Chronotaxic systems

Systems far from thermodynamic equilibrium that adjust their clocks

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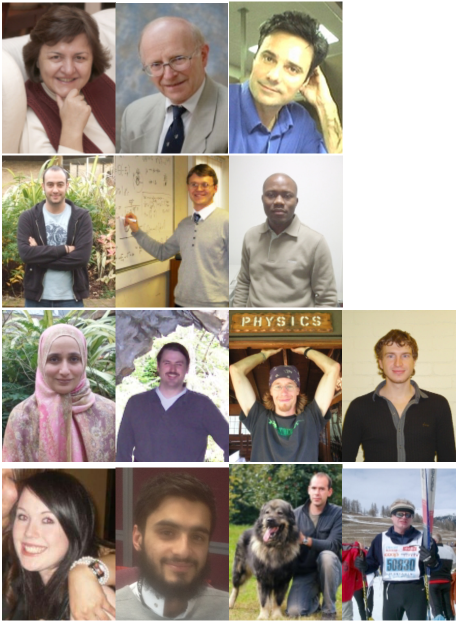
Outline

1. Collaborators
2. The approach
   - Analyses
   - The cardiovascular system brings fuel to each cell
   - Origin of biological oscillations?
   - The brain controls/supervises each cell
3. Characterising the dynamics
   - Systems with time-varying parameters
4. Novel methods are needed
   - Additional motivation
   - Dynamical inference
5. Chronotaxic systems

People in Nonlinear and Biomedical Physics

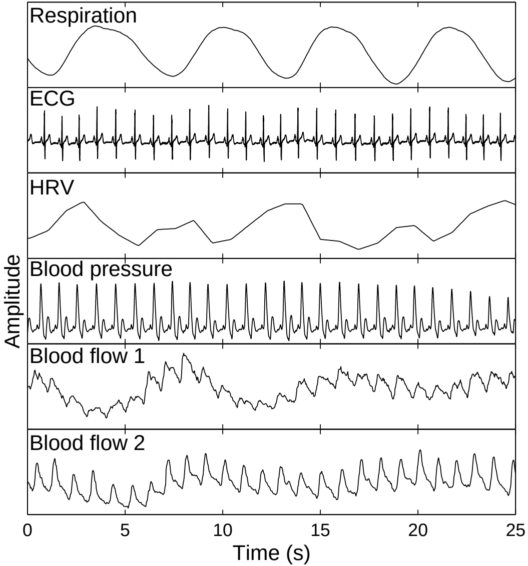
- **Academic staff**
  - Prof Aneta Stefanovska
  - Prof Peter McClintock
  - Dr Dmitry Luchinsky
- **Research Associates**
  - Dr Tomislav Stankovski
  - Dr Yevhen Suprunenko
  - Dr Rodrigue Tindjong
- **PhD students**
  - *Ms Suhir Abuhajar*
  - Mr Phil Clemson
  - *Mr Tom Hansard*
  - Mr Dima Iatsenko
  - Ms Gemma Lancaster
  - Mr Shakil Patel
  - Mr Spase Petkoski
  - *Mr Norman Turner*



A longstanding and ambitious goal

- More than 20 years of work on the question
  What are physical principles of living systems?
- The work involves
  - theory of coupled oscillators
  - development of novel numerical methods to analyse dynamics from recorded data
  - development and applications of novel recording/imaging methods
  - applications
- Many collaborators in almost all continents.
- With greatest thanks to **Professor Hermann Haken**

Insight from measured signals



The approach: combining theory, measurements and *a priori* knowledge to extract the basic dynamical principles of life.

