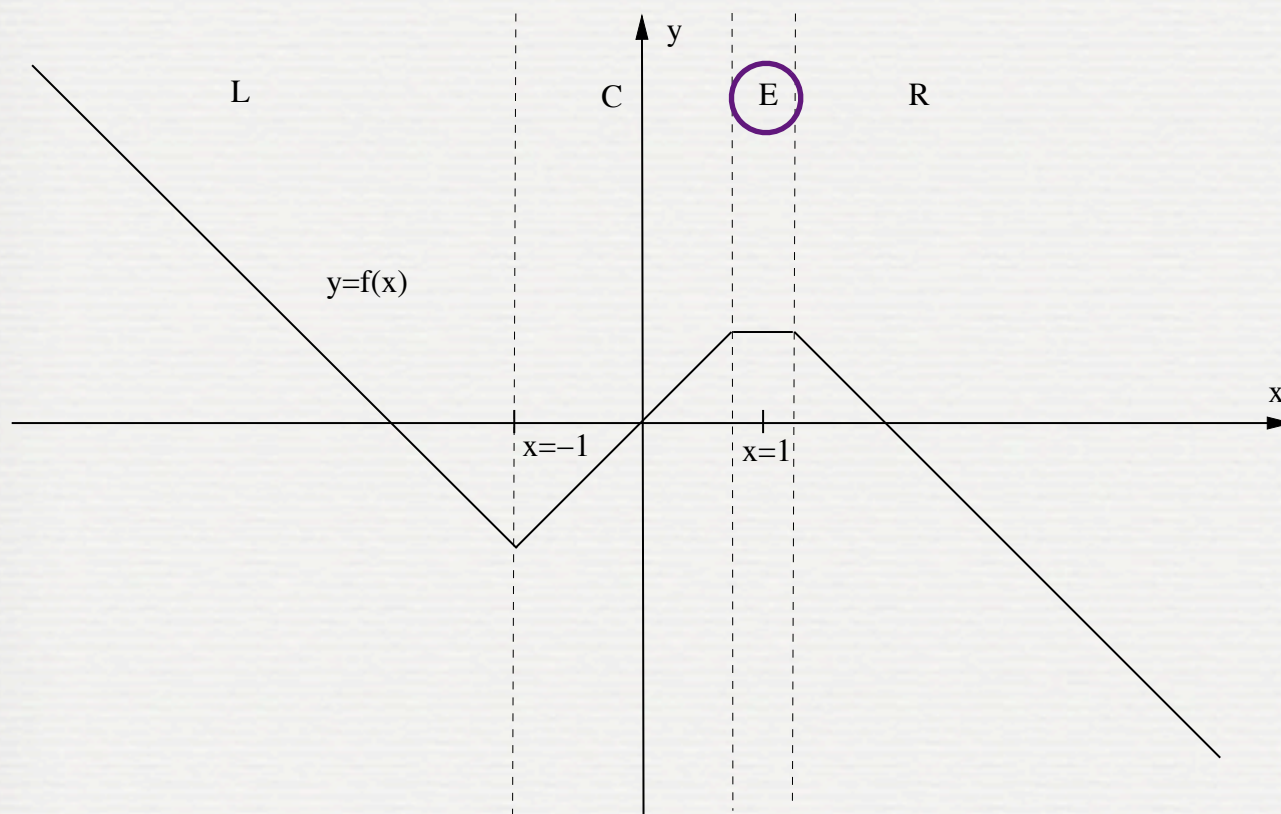


3) Mixed mode oscillations due to canard phenomena

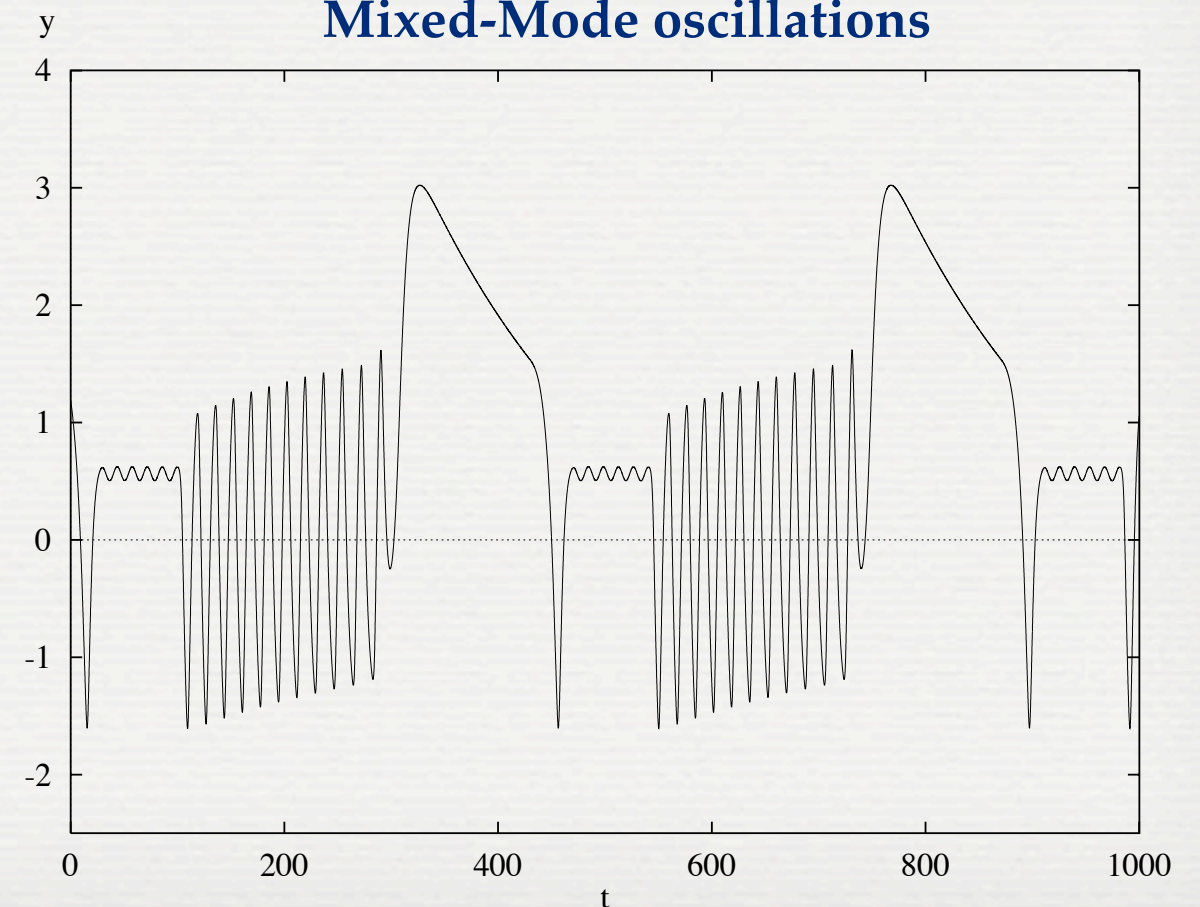
To obtain the analogous to a canard explosion in the PWL case, **we need to add one extra zone**

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \end{cases} \quad f(x) = \begin{cases} -x - 2, & \text{if } x \leq -1, \\ x, & \text{if } x \in [-1, 1 - \sqrt{\delta}), \\ 1 - \sqrt{\delta}, & \text{if } x \in [1 - \sqrt{\delta}, 1 + \sqrt{\delta}), \\ -x + 2, & \text{if } x \geq 1 + \sqrt{\delta}, \end{cases}$$

$$\begin{cases} \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases} \quad g(X) = \begin{cases} -X - k_2 - 1, & \text{if } X \leq -1, \\ k_2X, & \text{if } |X| \leq 1, \\ -X + k_2 + 1, & \text{if } X \geq 1, \end{cases}$$



