**RESETTING AND ENTRAINING BIOLOGICAL OSCILLATORS:**
**QLSC 600: Module 1 Notes**

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# 1 Course Outline and Information

We are happy to have the opportunity to help you learn about the field of nonlinear dynamics with applications to the understanding of resetting and entraining of biological oscillators. This is a small class and the people in the class have very different backgrounds from each other. We will try to structure the class so that everyone can get something that would be interesting and useful to them. By the end of the module everyone should have some basic functional knowledge about how mathematics has been applied to study biological oscillators. This means you should be able to read an article that has some technical mathematical aspects with understanding of the goals and conclusions.

Basic knowledge includes understanding the concept of iteration as applied to simple maps, e.g. expressions of the form $x_{t+1} = f(x_t)$, understanding how first and second order linear ordinary equations are used in biology, understanding the concept of the phase space and how it can be used to analyze nonlinear differential equations modeling biological systems. These topics are included in Chapters 1-5 of Daniel Kaplan and Leon Glass, *Understanding Nonlinear Dynamics*, Springer 1988. A much more condensed summary of the same material is in Chapter 2 of *Nonlinear Dynamics in Physiology and Medicine* ed. by Anne Beuter, Leon Glass, Michael C. Mackey, Michèle S. Titcombe, Springer, 2003 [3]. These books should be available online to all McGill students and staff with library privileges.

For the first class on September 7, please read the Nature Review article from 2001 [4]. On Monday, September 6 before 5PM, please send us one question related to this article that you think needs to be explained better, or that would be worthy of discussion. In the class on September 7, we will discuss this article and the questions you raise.

The second class on September 9 will be a bootcamp on differential and difference equations. These topics are too vast to cover in detail, and so this session will be a broad overview with some biological examples and exercises in Matlab. The bootcamp will require you to have Matlab installed and running on your personal computer.

For the third class on September 14, we will then introduce the concept of phase resetting of biological oscillations and how phase resetting experiments can be used to predict the effects of periodic stimulation using difference equations. This will lead naturally to an introduction of the projects for this section of the course. Students will be asked to self-organize into small groups working on the different projects listed later on. Our hope is that students with a stronger mathematics or computer science background will gravitate towards some of the more advanced projects. Also, that students with a weak background will pair with students with a stronger background. Several of the projects are sufficiently novel that strong results would be appropriate for publication. The projects should be written up briefly. Students should indicate the contribution of each team member.

For the fourth class on September 16, we will do an in-class problem involving a difference equation. No preparation is necessary for this. It will just require some knowledge of basic high school level math. We will then investigate a difference equation that describes modulated parasystole–a type of cardiac arrhythmia.

For the fifth class on September 21, we will be doing computer lab exercises (see below), which will require Matlab on your computer as well as the codes found at

`http://cube.cnd.mcgill.ca/ebook/index.html`

The codes in their current form should be simple enough to run without knowledge of Matlab. Exercises will require improving and revising the code, which can be done in Matlab or your favourite programming language. This computer code can also form the starting point for some of the group projects.

The last three classes will be finalized and organized depending on progress made, deficiencies identified and desires expressed in the initial classes. Presentations of the projects will be done in these classes - schedule to be determined.

Topics in these classes will include information about differential equations, resetting oscillations, entraining oscillations. Background material is in Chapters 2 and 5 in book [3]. Part of the classes will be doing exercises selected from a variety of sources. Computer exercises and projects could be carried out using any code that you are familiar with.

## 2 Grading

Since there are so many different starting levels for people in the class, grading based on accomplishments on an absolute scale would be difficult. Grading will be done on a passfail basis. All are expected to show up and participate in the classes. All are expected to participate in working on the project and contributing to the oral and written presentations. Oral presentations will take place during classes 7 & 8 and the write-up will be due on October 5. Projects involving more than one individual must include a section in the write-up that states the contributions made by each individual. Let us know of any difficulties as they arise.

# 3 Computer Laboratory Exercises

## 3.1 Laboratory 1. Iteration of one-dimensional finite-difference equations

This gives instructions for running the programs to study the quadratic map

$$x_{i+1} = \mu(1 - x_i)x_i \tag{1}$$

using Matlab. There are 4 programs.

- **quadratic(xzero,mu,niter)** This program iterates the quadratic map. There are three input arguments: **xzero** is the initial condition; **mu** is the bifurcation parameter in Eq. 1; **niter** is the number of iterations. The output is a vector **y** of length **niter** containing the iterated values.