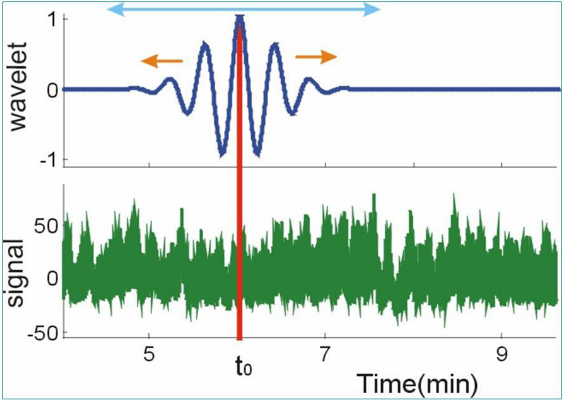
Analysis

- **Time domain**; methods for decomposition, like independent component analysis, principal component analysis, non-linear mode decomposition...
- **Frequency domain**, i.e. Fourier transform, bispectral analysis
- **Time-frequency domain**, i.e. wavelet transform, wavelet-based bispectral analysis, ...
- **Phase space**, i.e. Lyapunov exponents, correlation dimension
- **Complexity analysis**, i.e. Fractal and multifractal analysis, Horst exponent, entropy-based measures, Fokker-Planck analysis[1]
- **Methods for analysis of interactions**, i.e. synchronization, coherence, direction of coupling.

[1] A. Bahraminasab, F. Ghasemi, A. Stefanovska, P.V.E. McClintock, **R. Friedrich**. Physics of brain dynamics: Fokker-Planck analysis reveals changes in EEG $\delta - \theta$ interactions in anæsthesia. *NJP* **11**: 103051, 2009.

Time series analysis

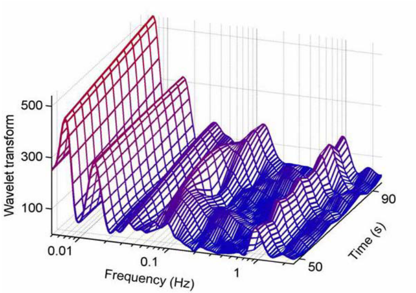
- Wavelet transform – transformation **from time to the time-frequency domain**



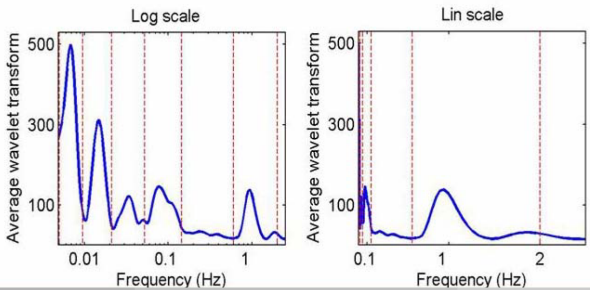
- Morlet mother wavelet ⇒ family of wavelets
- Time resolution: shifting the wavelet along the signal
- Frequency resolution: stretching/shortening of the wavelet

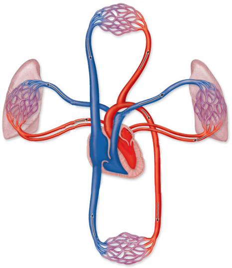
- Continuous WT – **tracing the oscillations in time**

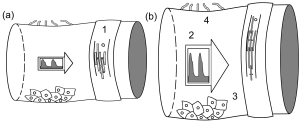
Wavelet transform

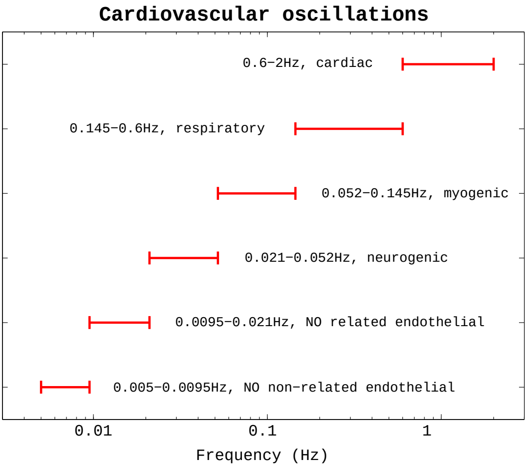


- WT coefficients in the time-frequency plane
- Six peaks in the interval from 0.005 Hz to 2 Hz
- Average wavelet transform with interval boundaries
- **Logarithmic frequency resolution**