In the new formulation, the PWL system displays
Mixed-Mode oscillations

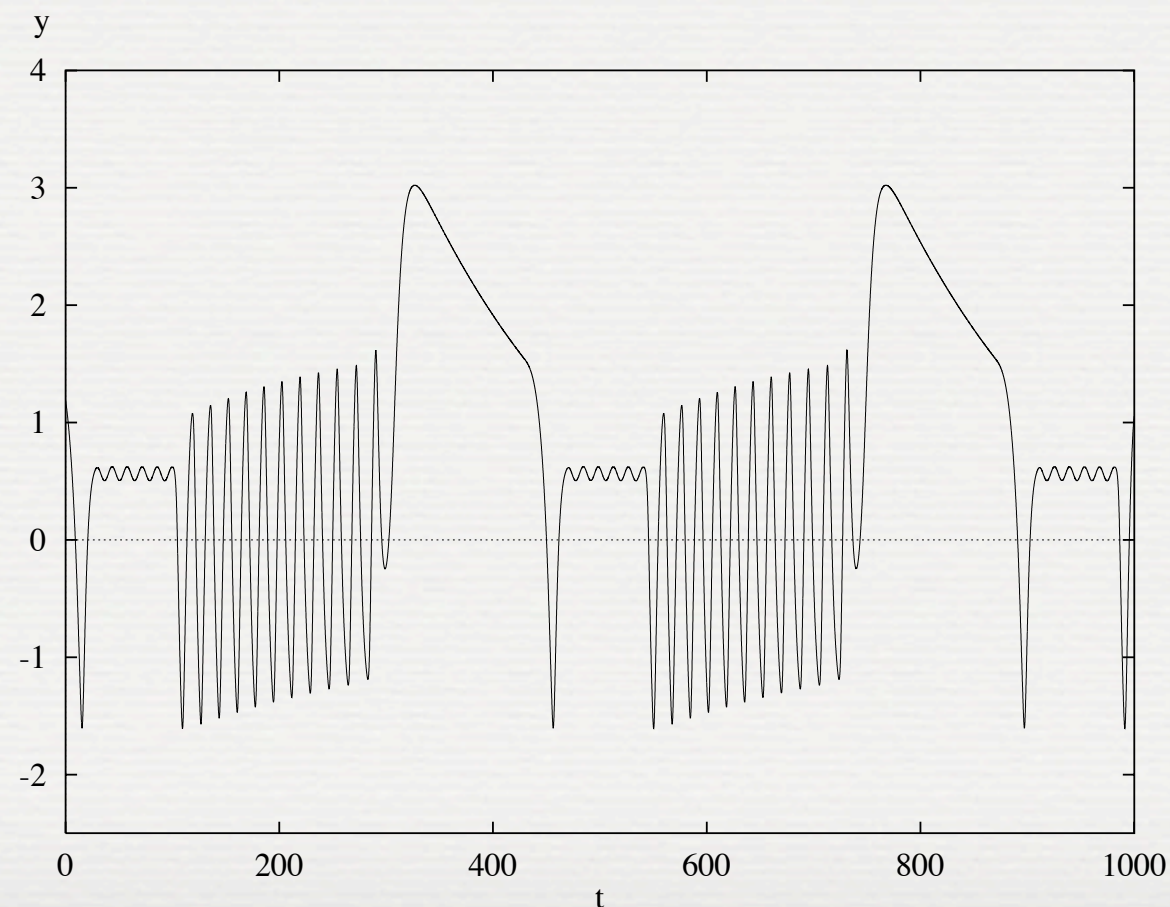


3) Mixed mode oscillations due to canard phenomena

We prove the **existence of an attractive and unique limit cycle** of MMOs type. Moreover,

1. If the rightmost position of the vertical nullcline is located in the center zone, the limit cycle consists of **a series of pulses and one surge**.
2. If the rightmost position of the vertical nullcline is located in the extra zone or in the right zone but close enough to the extra zone, a pause takes place between the surge and pulsatile regime. On the pause, small oscillations can occur and the limit cycle consists of **a series of small oscillations, a series of pulses and one surge**.

