State estimation in endocrine systems with pulsatile hormone secretion

Alexander Medvedev
Information Technology
Uppsala University
752 37 Uppsala
SWEDEN
alexander.medvedev@it.uu.se

Joint work with A. Churilov (S:t Petersburg State University and Zh.Zhasubaliyev (South-West State University of Russia)

UPPSALA UNIVERSITET

Informationsteknologi

UPPSALA UNIVERSITET

Informationsteknologi

Outline

- Vocabulary
- Endocrine regulation
- Mathematical model
- Properties of the mathematical model
- State estimation
- Conclusions

UPPSALA UNIVERSITET

Informationsteknologi

Why going biomedical?

- New challenging control and estimation problems
- Multifactorial diseases (diabetes, cancer, heart diseases, epilepsy, ect) need system approach
- Many unsolved problems of life science are due to dynamical phenomena
- Abundance of experimental data
- High societal impact

Citing Hiroaki Kitano: *"Although the road ahead is long and winding, it leads to a future where biology and medicine are transformed into precision engineering"*

UPPSALA UNIVERSITET

Endocrinology

- A **hormone** is a chemical messenger from one cell (or group of cells) to another.
- Hormones are produced by nearly every organ and tissue type in a multicellular organism.
- Hormones can be secreted in continuous (**basal**) or pulsatile (**non-basal**) manner.
- **Endocrinology** deals with disorders of the endocrine system and hormones.
- The use of dynamical **mathematical models** and methods in endocrinology is widespread
  - **Analysis** of feedback phenomena
  - **Estimation** of immeasurable hormone concentrations
  - **Control**: artificial pancreas, fertility therapies