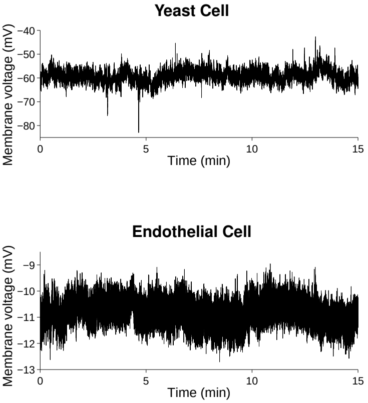




Stefanovska, Coupled oscillators – Complex but not complicated cardiovascular and brain interactions, *IEEE Eng Med Biol Mag* **26**: 25-29, 2007.

Non-excitable cells

- Non-excitable cells have time-dependent properties and functions, e.g. vascular endothelial cells.
- The action potential is a special case of membrane dynamics only observed in nerve and muscle cells.
- The vast amount of information in the subtle fluctuations of the membrane potential has been left unexplored.

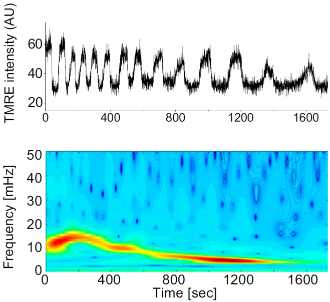


Mitochondrial oscillations

Experiments have found that the membrane potentials of mitochondria oscillate at a frequency $\sim$ 10mHz.

Single Mitochondrion

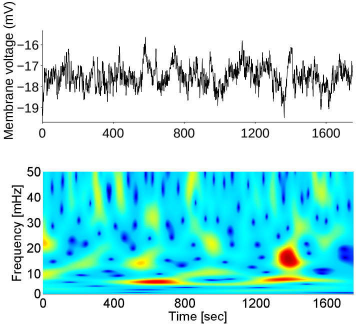
(fluorescence)



Ref: FT Kurz, MA Aon, B O'Rourke and AA Armoundas, *PNAS* **107**, 14315-14320 (2010)

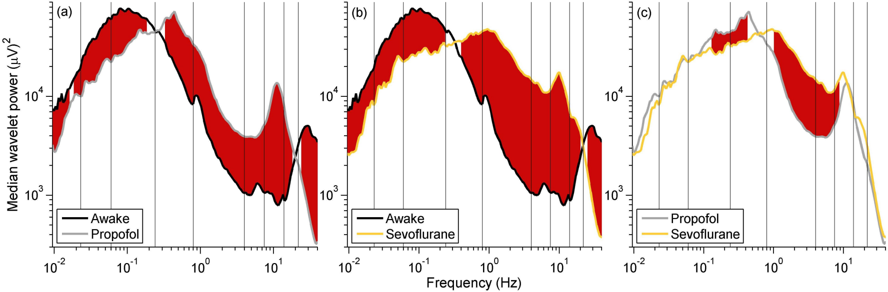
Whole Cell

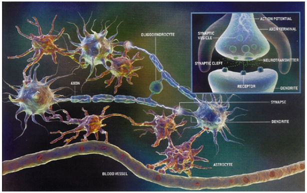
(patch clamp)



Ref: PT Clemson *et al*, *Proc ESGCO 2010*, (2010)

Astrocytes – linking the CVS with brain dynamics





- Glial cells provide nutrition for the neurons.
- They **couple** the cardiovascular oscillations to brain waves.