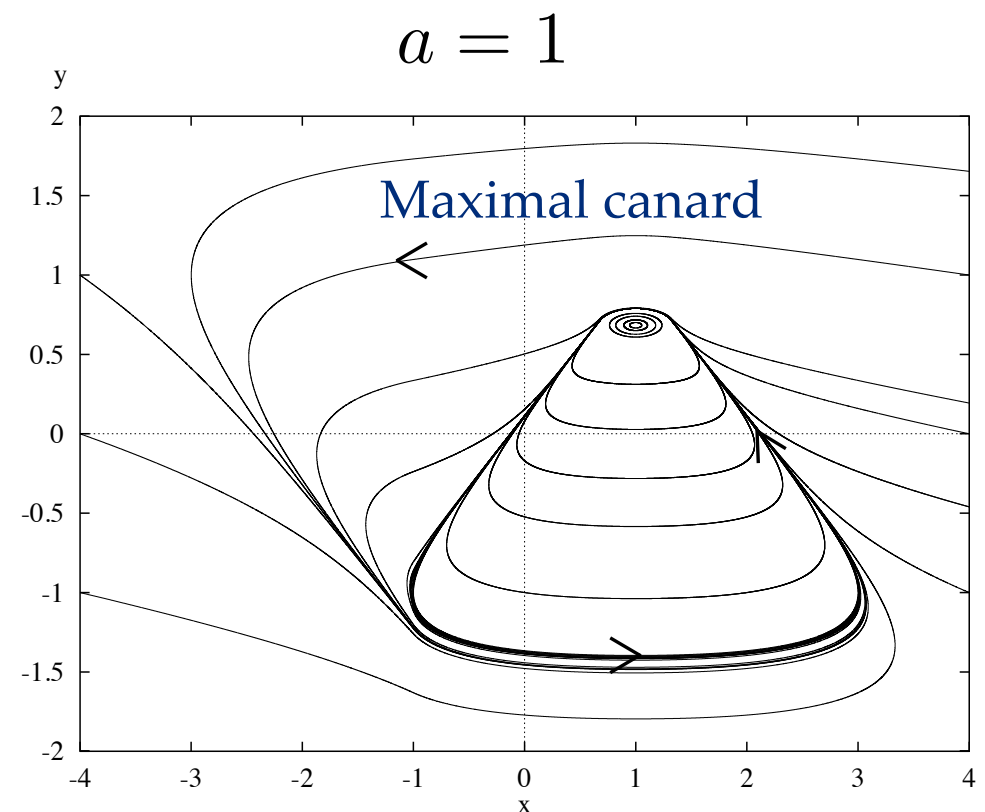
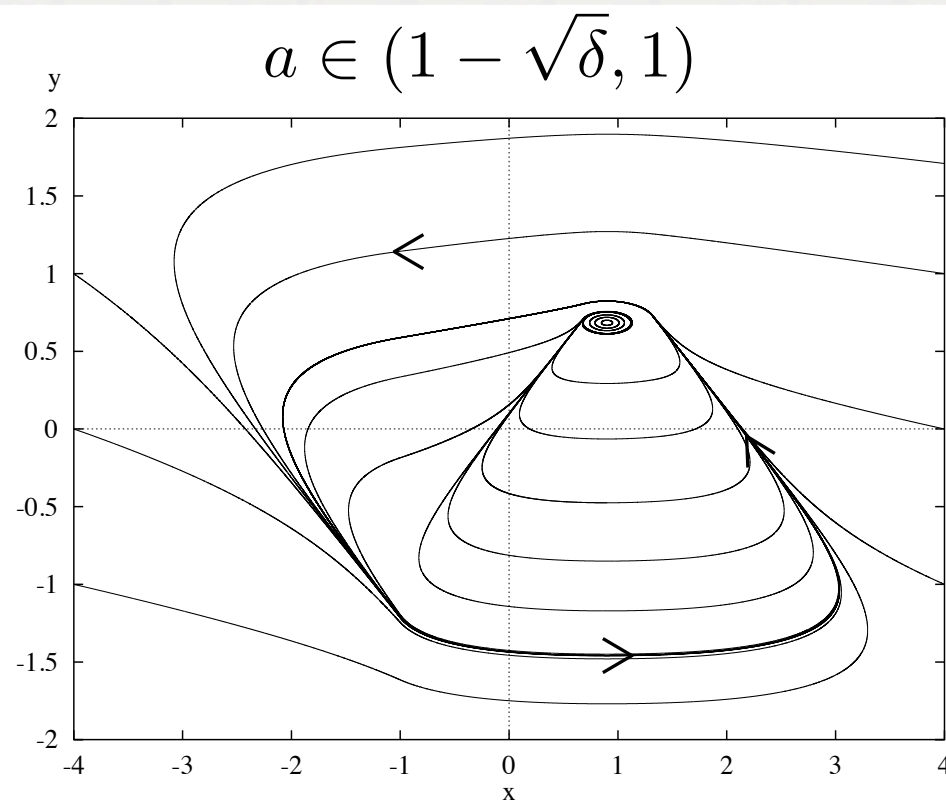
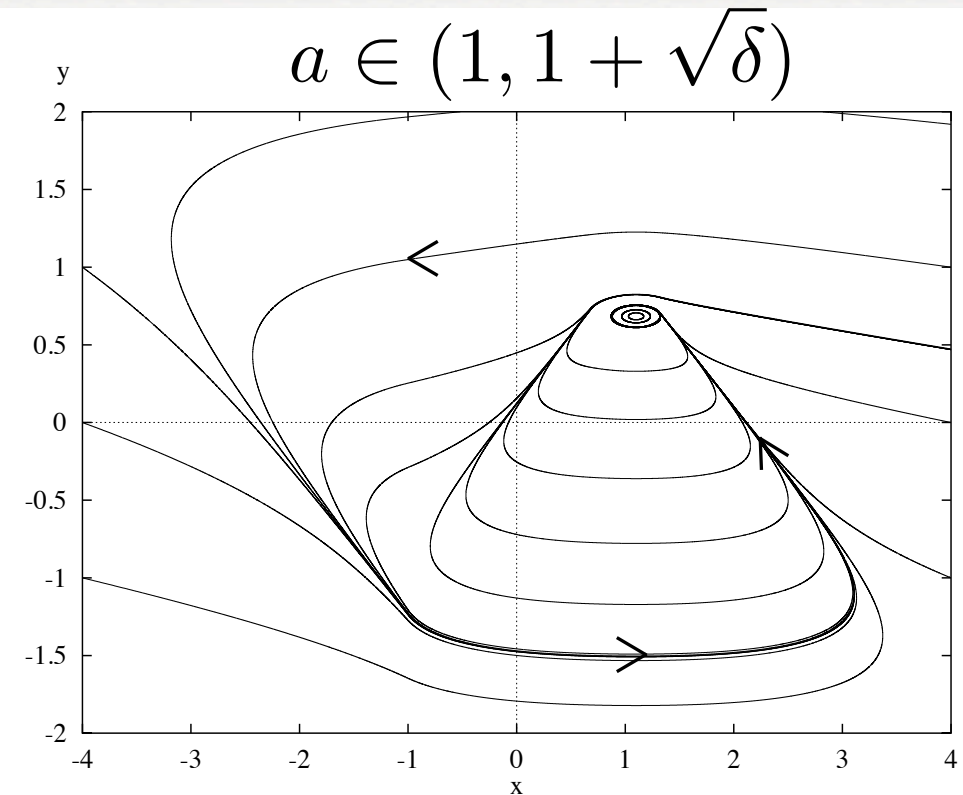
The **period** of limit cycle corresponds to the period of the relaxation cycle of the forcing system.



3) Mixed mode oscillations due to canard phenomena

Can we go further into the canard-mediated compensation of small oscillations and pulses?

First, we observe that, if the rightmost position of the vertical nullcline is at the left of the maximal canard, small oscillations do not take place.



3) Mixed mode oscillations due to canard phenomena

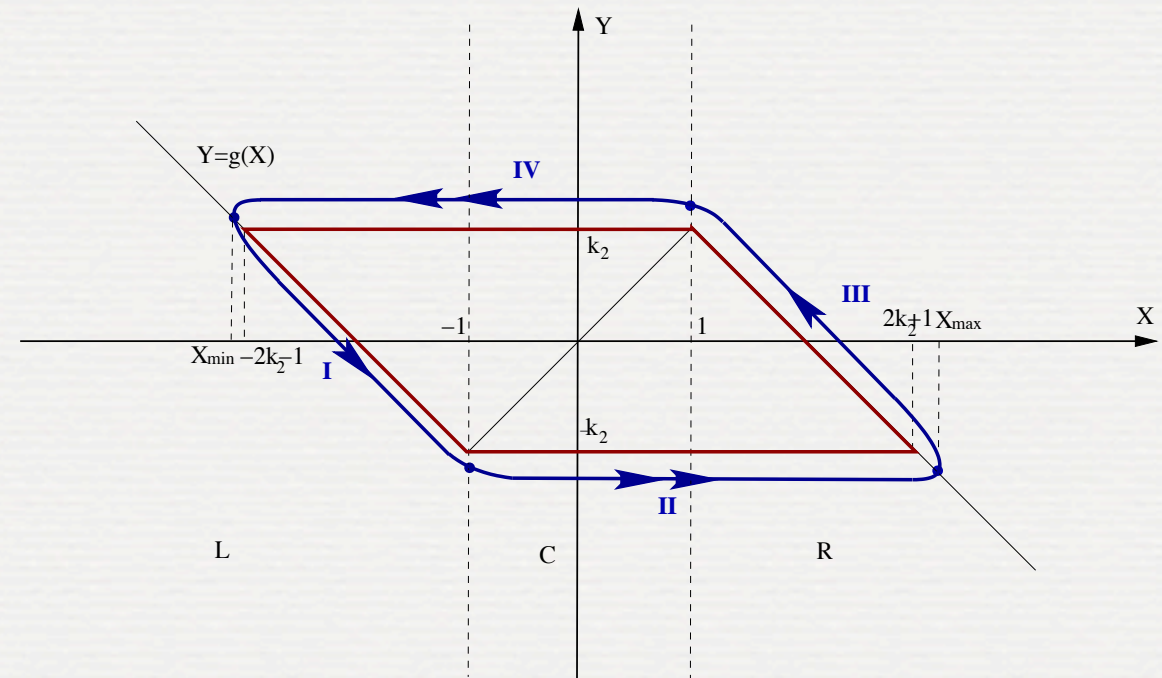
Number of small oscillations. Passage through primary and secondary canards

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \end{cases}$$
$$\begin{cases} \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases}$$

3) Mixed mode oscillations due to canard phenomena

Number of small oscillations. Passage through primary and secondary canards

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \\ \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases}$$