UPPSALA UNIVERSITET

Informationsteknologi

Modeling, analysis and estimation of the tes ... male

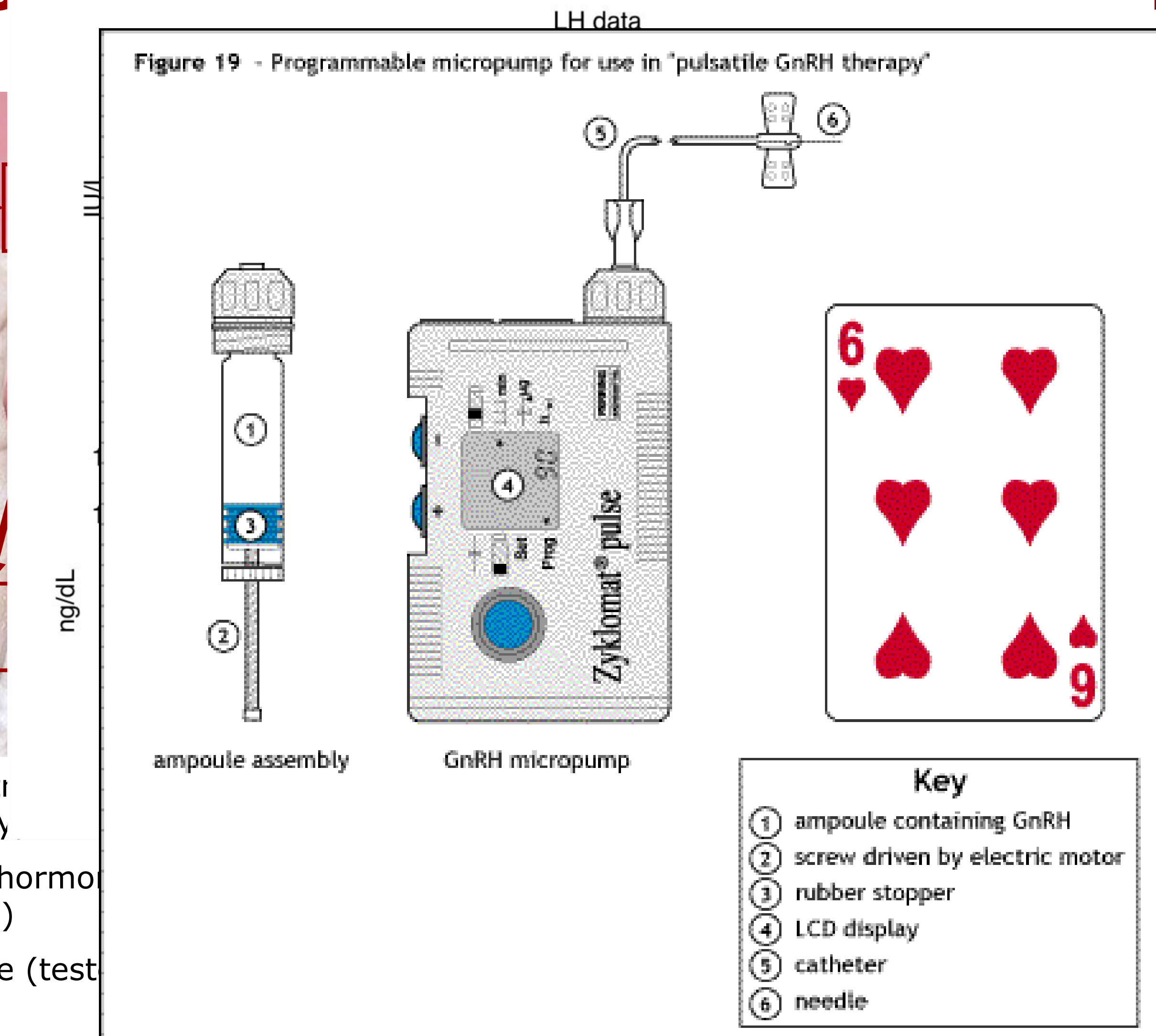


Figure 19 - Programmable micropump for use in 'pulsatile GnRH therapy'

GnRH – gonadotr... hormone (hy...

LH – luteinizing hormo... (hypophysis)

Te – testosterone (test...

UPPSALA UNIVERSITET

Informationsteknologi

Model: Pulsatile secretion

$$\dot{x} = Ax + B\xi(t)$$

$$x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}, A = \begin{bmatrix} -b_1 & 0 & 0 \\ g_1 & -b_2 & 0 \\ 0 & g_2 & -b_3 \end{bmatrix}, B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}.$$

x_1 – GnRH

x_2 – LH

x_3 - Te

b_1, b_2, b_3 are positive and distinct

GnRH is released in a pulsatile manner:

$$\xi(t) = \sum_{k=0}^{\infty} \gamma_k \delta(t - t_k)$$

γ_k and t_k are evaluated by pulse modulation algorithm: when Te rises, the pulses of GnRH become sparser and their amplitude diminishes