Impact

Clinical studies

- Hypertension (RLI, Pisa)
- Post myocardial infarction (Ljubljana)
- Heart failure (RLI)
- Diabetes mellitus (Ljubljana)
- Brain injury critical care (Oslo)
- Tetraplegia (Mt Sinai Hospital, NY)
- Cancer (Pisa, RLI)

States

- Anæsthesia (RLI, Ljubljana, Olso)
- Ageing (Ljubljana, RLI)
- Exercise (Oslo, Physics Department)
- Breath-hold (Physics Department)
- Part or whole body heating (Physics Department, Nagoya, Virginia)

Ways to treat living systems

Various approaches to living systems, in particular to treat them as –

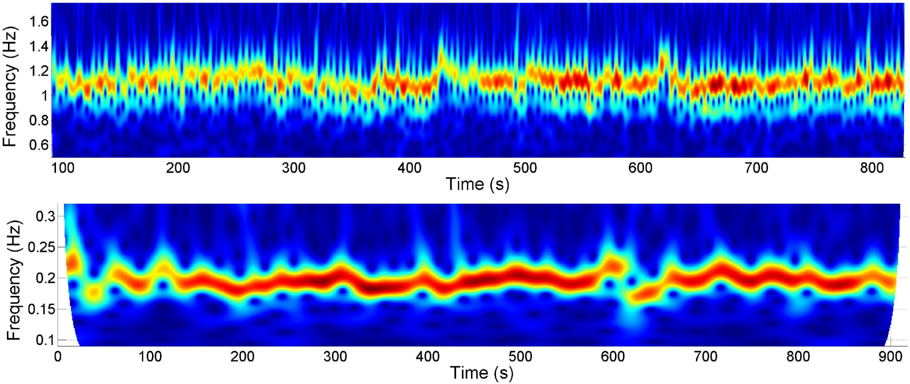
- **Stochastic?** No. Although random fluctuations can be important, the underlying dynamics is not stochastic
- **Chaotic?** No. Again, the ideas of chaos theory do not describe well a dynamics that exhibits a lot of determinism

But their parameters vary in time... If the variations are caused by external influences, can treat them as –

- **Non-autonomous?** Yes...

The mathematical theory of non-autonomous systems is potentially able to provide an excellent description of the parameter variations observed in living systems.

Complex oscillations in the cardiovascular system

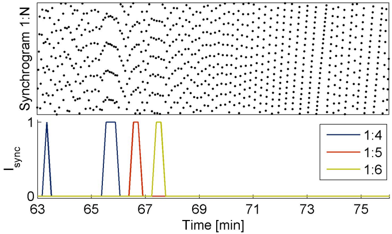


Bračič Lotrič, Stefanovska, *Physica A* **283**: 451-461, 2000
Stefanovska, Haken, McClintock, *et al*, *Phys Rev Lett* **85**: 4831-4834, 2000
Jamšek, Stefanovska, McClintock, *Phys Med Biol* **49**: 4407-4425, 2004
Bahraminasab, Kenwright, Stefanovska, *et al*, *IET Syst Biol* **2**: 48-54, 2008
Kenwright, Bahraminasab, Stefanovska, McClintock, *Eur Phys J B* **65**: 425-433, 2008
Shiogai, Stefanovska, McClintock, *Phys Rep* **488**: 51-110, 2010

Dynamical inference

- Inverse problem – starting from time series, one tries to understand the dynamics of interacting oscillators in nature
- Time-variability of parameters presents an almost inevitable challenge

Cardio-respiratory interactions



- Questions raised
  - Why qualitative transitions exist (from 1:4 to 1:5 to 1:6 ratio, sync to no-sync)?
  - Is it because the frequency or the coupling parameter is time-varying?
  - Are the parametric and/or functional relationships influenced?