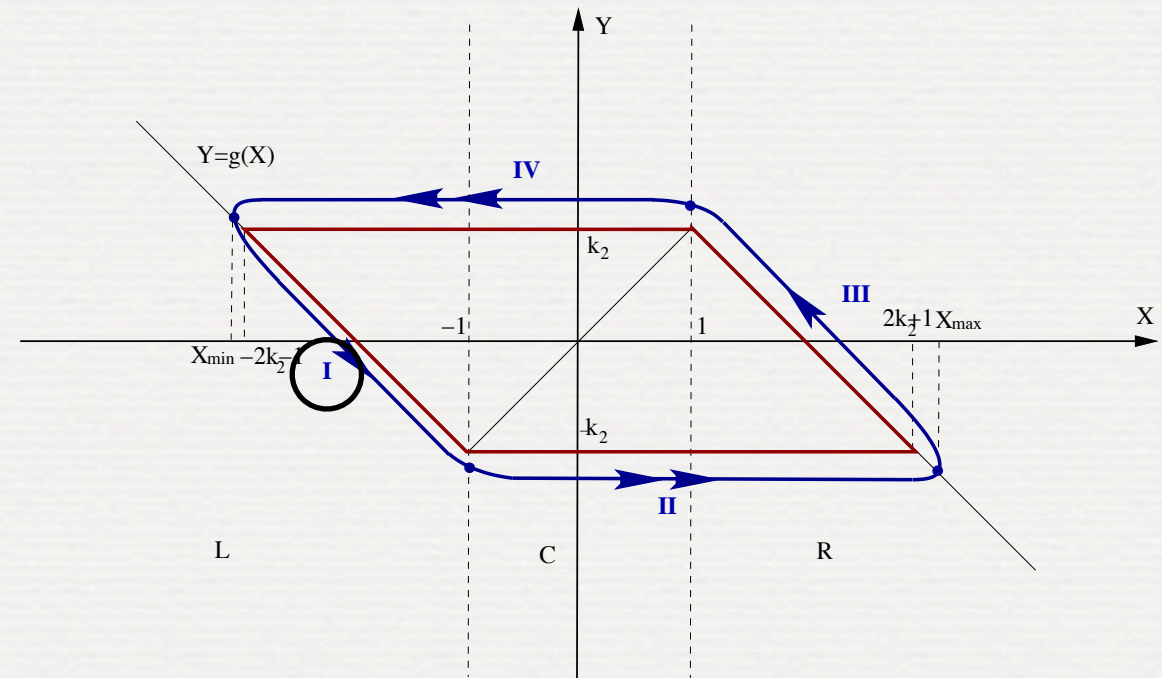


3) Mixed mode oscillations due to canard phenomena

Number of small oscillations. Passage through primary and secondary canards

Three-dimensional reduction with three time scales during the **pause and pulsatile regime**

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \\ \dot{X} = \delta(-Y + g(X)), \\ \dot{Y} = \varepsilon\delta(X + b_1Y + b_2), \end{cases}$$



During phase I of the limit cycle of the forcing system, variables X and Y follow the slowest time scale and the current (X, Y) point remains in an $O(\varepsilon)$ neighborhood of the X -nullcline

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \\ \dot{X} = \varepsilon\delta\left(\frac{X + b_1(-X - k_2 - 1 + O(\varepsilon)) + b_2}{-1 + O(\varepsilon)}\right). \end{cases}$$

3) Mixed mode oscillations due to canard phenomena

Number of small oscillations. Passage through primary and secondary canards

$$\begin{cases} \dot{x} = -y + f(x), \\ \dot{y} = \delta(x + a_2 + cX), \\ \dot{X} = \varepsilon\delta \left(\frac{X + b_1(-X - k_2 - 1 + O(\varepsilon)) + b_2}{-1 + O(\varepsilon)} \right). \end{cases}$$

In this system, there exists a canonical choice of the **attracting and repelling Fenichel slow manifolds**, which are planes.

$$S_{a,\delta} \equiv \{x + a_2 + c\hat{X} - \frac{\lambda_s^R}{\delta}(y - 2 - a_2 - c\hat{X}) + \frac{c(2\delta + (\sqrt{1-4\delta}-1)(\lambda_{ss}+1))}{2(\delta + \lambda_{ss}(\lambda_{ss}+1))}(X - \hat{X}) = 0\}$$

$$S_{r,\delta} \equiv \{x + a_2 + c\hat{X} - \frac{\lambda_s^C}{\delta}(y + a_2 + c\hat{X}) + \frac{c(2\delta - (\sqrt{1-4\delta}-1)(\lambda_{ss}-1))}{2(\delta + \lambda_{ss}(\lambda_{ss}-1))}(X - \hat{X}) = 0\}$$

$$\hat{X} = \frac{b_2 - b_1(1 + k_2)}{b_1 - 1}$$

3) Mixed mode oscillations due to canard phenomena

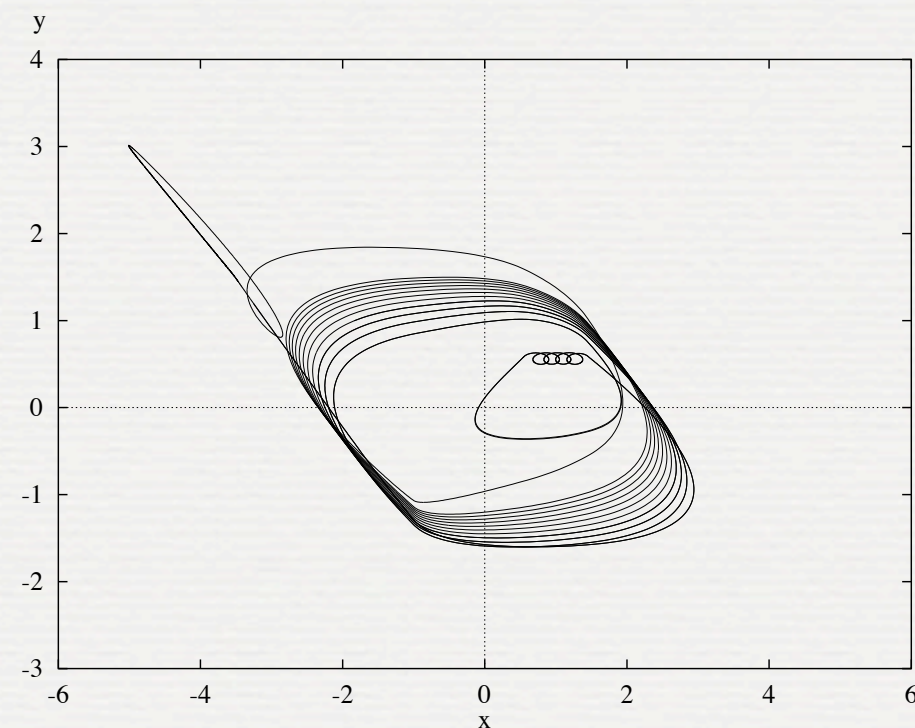
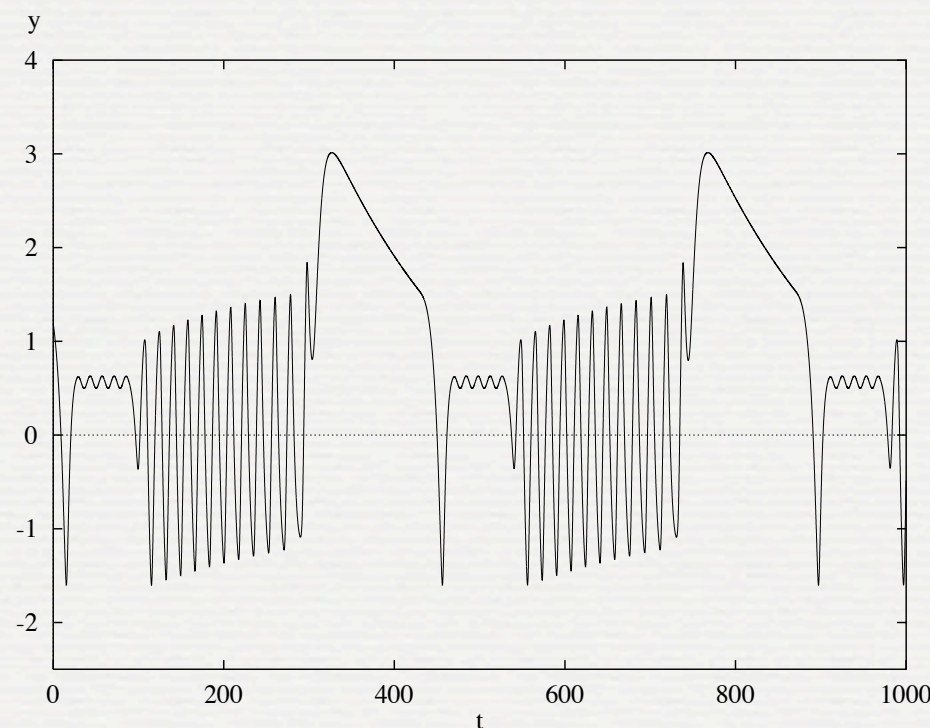
Number of small oscillations. Passage through primary and secondary canards