UPPSALA UNIVERSITET

Informationsteknologi

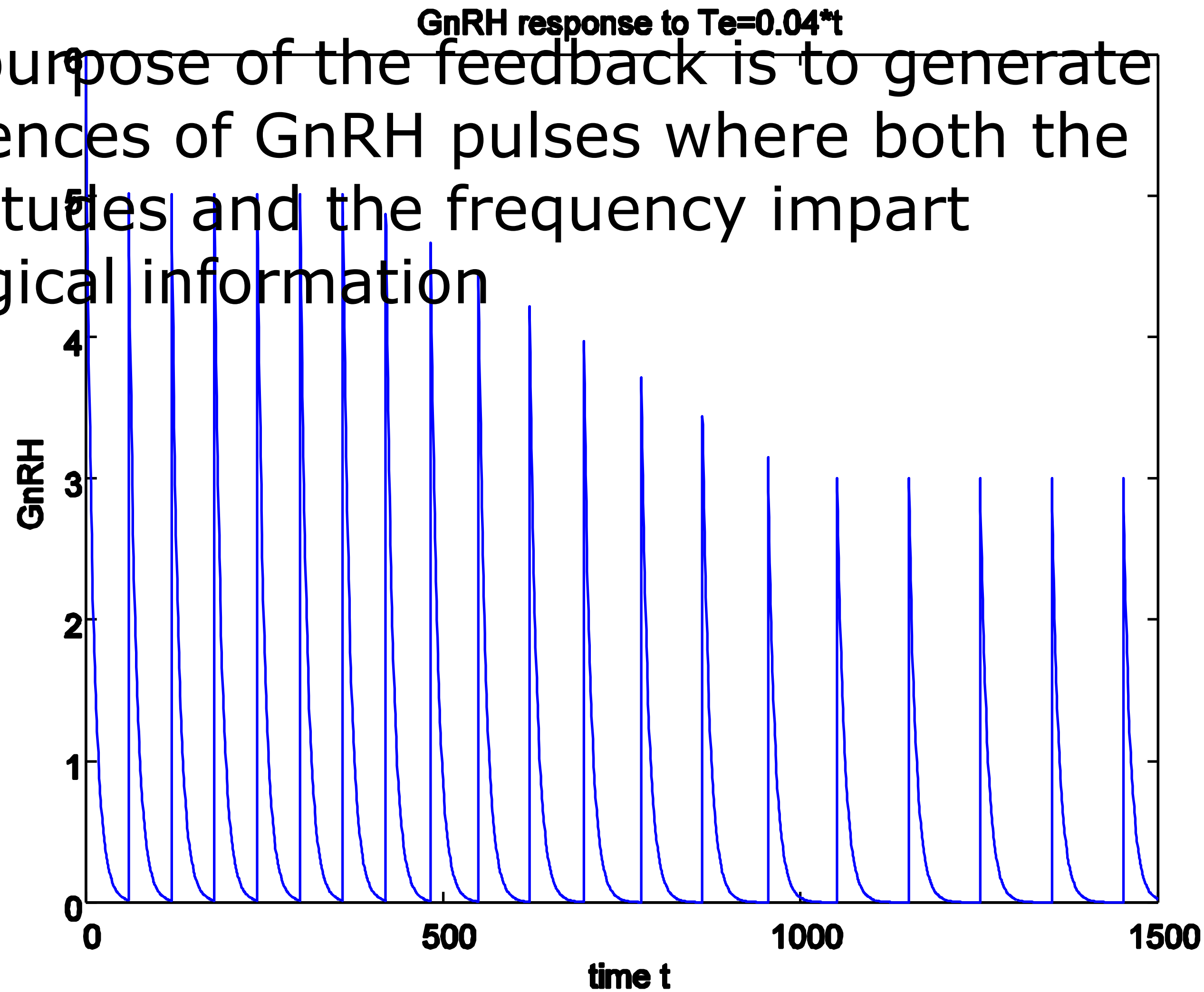
Pulse modulation in release hormone GnRH

The purpose of the feedback is to generate sequences of GnRH pulses where both the amplitudes and the frequency impart biological information