Main Concept

Phase time-series from noisy interacting oscillators

↓

Bayesian inferential framework

↓

Time-varying parameters

↙ ↓ ↘

Synchronization | Directionality | Coupling function

Phase dynamics and base functions

- When N-dimensional limit cycle oscillators $d\mathbf{x}_i/dt = \mathbf{f}_i(\mathbf{x}_i(t))$ interact weakly, it is common to describe their motion by their respective phase dynamics:

$$\dot{\phi}_i = \omega_i + f_i(\phi_i) + q_i(\phi_i, \phi_j) + \xi_i$$

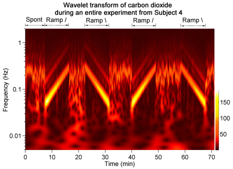
- Periodic solution $\rightarrow$ periodic base functions
- Fourier series to decompose both f_i and q_i:

$$f_i(\phi_i) = \sum_{k=-\infty}^{\infty} \tilde{c}_{i,2k} \sin(k\phi_i) + \tilde{c}_{i,2k+1} \cos(k\phi_i)$$

$$q_i(\phi_i, \phi_j) = \sum_{s=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} \tilde{c}_{i;r,s}\, e^{i2\pi r\phi_i} e^{i2\pi s\phi_j}$$

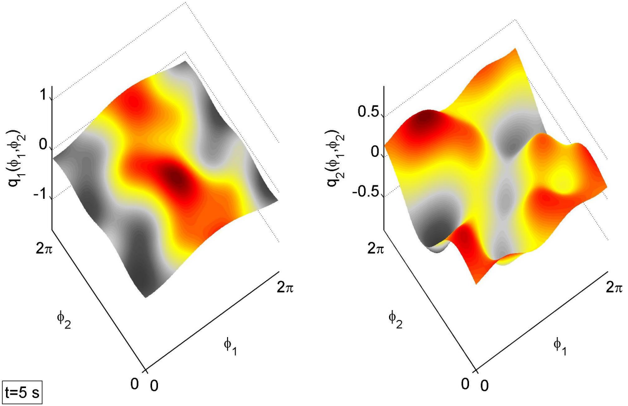
- Approximation to finite number K of selected Fourier terms:

$$\dot{\phi}_l = \sum_{k_i=-K}^{K} c_{k_i}^{(l)}\, \Phi_{l,k_i}(\phi_1, \phi_2) + \xi_l(t)$$



Stankovski, Duggento, McClintock, Stefanovska, Inference of time-evolving coupled dynamical systems in the presence of noise, *Phys Rev Lett* **109**: 024101, 2012.

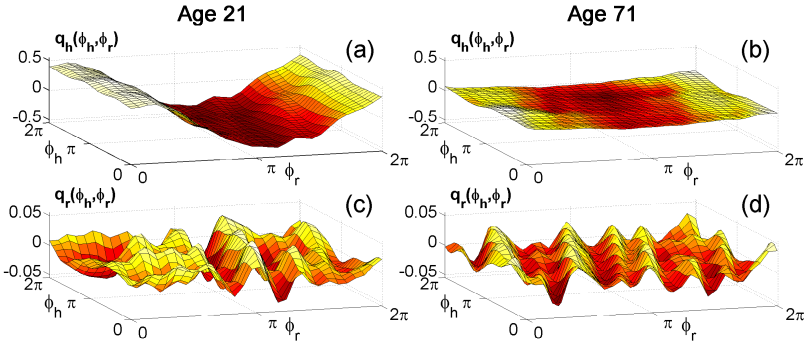
Time-evolution of coupling functions from cardio-respiratory interactions



Coupling function

$$\dot{\phi}_h = \omega_h + q_h(\phi_h, \phi_r) + \xi_h$$
$$\dot{\phi}_r = \omega_r + q_r(\phi_h, \phi_r) + \xi_r$$

Time-averaged coupling function of heart (q_h) and respiration (q_r)



The heart coupling function is dominated by RSA, which decreases with age, whereas the respiratory coupling function seems to be irregular and unaffected by age.

Iatsenko *et al*, Evolution of cardio-respiratory interactions with age, *Phil Trans A*, accepted.