Now that we have defined the **attracting and repelling Fenichel slow manifolds**, it is possible to define the primary and secondary canards:

We call **canard** a connection between the attracting and repelling Fenichel slow manifolds, through the flow in the extra zone $x \in (1 - \delta, 1 + \delta)$.

If the connection is such that the flow does not make any loop, it is called the **primary canard**.

If during the connection the flow makes n loops, it is called the **n^{th} -secondary canard**.



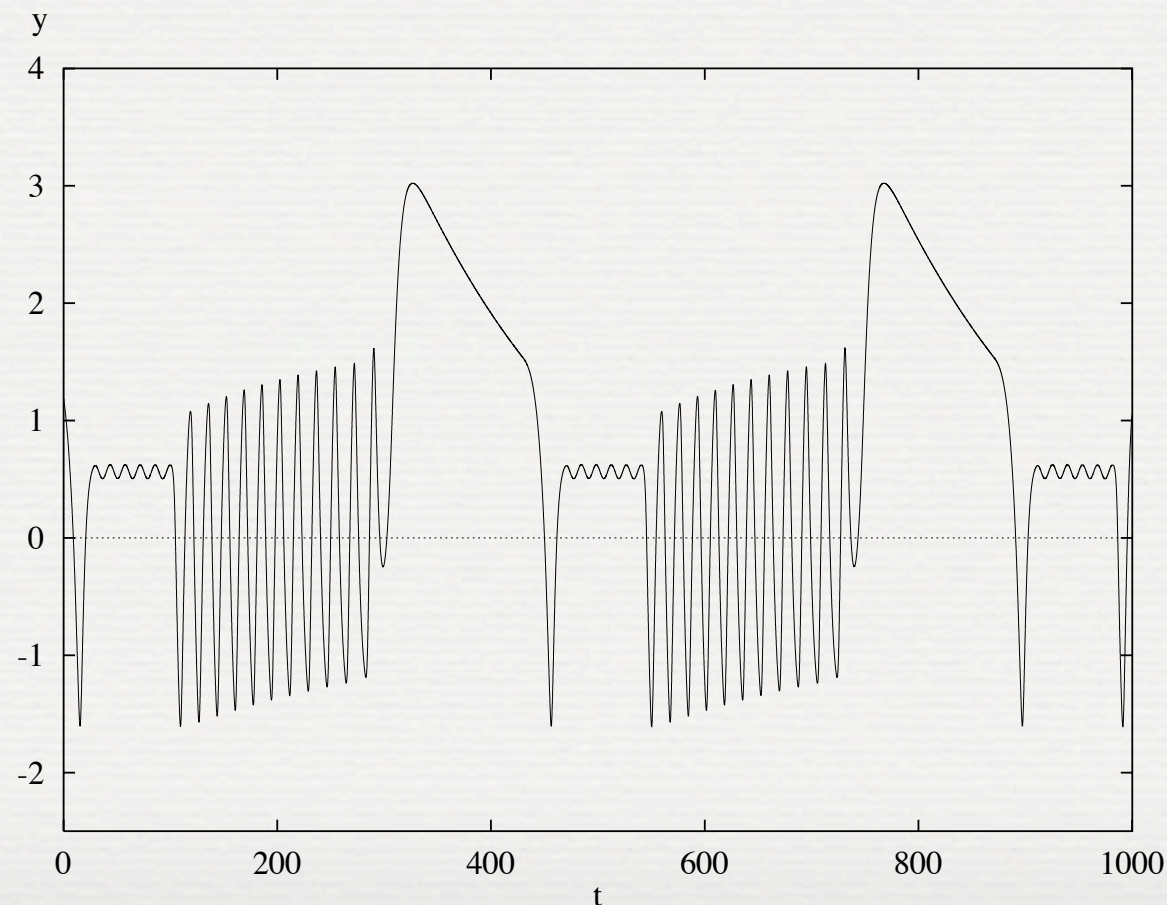
3) Mixed mode oscillations due to canard phenomena

Number of small oscillations. Passage through primary and secondary canards

An approximation of the values for which the limit cycle passes very close to the primary or the n^{th} -secondary canard, is given by:

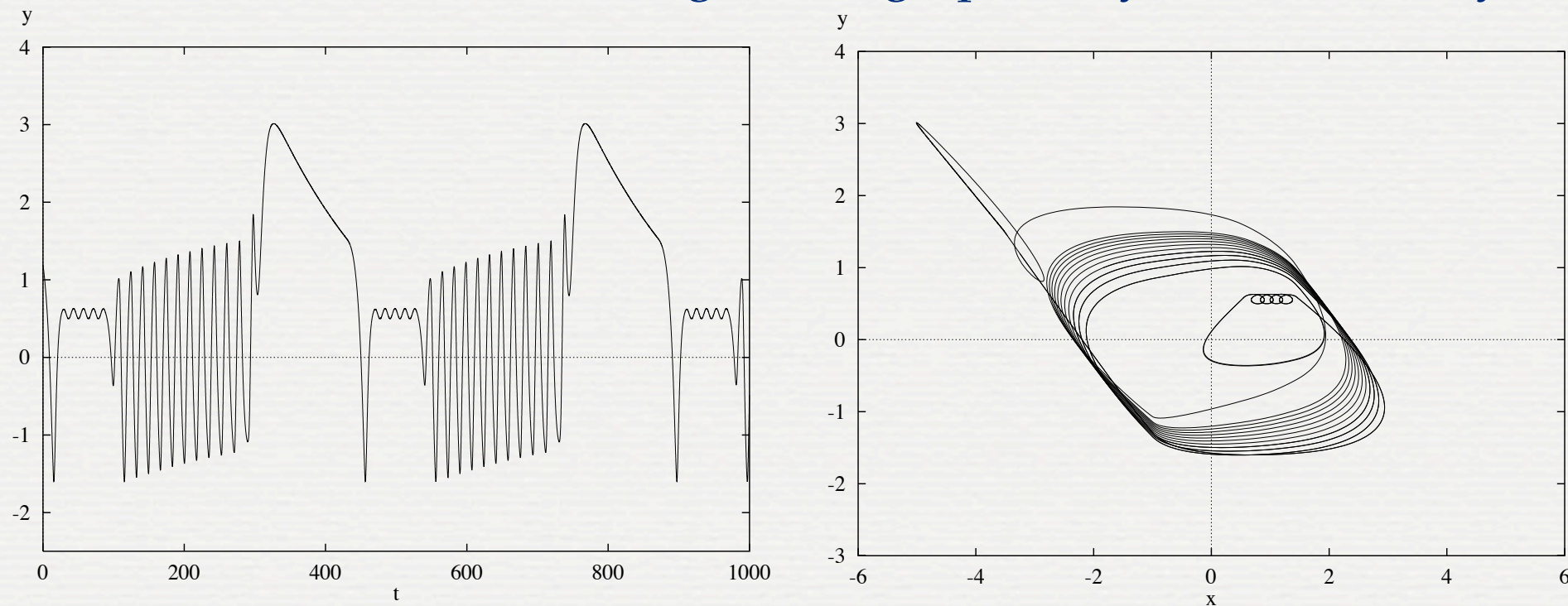
$$c_n(X_{\min}) = -\frac{a_2 + 1}{X_{\min}} - \frac{((a_2 + 1)\varepsilon(b_2 + X_{\min} - b_1(k_2 + X_{\min} + 1)) + X_{\min})\sqrt{\delta}}{X_{\min}^2} \\ + \frac{(\varepsilon(\pi(a_2 + 1)(4n + 1) - 2a_2)(b_1(k_2 + X_{\min} + 1) - b_2 - X_{\min}) + 4X_{\min})\delta}{2X_{\min}^2} \\ + O(\delta^{3/2}),$$