- **testperiod(y,epsilon,maxper)** This program determines if there is a periodic orbit in the sequence given by the vector **y** whose period is less than or equal to **maxper**. The convergence criterion is that two iterates of **y** are closer than **epsilon**. The output is the period **per**. If no convergence is found the output is **-1**.

- **bifurcation(mubegin,muend)** This plots the bifurcation diagram for 100 steps of $\mu$ between **mubegin** and **muend**.

- **cobweb(xzero,mu,nstep)** This program iterates the quadratic map. There are three input arguments: **xzero** is the initial condition; **mu** is the parameter; **nstep** is the number of iterations for which you will compute the cobweb.

### 3.1.1 How to run the programs

The following steps give an illustration example of how to run these programs.

1. Open up a Matlab window. All instructions are carried out in this window.

2. To generate 100 iterations of the quadratic map with an initial condition of $x_1 = 0.5$, $\mu = 3.973$ type
`y=quadratic(0.5,3.973,100);`

3. To plot the time series from this iteration type
`plot(y,'+');`

4. To determine if there is a period of length less than or equal to 20 with a convergence of 0.00001 of the time series **y** type
`per=testperiod(y,.00001,20);`
In this case there is no period and the program returns **per**$= -1$. If a value $\mu = 3.2$ had been used to generate the time series in the quadratic program, the program testperiod returns a value of **per**$= 2$.

5. To plot a cobweb diagram for the quadratic map with an initial condition of **xzero=0.3** and $\mu = \mathbf{3.825}$ with 12 steps, type
`cobweb(0.3,3.825,12);`

### 3.1.2 Exercises

Find a parameter values for the quadratic map that give a steady state that is approached without oscillation. Find a parameter value that gives a stable period 2 orbit. Find a parameter value that gives a stable period 3 orbit. Find a parameter value that gives a stable period 4 orbit. Find a parameter value that gives an aperiodic orbit. For each give the cobweb diagram and a time series.

## 3.2 Laboratory 2. Geometry of Fixed Points in Two-Dimensional Maps

This laboratory enables you to generate correlated random dot patterns. The laboratory is based on observations made in following papers.

Glass, L. Moiré effect from random dots. Nature 223, 578-580 (l969); Glass, L., R. Perez. Perception of random dot interference patterns. Nature 246, 360-362 (l973).

The programs show a random pattern of 400 dots superimposed on itself following a rescaling **a** in the $x$ coordinate, **b** in the $y$ coordinate, and a rotation by the angle $\theta$. There is a fixed point at $x = y = 0$.

This transformation is given by the equations

$$x' = ax\cos\theta - by\sin\theta \tag{2}$$

$$y' = ax\sin\theta + by\cos\theta \tag{3}$$

The eigenvalues of this transformation are given by

$$\lambda_{\pm} = \frac{(a+b)\cos\theta \pm \sqrt{(a-b)^2 - (a+b)^2\sin\theta}}{2} \tag{4}$$

The eigenvalues of this transformation can be related to the geometry of the transformation in the neighborhood of the fixed point at $x = y = 0$. If the eigenvalues are complex numbers, the fixed point is a focus, if the eigenvalues are real and are both inside or outside the unit circle, the fixed point is a node, if the eigenvalues are real and one is inside the unit circle, and the other is outside the unit circle, the fixed point is a saddle. If the eigenvalues are pure complex the fixed point is a center.

There is one program.

- **dots(a,b,thetam,numb)**. This program generates 400 random dots and **numb** iterates of each of these dots using the transformation above. (Use 4 iterates for better visualization but a single iterate would also suffice if it were possible to make big dots.) The dots are plotted, and the eigenvalues of the transformation are given underneath the figure.

### 3.2.1 How to run the program

The following steps give an illustration example of how to run these programs.

1. Open up a Matlab window. All instructions are carried out in this window.

2. To display a plot with $a = 0.95$, $b = 1.05$, and $\theta = 0.4/\pi$ type

```
dots(0.95,1.05,0.4/pi,4);
```

### 3.2.2 Exercises

You may wish to see what happens for particular values of the parameters. Try to find parameters that give centers, focuses, nodes, and saddles. Try increasing the angle of rotation until you can no longer perceive the geometry of the transformation. Can you predict theoretically the critical parameters that destroy your ability to perceive the geometry? If so, this might be a good result in the field of visual perception.