Chronotaxic systems

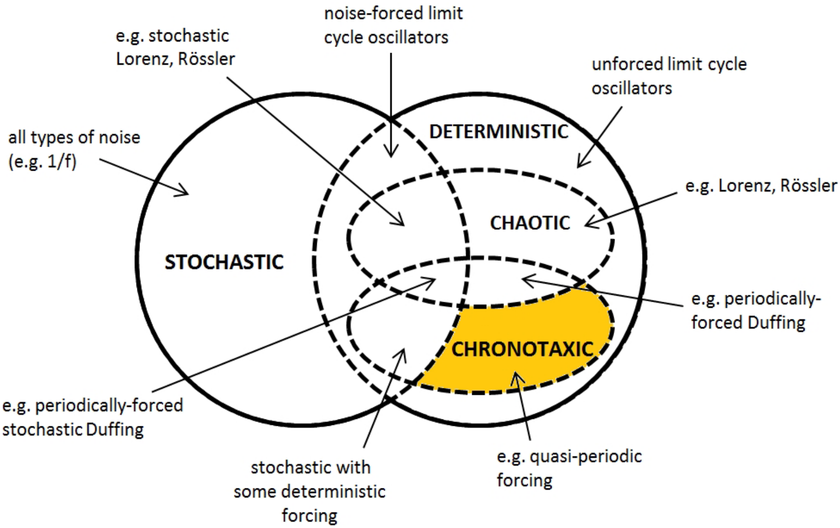
We have identified a new family of dynamical systems: self-sustained oscillators subject to deterministic (periodic) parametric modulation –

- **Chronotaxic systems:**
  - From *chronos* (time) + *taksi* (order, class)
  - Deterministic
  - Explicitly time-dependent
  - Non-chaotic
- **Mathematically:**

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}(\mathbf{t_0}), t_0, t)$$

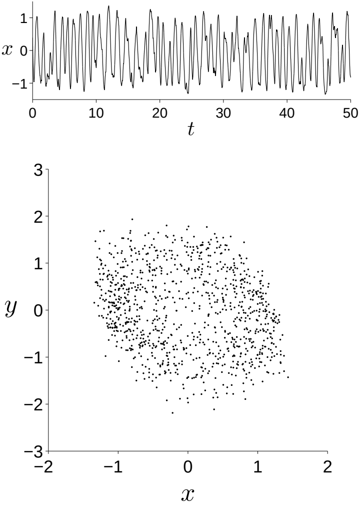
  The additional dependence on t_0 is the defining characteristic.
- **Nature** abounds with chronotaxic systems
- Observed also in **physical systems**: similar, reproducible dynamics have been measured in the currents of surface state electrons on liquid helium.