If $c \in (c_n, c_{n+1})$, the number of small oscillations of the limit cycle equals $n + 1$.

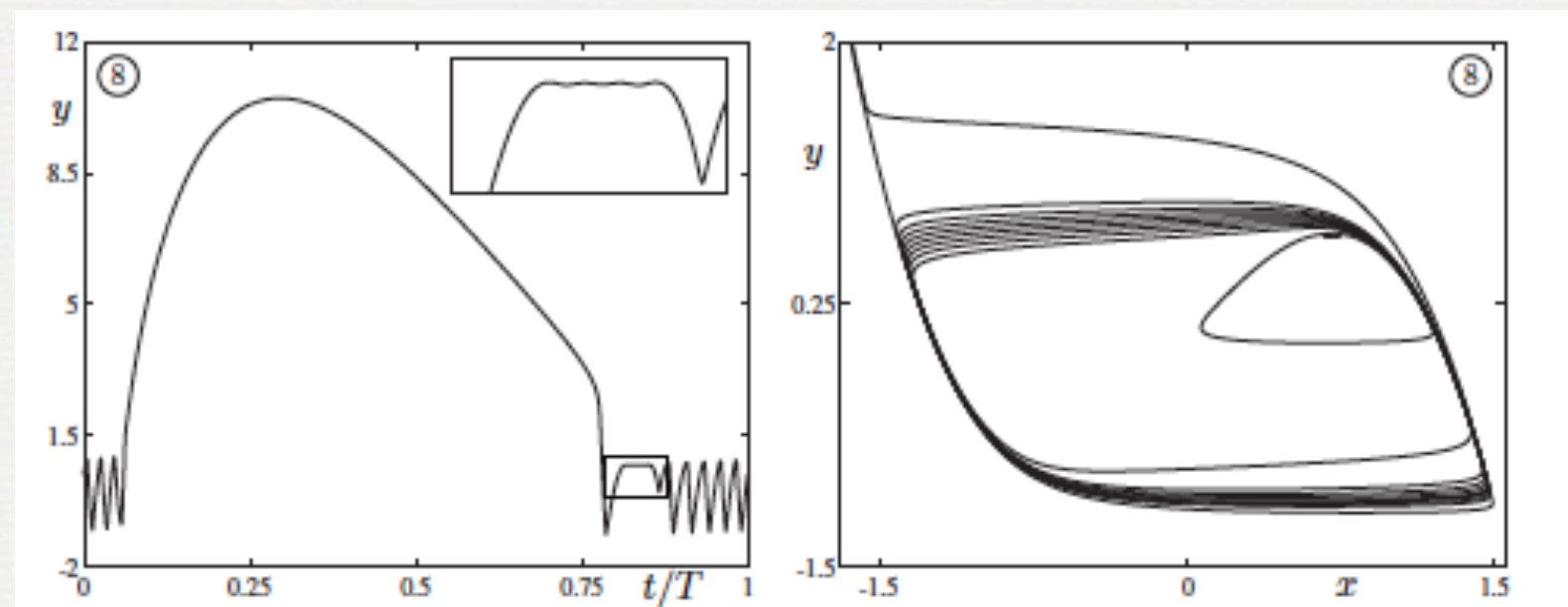


3) Mixed mode oscillations due to canard phenomena

Number of small oscillations. Passage through primary and secondary canards



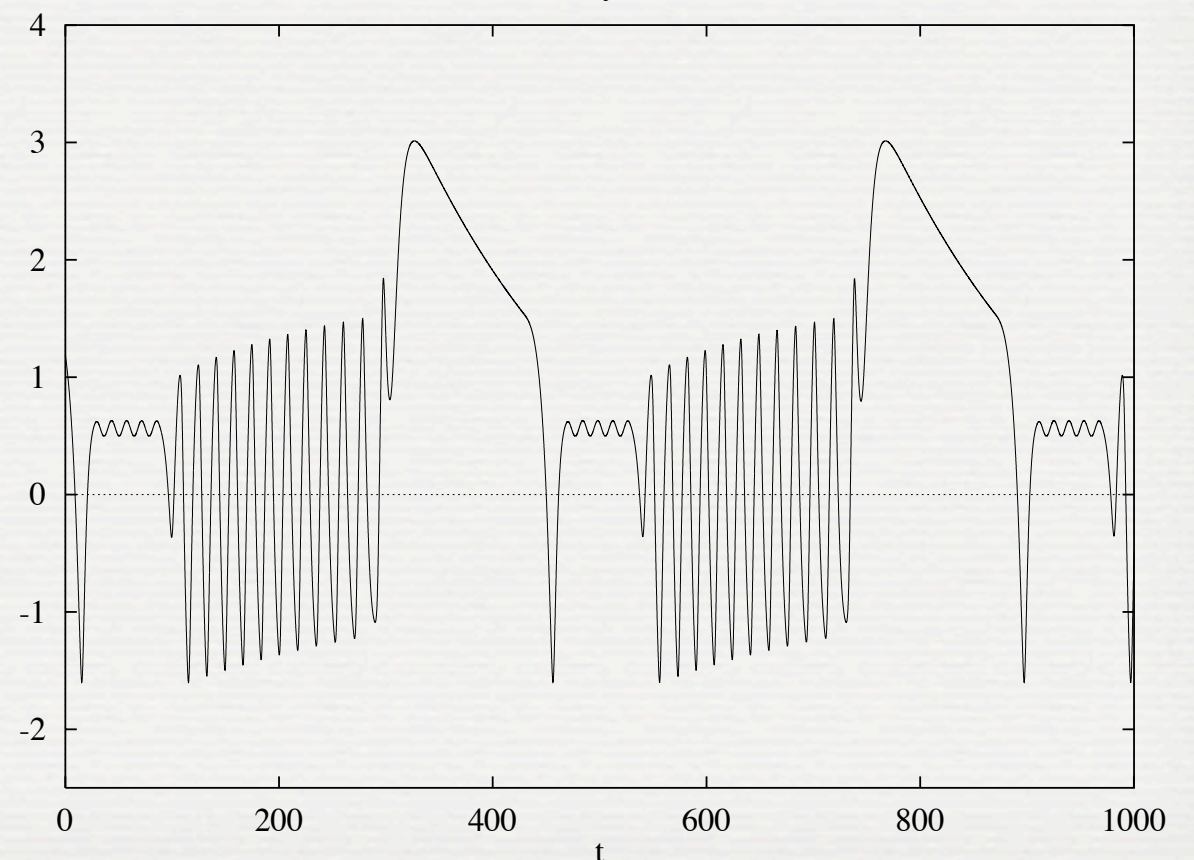
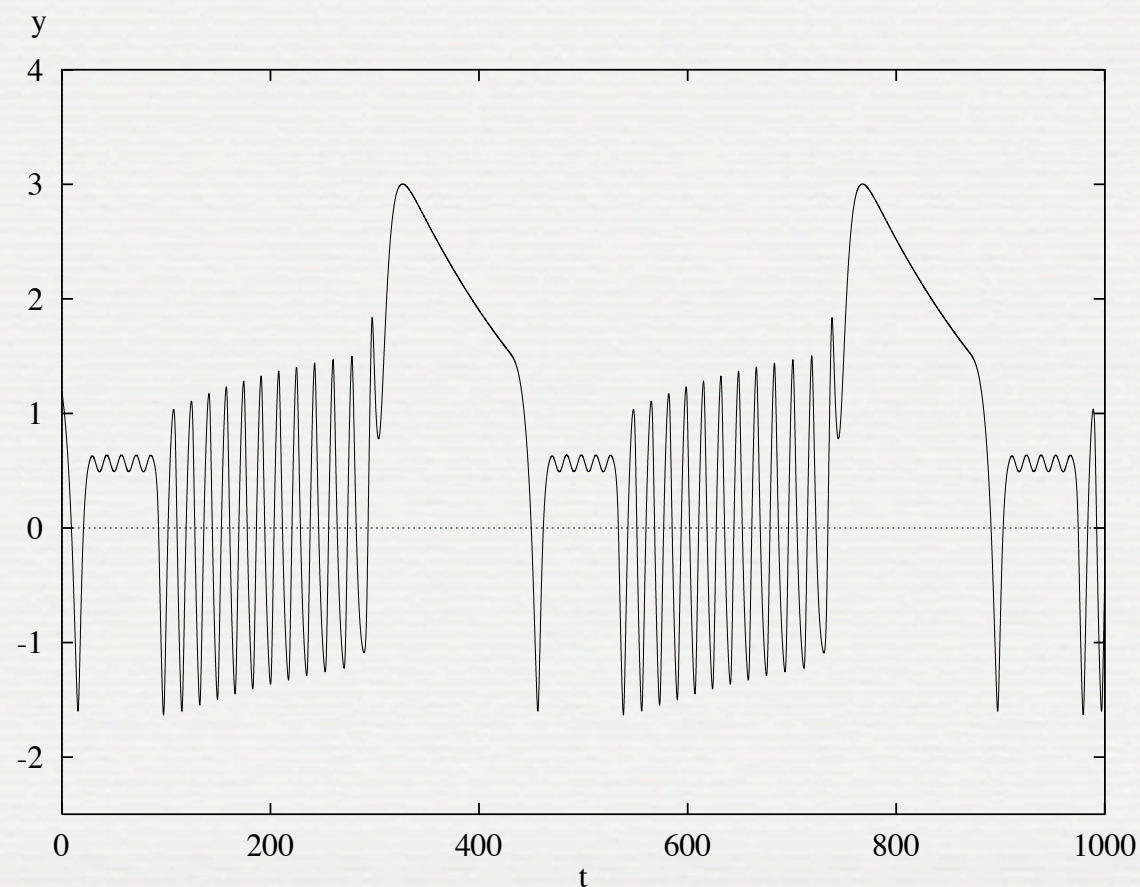