Here is a problem. In general, it should be impossible to find a bifurcation from a saddle to a focus except in exceptional cases. Consider the bifurcations observed with $a = 0.95$, $b = 1.05$ as $\theta$ varies. Is there a direct bifurcation from a saddle to a focus? Try to determine this by looking at the pictures and analytically. Which is simpler and which is more informative?

## 3.3 Laboratory - Resetting curves for Poincaré oscillator

One of the simplest models of a limit cycle oscillation is the Poincaré oscillator. The equations for this model are

$$\begin{aligned} \frac{dr}{dt} &= kr(1-r), \\ \frac{d\phi}{dt} &= 2\pi, \end{aligned} \tag{5}$$

where $k$ is a positive parameter. Starting at any value of $r$, except $r = 0$, there is an evolution until $r = 1$. The parameter $k$ controls the relaxation rate. In this laboratory we consider the relaxation in the limit $k \to \infty$.

There are two programs in this laboratory.

- **resetmap(b)** This program computes the resetting curve (new phase versus old phase) for a stimulus strength **b**. The output is a matrix with 2 columns and 102 lines. There are two points just less than and just greater than $\phi = 0.5$. These points are needed especially for the case where $b > 1$.

- **poincare(phizer,b,tau,niter)** This program does an iteration of the periodically stimulated Poincaré oscillator, where `phizer` is the initial phase, **b** is the stimulation strength, **tau** is the period of the stimulation, and **niter** is the number of iterations. It is valid for $0 < \tau < 1$. The output consists of two arrays. `phi` is is a listing of the successive phases during the periodic stimulation. `beats` is a listing of the number of beats that occur between successive stimuli.

### 3.3.1 How to run the programs

1. Open a Matlab window. All the instructions are carried out in this window.

2. To compute the resetting curve for $b = 1.10$, you type
   `[phi,phiprime]=resetmap(1.10);`

3. To plot out the resetting curve just computed type
   `plot(phi,phiprime,'*')`

4. To simulate periodic stimulation of the Poincaré oscillator type
   `[phi,beats]=poincare(.3,1.13,0.35,100);`

   This will generate two time series of 100 iterates from an initial condition of $\phi = 0.3$, with $b = 1.13$ , and $\tau = 0.35$. The array `phi` is the successive phases during the stimulation. The array `beats` is the number of beats between stimuli.

5. To display the output as a return map, type
   `plot(phi(2:99),phi(3:100),'*')`

   This plots out the successive phases of each stimulus as a function of the phase of the preceding stimulus. The points lie on a one-dimensional curve. The dynamics in this case are chaotic. In fact, what is observed here is very similar to what is actually observed during periodic stimulation of heart cell aggregates described in the first lecture of the course.

6. To display the number of beats between stimuli, type
   `plot(beats,'*')`

7. The rotation number gives the ratio between number of beats and the number of stimuli during a stimulation. This is the average number of beats per stimulius. To compute the rotation number type
   `sum(beats)/length(beats)`

### 3.3.2 Exercises

Try the following exercises.

1. Use the program **resetting** to compute the resetting curves for several values of **b** in the range from 0 to 2. In particular determine the value of **b** at which the topology of the resetting curve changes.

2. Determine whether or not the successive iterates of `phi` are periodic assuming different value of **(b,**$\tau$**)** (use program `testper`). (i) What do you find for different values of $b$ and $\tau$? What is the ratio of the number of stimuli to the number of action potentials? (ii) Find values for which there are different asymptotic behaviors depending on the initial condition? (iii) Find values that give quasiperiodic dynamics (for nonzero **b**) (iv) Can you find a period-doubling route to chaos?

Do you agree that it is important to understand this example as well as the ionic mechanisms of heart cell aggregates to understand the effects of periodic stimulation of the aggregates?

# 4 Computer Projects

## 4.1 Project 1: Compute Feigenbaum's number

Feigenbaum's number is defined as follows. Call $\Delta_n$ the range of $\mu$ values that give a period $n$ orbit. Then Feigenbaum found that in a sequence of period-doubling bifurcations

$$\lim_{n\to\infty} \frac{\Delta_n}{\Delta_{2n}} = 4.4492\ldots$$

The constant, 4.6692 ... is now called **Feigenbaum's number**.

According to Feigenbaum, he initially discovered this number by carrying out numerical iterations on a hand calculator. As the period of the cycle gets longer, the range of parameter values over which a given period is found gets smaller. Therefore, it is necessary to think carefully about what is involved in the calculation. Try to numerically compute

$$\frac{\Delta_8}{\Delta_{16}}$$

and

$$\frac{\Delta_6}{\Delta_{12}}.$$

You will want to vary $\mu$ over a range of values. How should you locate the value of $\mu$ where the period changes?