Physical context of chronotaxic systems

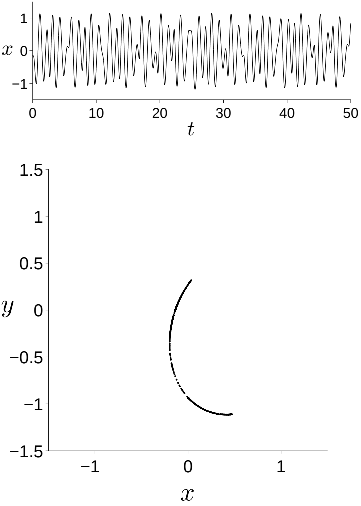


Stochastic versus chronotaxic

Stochastic forcing

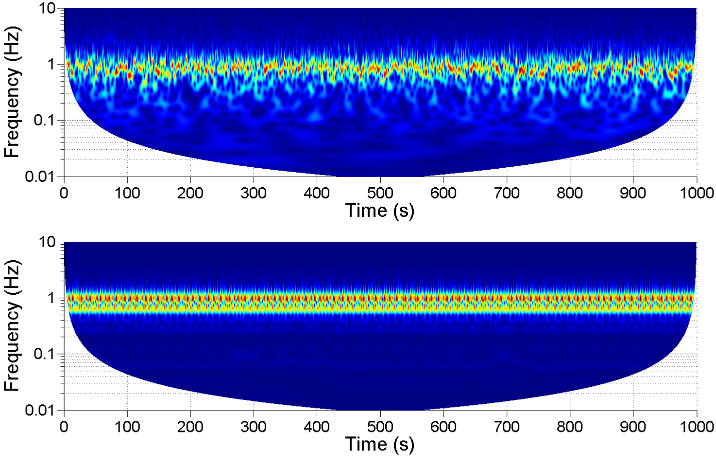


Quasi-periodic forcing



Inverse problems

When given only a single time series from a chronotaxic system, a time-dependent representation can reveal the hidden limit cycle behaviour and stability of the system parameters.



Stochastic

forcing

Quasi-periodic

forcing

Chronotaxic systems

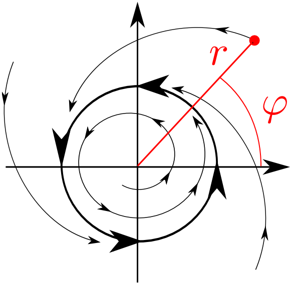
- The time-dependent perturbations of a self-sustained oscillatory system can result in a complex dynamics.
- Under such perturbations the stability evident in the unperturbed limit cycle may be lost.
- However the chronotaxic systems are able to retain their stability through the time dependent adjustments of the initial limit cycle.

Limit cycle

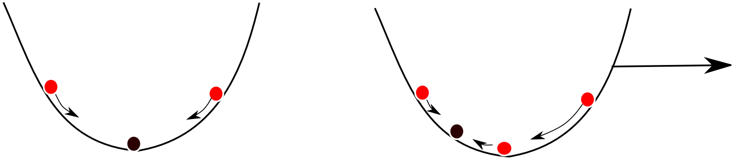
- Limit cycle in autonomous systems.
  Example 1:

$$\begin{cases} \dot{r} = 2 - r \\ \dot{\varphi} = \omega_0 \end{cases}$$

Limit cycle $r^* = 2$.



- Under the time-dependent perturbation limit cycle becomes time-dependent, if limit cycle still exists.



The time-dependent adjustments of the limit cycle

- Example 2:

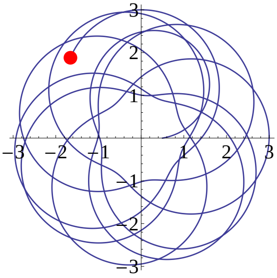
$$\begin{cases} \dot{r} = 2 - r + F(t) \\ \dot{\varphi} = \omega_0 \end{cases}$$

Time-dependent perturbation:
$F(t) = \sin(\sqrt{2}t) + \sqrt{2}\cos(\sqrt{2}t).$

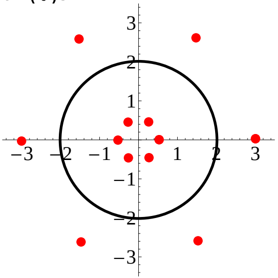
Time-dependent limit cycle:

$$r^*(t) = 2 + \sin(\sqrt{2}t).$$

Typical trajectory:



If using $r^*(t)$:



Summary

- Chronotaxic systems are not new (they also fall under old categories, e.g. *non-autonomous*).
- But they have certain features which allow us to put them in a separate class that we now define.
- Chronotaxic systems retain their stability. When perturbed, their limit cycles are not destroyed but can instead become time-dependent.
- Instead of the traditional view of this type of dynamics as stochastic, we now propose a new class of systems that categorizes them as deterministic.

Summary continued

- Benefits for theory: once we are aware that chronotaxic systems may exist, it is reasonable to improve the existing descriptions of systems with time-dependent limit cycles, e.g.
  - the identification of time-dependent limit cycles and corresponding parameters,
  - amplitude and phase separation.
- Benefits for inverse problem approach: avoid misinterpreting these systems as stochastic; further develop appropriate methods to capture their time variability.