$\xi(t$

t_{n+}

Te

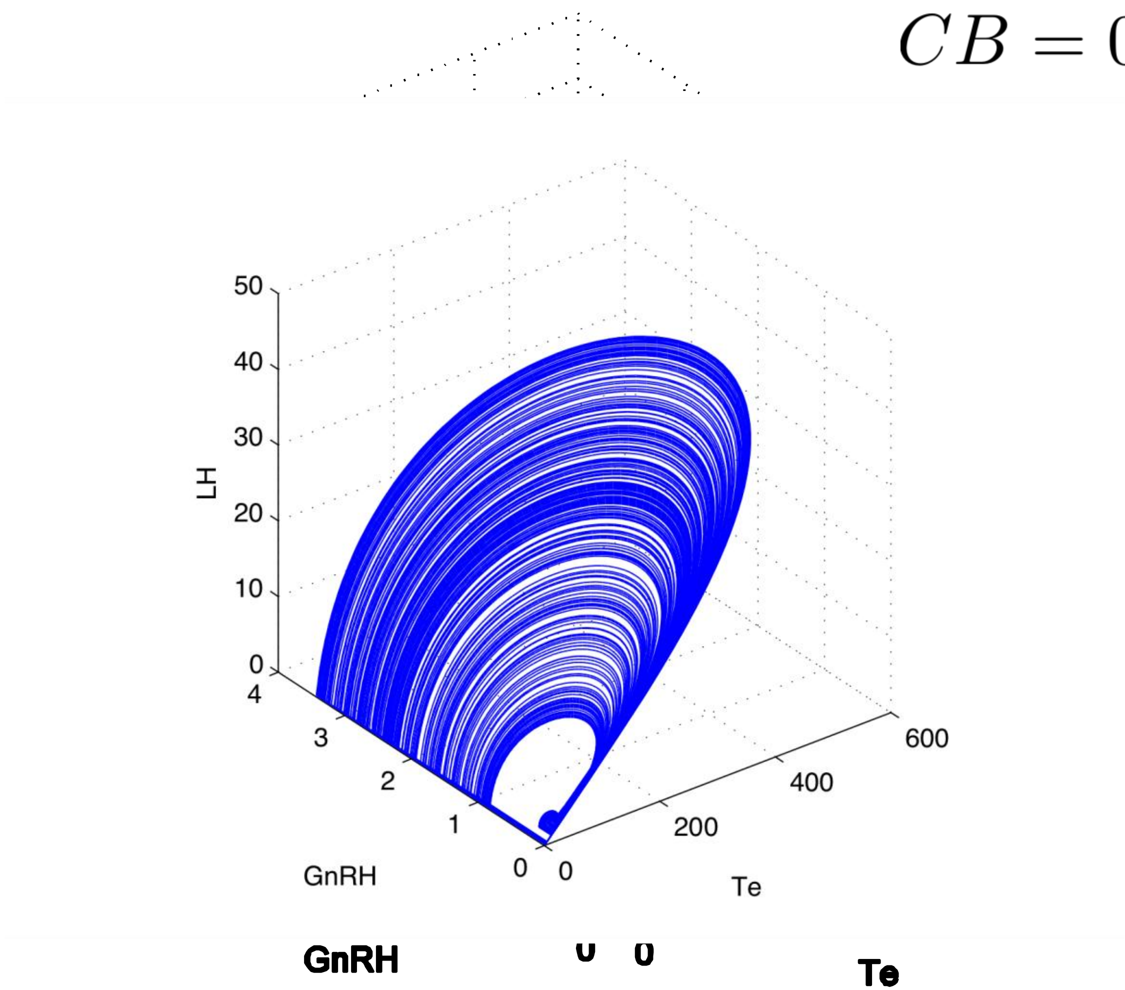


$t),$

$x.$

Complex dynamics

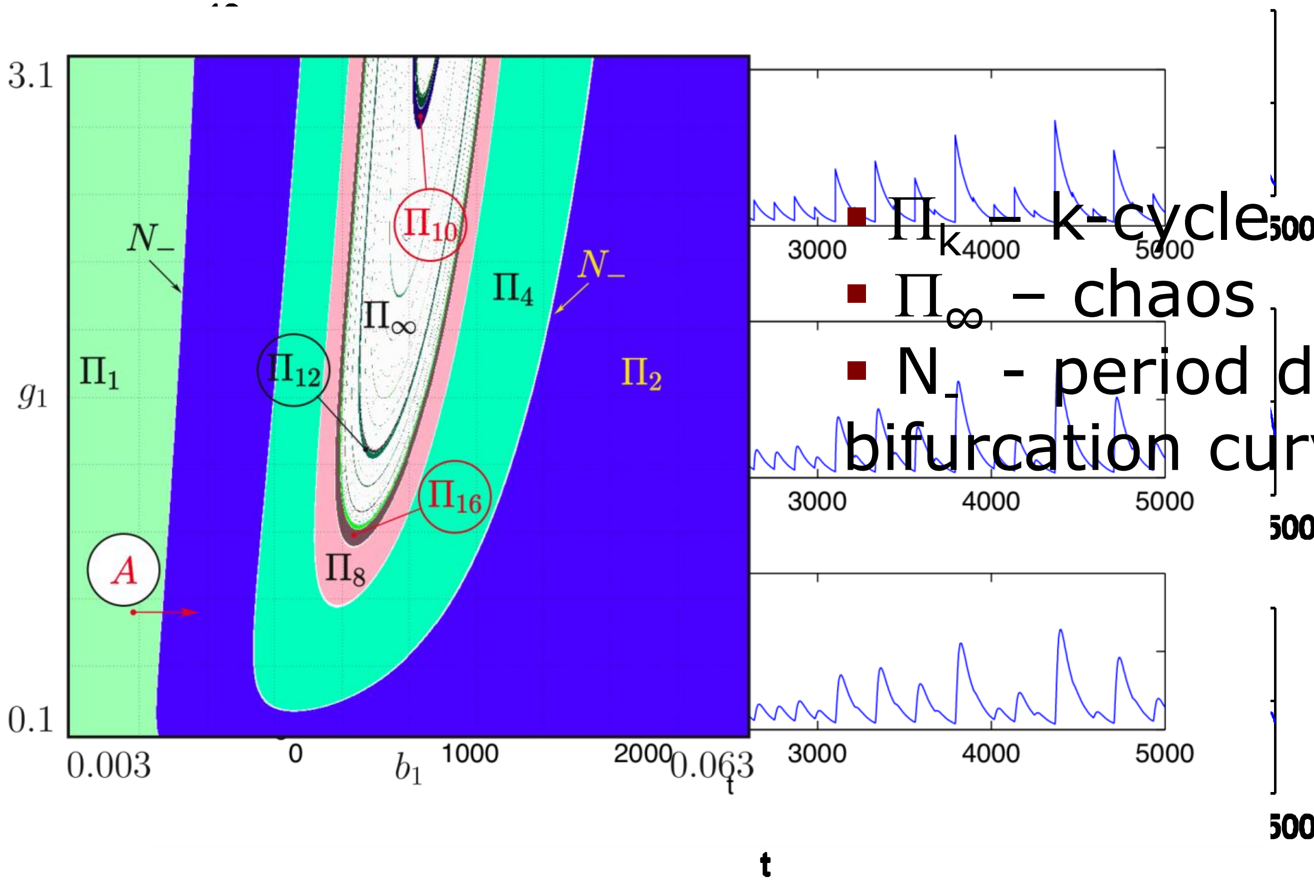
$$CB = 0, \quad LB = 0$$



UPPSALA UNIVERSITET

Informationsteknologi

Chart of dynamic modes

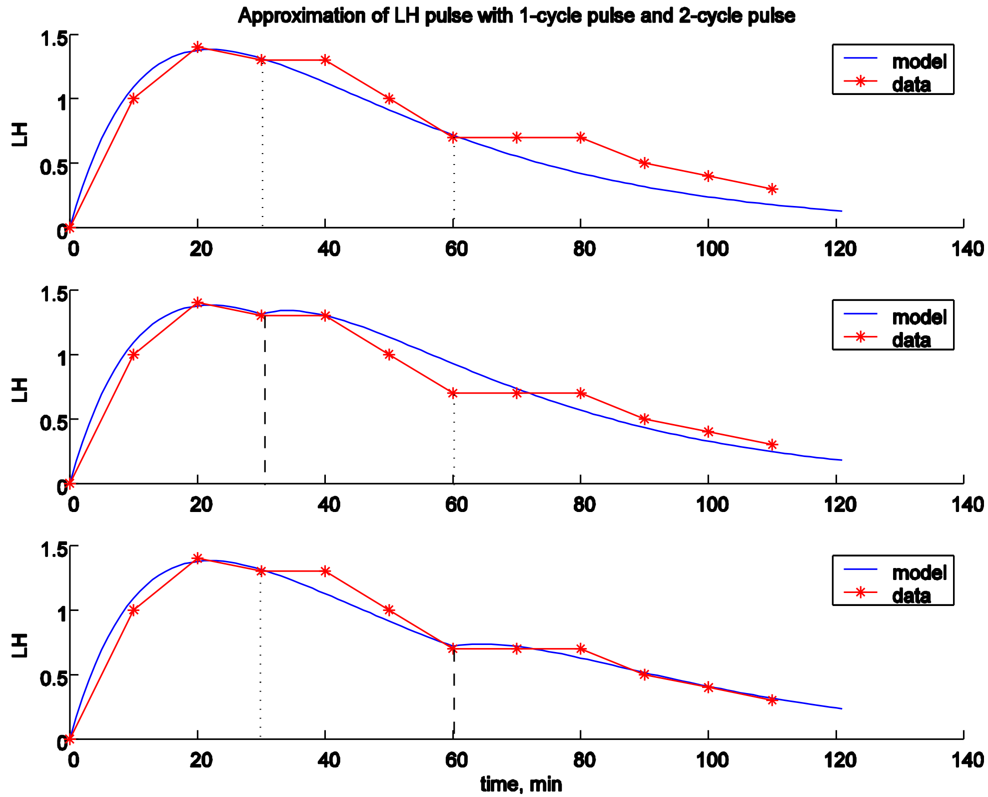


- Π_k – k-cycle
- Π_∞ – chaos
- N_- - period doubling bifurcation curve

UPPSALA UNIVERSITET

Informationsteknologi

Validation on clinical data



Release hormone observer

- Pulsatile release of GnRH is of high interest but not measured in the human