The behaviors found for the quadratic map here are also found in other simple maps, complicated equations, and a variety of experimental systems. It is this **universal** behavior that has attracted the attention of physicists and others.

By making appropriate modifications in the Matlab programs, you can adapt the programs so that they carry out similar computations for the single-humped sine map

$$x_{i+1} = \mu \sin(\pi x_i), \tag{6}$$

where $0 < \mu < 1$.

## 4.2 Project 2: Entrainment zones for modulated parasystole

Parasystole describes an arrhythmia whereby an ectopic pacemaker competes with the sinus pacemaker for control of the heart. In the case of modulated parasystole[12], the electrical propagation from the sinus node resets the ectopic pacemaker, according to some phase response curve.

Let $t_s$ be the period of the sinus pacemaker, $t_e$ be the period of the ectopic pacemaker, $\phi_i$ be the phase of the $i$th sinus beat in the ectopic cycle, and $\theta$ be the refractory period of the heart. Then the phase of the $(i+1)$th sinus beat is given by

$$\phi_{i+1} = \begin{cases} \phi_i + \frac{t_s}{t_e} \text{ (mod1)} & 0 \le \phi_i < \frac{t_s-\theta}{t_e} \\ \phi_i - f(\phi_i) + \frac{t_s}{t_e} \text{ (mod1)} & \frac{t_s-\theta}{t_e} \le \phi_i < 1 \end{cases} \tag{7}$$

where $f(\phi_i)$ is the phase response curve. The value of the phase response curve $f(\phi_i) = T/t_e$ where $T$ is the perturbed ectopic cycle length.

(i) Write down the phase response curve $f(\phi)$ that results in pure parasystole. Verify that in the case Eqn. 7 corresponds to pure parasystole.

(ii) Describe the impact of sinus beats on the ectopic cycle length in the case where $f(\phi) = \phi$. Consider the case where the phase response curve takes the piecewise linear form

$$f(\phi) = \begin{cases} k\phi + 1 & 0 \le \phi < \phi_c \\ k(\phi - 1) + 1 & \phi_c \le \phi < 1, \end{cases} \tag{8}$$

where $k$ represents the 'strength of modulation' and $\phi_c$ is the phase at which the sinus beat changes from lengthening the ectopic cycle to shortening the ectopic cycle.

(iii) Make a cobweb plot for the difference equation (Eqn.7) using the parameters $t_s = 0.64$, $t_e = 1.5$, $\theta = 0.4$, $k = 0.4$, $\phi_c = 0.5$. Try different initial conditions for $\phi$. Do the dynamics converge to a limit cycle, and if so what is the period of this cycle? What sequence of sinus vs. ectopic beats does this correspond to in the heart?

(iv) Investigate how these dynamics depend on the sinus cycle length $t_s$ and the phase resetting strength $k$. For example you could plot the period, or the ratio of ectopic beats to sinus beats, as a function of these parameters.

## 4.3 Project 3: Coupling interval variability in ECG records

This project uses ECG beat-to-beat interval data which will be posted on shared Dropbox. The data must not be shared outside of this course.

The coupling interval of a PVC is the time elapsed between a PVC and the preceding sinus beat. The variability of the coupling interval can provide insight into the mechanism of the underlying PVCs–high variability is often regarded as parasystole, whereas low variability is generally considered to be due to reentry or triggered activity [13]. In this project, participants will investigate the coupling interval variability among patients in the PVC cohort. What proportion of the cohort show a fixed vs. a variable coupling interval? How does the coupling interval variability in this cohort compare to that of specific pathologies analysed in de Vries et al.[13]?

## 4.4 Project 4: Coupling interval as a function of heart rate in ECG records

Investigate how the coupling interval (see project 3) varies as a function of heart rate? Heart rate can be approximated using the average interval between beats over some time window.

## 4.5 Project 5: PVC frequency as a function of heart rate

A standard treatment for frequent PVCs is a beta-blocker prescription. However a recent study[14] has shown that this treatment is not effective in all individuals. In particular, patients with a positive correlation between heart rate and PVC frequency were found to benefit from beta-blockers, whereas those with no or negative correlation received no benefit.

In this project, participants will investigate how PVC frequency varies as a function of heart rate in the PVC cohort. How many patients show correlation between these variables, and how does this compare to the patient numbers found in Hamon et al[14]? Which patients are most likely to benefit from beta-blockers?