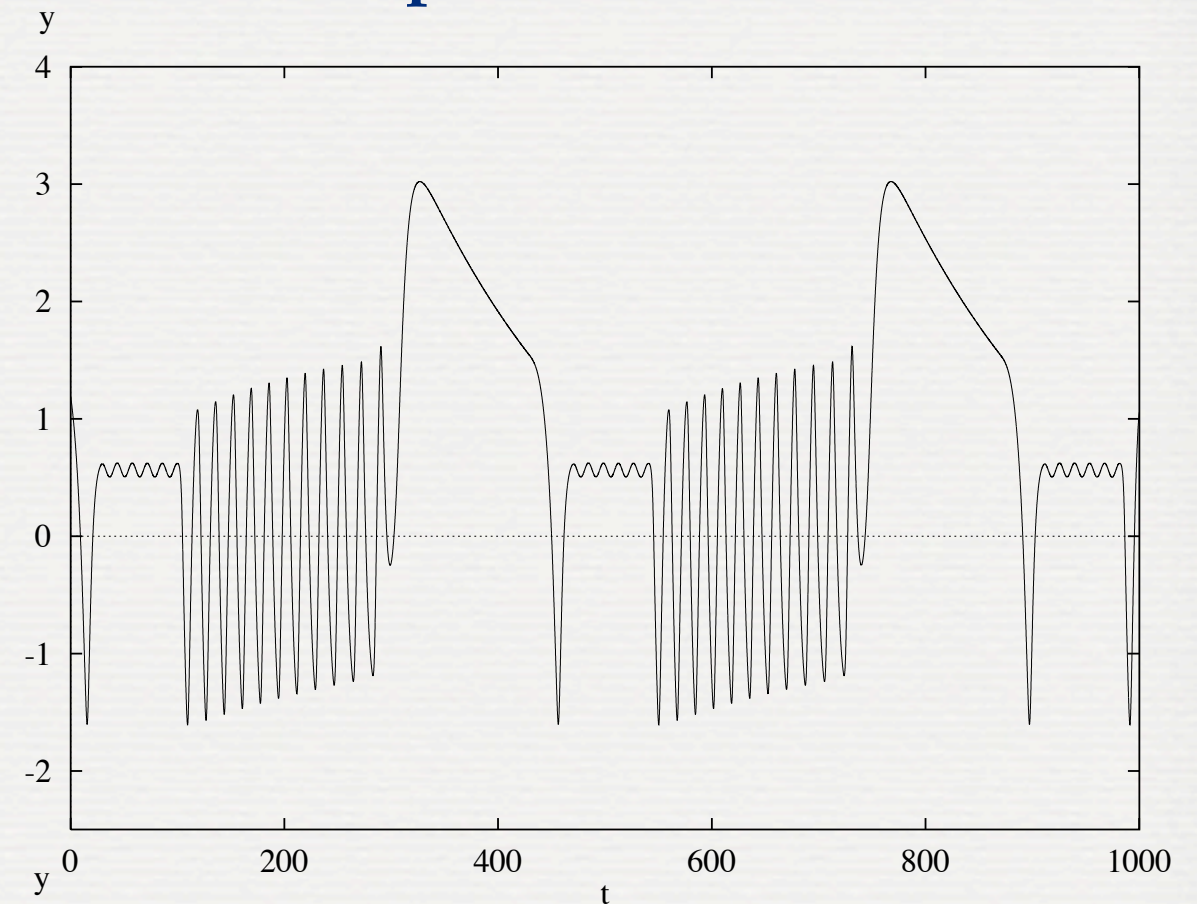
Similar mechanism to the smooth case



3) Mixed mode oscillations due to canard phenomena

Decreasing c , the system passes through a secondary canard, and one small oscillation is subtracted.

Is this small oscillation lost compensated by one pulse? Attending to these figures, it seems so...