- An observer is used for model-based estimation of GnRH concentration

$$\frac{d\hat{x}}{dt} = A\hat{x} + B\hat{\xi}(t) + K(y - \hat{y})$$

$$\hat{\xi}(t) = \sum_{n=0}^{\infty} \hat{\lambda}_n \delta(t - \hat{t}_n)$$

$$\hat{t}_{n+1} = \hat{t}_n + \hat{T}_n, \quad \hat{T}_n = \Phi(\hat{z}(\hat{t}_n)), \quad \hat{\lambda}_n = F(\hat{z}(\hat{t}_n))$$

$$D = A - KL \qquad \text{is Hurwitz}$$

Synchronous observer mode

Let $(x(t),\, t_n)$ be a solution of the plant equations

with $\lambda_k,\ T_k$ and $x_k = x(t_k^-)$.

Consider the observer solution $(\hat{x}(t),\, \hat{t}_n)$

with i. c. $\hat{t}_0 = t_a, \hat{x}(\hat{t}_0^-) = x(t_a^-)$, for some a.

Such $(\hat{x}(t),\, \hat{t}_n)$ is called *a synchronous mode*

w. r. t. $(x(t),\, t_n)$ if

$$\hat{x}_n = x_{n+a},\ \hat{t}_n = t_{n+a},\ \hat{\lambda}_n = \lambda_{n+a},\ n = 0,\, 1,\, 2,\, \ldots,$$

Locally asymptotically stable: any $(\hat{x}(t),\, \hat{t}_n)$ such that

small $|\hat{t}_0 - t_a|$ and $\|\hat{x}(\hat{t}_0^-) - x(t_a^-)\|$ imply

$\hat{t}_n - t_{n+a} \to 0$ and $\|\hat{x}(\hat{t}_n^-) - x(t_{n+a}^-)\| \to 0$ as $n \to \infty$.