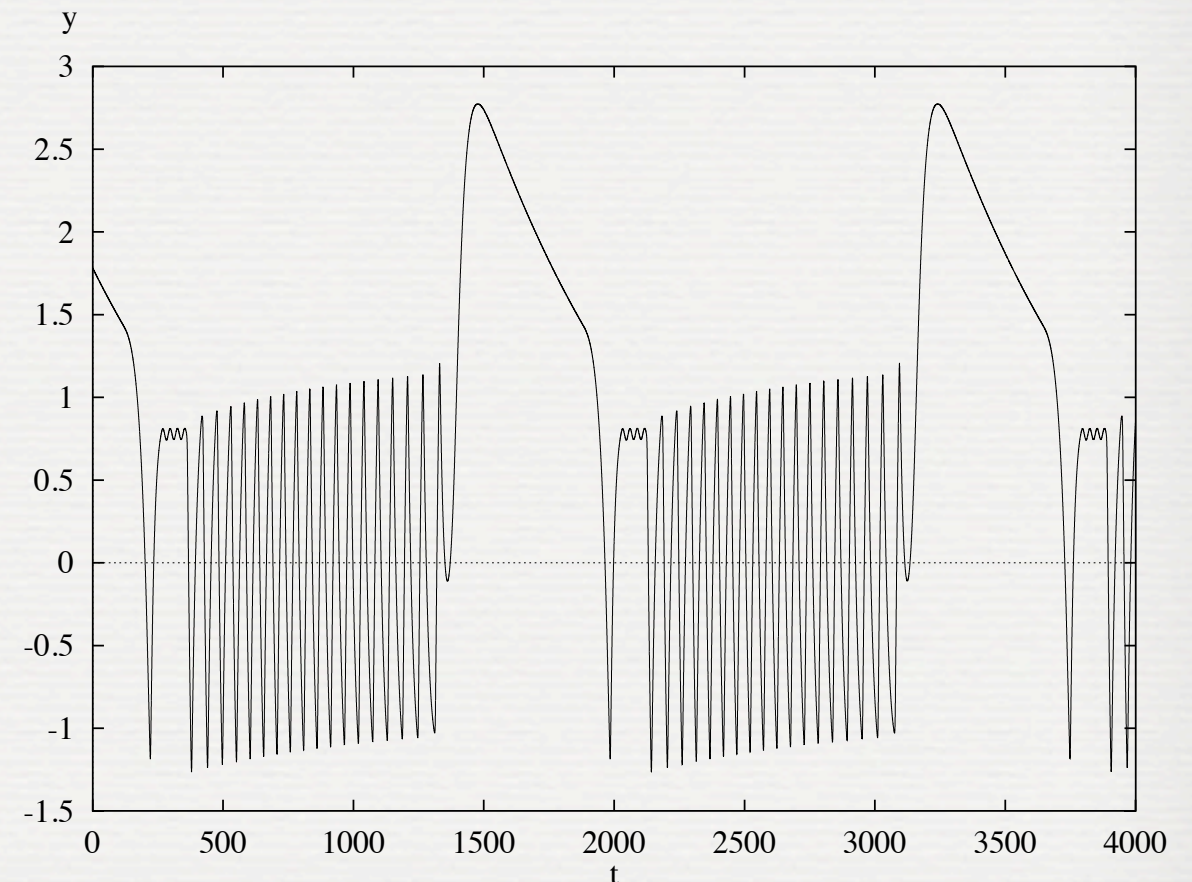
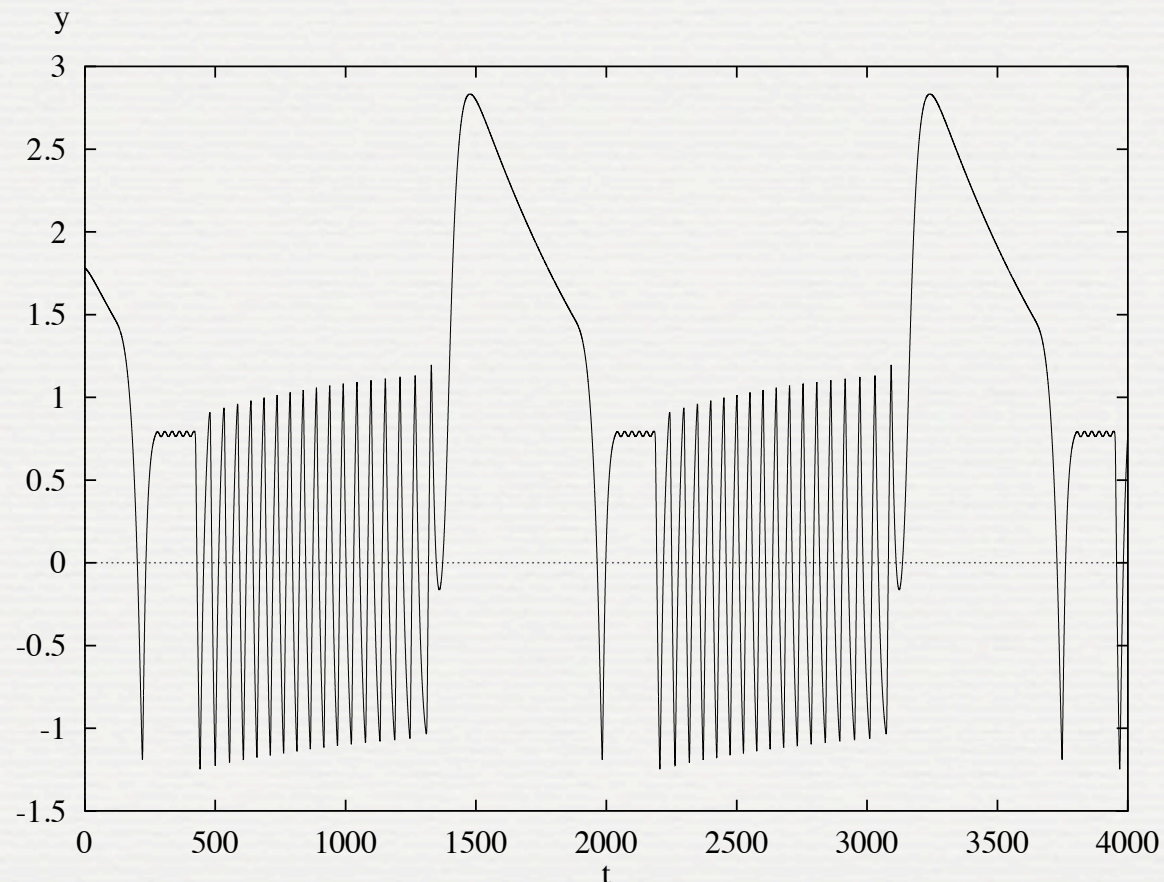


3) Mixed mode oscillations due to canard phenomena

While decreasing c , there may exist two different types of c_n , for which the number of small oscillations exhibited by the limit cycle is depleted by one, namely,

1. $c_n = c_n^0$, the number of pulses remains the same after the passage through c_n^0 while decreasing c .
2. $c_n = c_n^1$, one extra pulse appears after the passage through c_n^1 while decreasing c , to compensate for the decrease in the duration covered by small oscillations.

The number of c_n^0 values that we find between two c_n^1 depends on δ and increases while δ decreases.



Conclusions

- 1) We have analyzed qualitatively and quantitatively the PWL model.
- 2) It is possible to better control quantitative aspects.
- 3) The system reproduces well the GnRH secretion patterns.
- 4) Analysis of MMOs in an extension of the PWL model.

Future work

- 1) Change the slope of the extra piece, allowing for increasing or decreasing the size of the small oscillations.
- 2) Change the slope of the middle zone, allowing for the existence of saddle-node of canards.
- 3) PWL equivalent of an extended 6D version of the model, in which two fast subsystems are coupled together, while still being forced by the slow subsystem.

Mixed-Mode Oscillations in coupled multiple time scale piecewise linear oscillators. Application to a neuroendocrine system.

S. Fernández-García, M. Desroches, M. Krupa and F. Clément



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INVENTEURS DU MONDE NUMÉRIQUE
INNOVATEURS DU MONDE VIRTUEL

Mycenae

Multiscale dYnamiCs in neuroENdocrine AxEs