Pointwise mapping

Consider the pointwise mapping:

$$(\hat{x}(\hat{t}_n^-),\ \hat{t}_n) \mapsto (\hat{x}(\hat{t}_{n+1}^-),\ \hat{t}_{n+1}).$$

Select k and s, $k \le s$, such that

$$t_k \le t < t_{k+1}, \quad t_s \le t + \Phi(Cx) < t_{s+1}.$$

The mapping is given by

$$\hat{x}_{n+1} = P(\hat{x}_n, \hat{t}_n), \quad \hat{t}_{n+1} = \hat{t}_n + \Phi(C\hat{x}_n).$$

$$P(x,t) = P_{k,s}(x,t) = e^{A(t+\Phi(Cx)-t_s)}x(t_s^+)$$
$$- e^{D\Phi(Cx)}\left[e^{A(t-t_k)}x(t_k^+) - x - F(Cx)B\right]$$
$$- \sum_{j=k+1}^{s} \lambda_j e^{D(t+\Phi(Cx)-t_j)}B.$$

Informationsteknologi

UPPSALA UNIVERSITET

Pointwise mapping

UPPSALA UNIVERSITET

Informationsteknologi

$$\text{Define } Q_{k,s}(q) = \begin{bmatrix} P_{k,s}(x,t) \\ t + \Phi(Cx) \end{bmatrix}, \quad \text{where } q = \begin{bmatrix} x \\ t \end{bmatrix}.$$

$$\text{Set } Q(q) = Q_{k,s}(q) \text{ for } t_k \le t < t_{k+1},$$
$$t_s \le t + \Phi(Cx) < t_{s+1}.$$

$$\text{Then } \hat{q}_{n+1} = Q(\hat{q}_n), \text{ where}$$

$$\hat{q}_n = \begin{bmatrix} \hat{x}_n \\ \hat{t}_n \end{bmatrix}, \quad Q(q) = \begin{bmatrix} P(x,t) \\ t + \Phi(Cx) \end{bmatrix}.$$

- The mapping *P(.)* is continuous
- The derivatives of *P(.)* w. r. t. *x* and *t* are also continuous

Jacobian matrix

UPPSALA UNIVERSITET

Informationsteknologi

The Jacobian of $Q(q)$: $Q'(q) = \begin{bmatrix} P'_x(x,t) & P'_t(x,t) \\ \Phi'(Cx)C & 1 \end{bmatrix}$.

Synchronous mode: $\hat{q}_n^0 = \begin{bmatrix} x_{n_a} \\ t_{n_a} \end{bmatrix}$.

The Jacobian at $\hat{q}_n^0$: $J_{n_a} \stackrel{def}{=} Q'(\hat{q}_n^0)$ is comprised of

$$(J_k)_{11} = \Phi'_k A x_{k+1} C + e^{DT_k} \left(I_{n_x} + F'_k BC \right),$$

$$(J_k)_{12} = A x_{k+1} - e^{DT_k} A (x_k + \lambda_k B),$$

$$(J_k)_{21} = \Phi'_k C, \qquad (J_k)_{22} = 1.$$

By the chain rule, for $m \geq 1$

$$\left(Q^{(m)} \right)' (\hat{q}_n^0) = J_{n_a+m-1} J_{n_a+m-2} \dots J_{n_a+1} J_{n_a}.$$

Local asymptotic stability

Let $(x(t), t_n)$ be a $m-$cycle. Then $J_{n+m} \equiv J_n$.

1) The synchronous observer mode w. r. t. $(x(t), t_n)$ is locally asymptotically stable if $J_0 \ldots J_{m-1}$ is Schur stable.

2) Suppose

$$-1 < \prod_{k=0}^{m-1} (\Phi'_k C A x_{k+2} + 1) < 1.$$

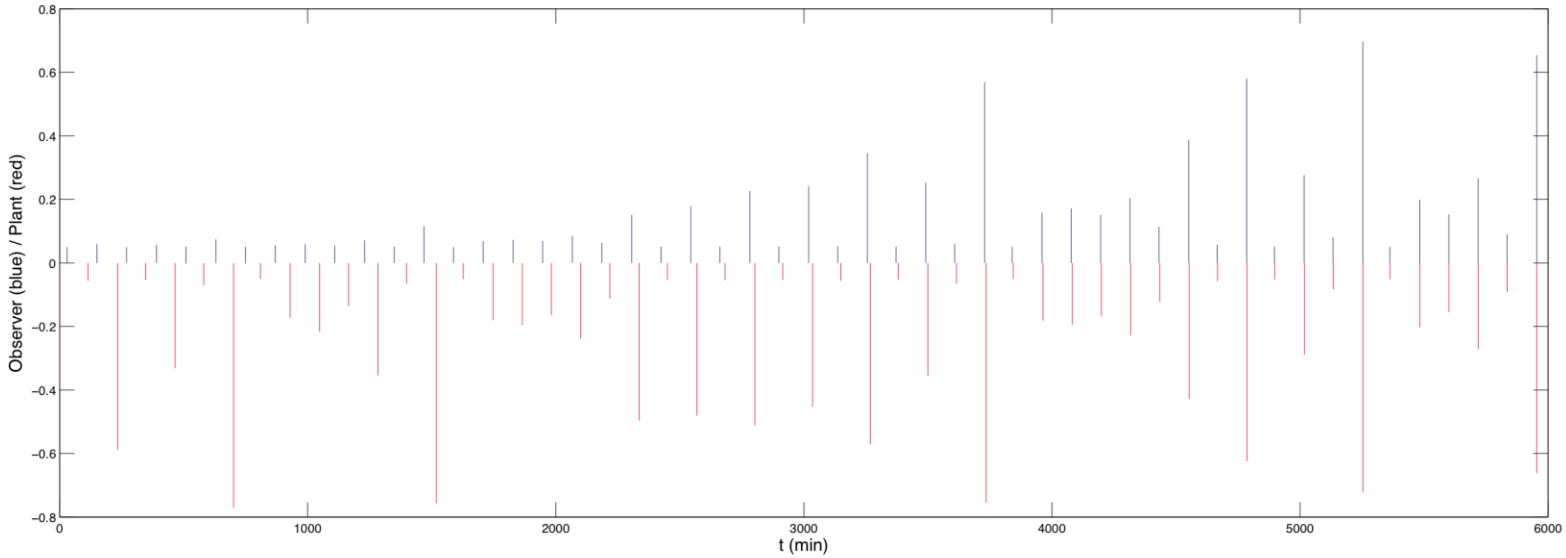
Then there is always K such that $J_0 \ldots J_{m-1}$ is Schur stable.

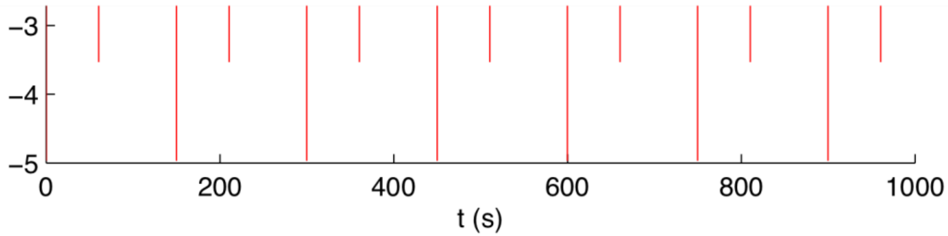
Informationsteknologi

UPPSALA UNIVERSITET

UPPSALA UNIVERSITET

Simulation





Informa

Chaotic solution in the plant

2-cycle with non-zero initial conditions

Conclusions

- A hybrid model of hormone regulation with intrinsic impulse-modulated feedback is shown to possess complex dynamics.
- An observer with a static output estimation error feedback for the closed-loop endocrine regulation model is suggested.
- A condition for the state estimation error stabilizability is obtained.
- Conditions for local asymptotic stability of the state estimation error under *m*-cycle in the endocrine plant are derived.