# 5 Very Theoretical Projects

**For students with an interest in phase locking, we suggest research level problems. Students require advanced knowledge of nonlinear dynamics and strong computer skills to make progress on these problems. Please feel free to discuss these problems with us.**

Interaction of biological oscillations with periodic inputs represent a fundamental problem that recurs in many contexts [4]. Our group has studied the effects of periodic stimuli on the heart [6, 7, 5, 8]. Several years ago, I worked with N. Q. Balaban at the Hebrew University who has studied the correlations of the cell cycle time between mother and daughter cells [1, 11].

I suggest two projects, but many aspects of the first project have been published in collaboration with Wilson Façanha and B. Oldeman [9]. The second relates to the work of Balaban and collaborators. If you make sufficient progress on the numerics, I could suggest directions that we still do not understand very well, where good new results (especially if they have new analytic insights) would be worthy of publication.

### Project A. Entraining the 2D Poincaré Oscillator

Perhaps the simplest ordinary differential equation that has been used to model biological oscillations is the Poincaré oscillator (AKA the Radial Isochron Clock) [7, 5, 8]. In a polar $(r, \phi)$ coordinate system, the equations for this system are:

$$\frac{dr}{dt} = kr(1-r), \qquad \frac{d\phi}{dt} = 2\pi \tag{9}$$

The model for resetting the oscillator is to apply a $\delta$ function stimulus to the state point leading to an instantaneous increase of the $x$-coordinate by a magnitude $b$. Following the stimulus, the equations of motion take over and the analytic formula for the trajectory therefore be computed. Consequently, if a stimulus is given when the system is at state point $(r', \phi')$ we have

$$\begin{aligned} r'_i &= (r_i^2 + b^2 + 2br_i \cos 2\pi\phi_i)^{1/2}, \\ \phi'_i &= \frac{1}{2\pi} \arccos \frac{r_i \cos 2\pi\phi_i + b}{r'_i}. \end{aligned} \tag{10}$$

where $(r'_i, \phi'_i)$ are the coordinates immediately after the stimulus.

Consider periodic stimulation with a time interval of $\tau$ between stimuli. There are many different dynamical behaviors possible. One is called phase locking in which there are $N$ cycle of the stimulus for each $M$ cycles of the oscillator. But there can also be chaotic dynamics or quasiperiodic dynamics. The different dynamics are found for different ranges of the frequency and amplitude of the periodic $\delta$ function pulse.

The effects of periodic stimulation can be represented as a 2D map.

$$\begin{aligned} r_{i+1} &= \frac{r'_i}{(1-r'_i)\exp(-k\tau)+r'_i}, \\ \phi_{i+1} &= \phi'_i + \tau (\text{mod } 1). \end{aligned} \tag{11}$$

Your project is to compute the different locking regions as a function of $(k, b, \tau)$. What is the maximum number of fixed points and periodic points possible for any choice of parameters? For what parameters and initial conditions is there chaos? Can you prove chaos? Considering the locking zones in $(b, \tau)$ for $k$ fixed. What is the organization of the zones for some fixed value of $k$ and how does picture evolve as $k$ increases. The results for $k$ infinite are in [7, 5, 8]. This is a fascinating research level problem that has been rarely studied. An early paper [5] left many questions open. A more recent paper answered some of them [9] but there is still a lot that could be done.

Algebraically, compute the boundaries (in the stimulus amplitude - stimulus period plane) along which the 1:1 phase locking rhythm of the Poincaré oscillator in the infinite relaxation limit ($k \to \infty$) loses stability and determine the type of bifurcation along the boundary.

Computer project. Determine the phase locking regions in the infinite relaxation limit ($k \to \infty$). Now do the same for the $k$ finite.

### Project B. Phase locking in fattened Arnold map

Balaban and colleagues [1, 11], proposed a model for the cell cycle that takes into account the cycle time of the mother cell and also the phase of another (for example the circadian) oscillator. It turns out that this model is the same with a change of variables to a model studied earlier called the fattened Arnold map [2].

The model for analysis is:

$$T_{n+1} = T_0(1-\alpha) + \alpha T_n + k \sin\left(\frac{2\pi t_{n+1}}{T_{osc}}\right) \tag{12}$$

$$t_{n+1} = T_n + t_n \tag{13}$$

where $T_n$ is the $n$th cycle time, $t_n$ is the actual time of the $n$th division, $\alpha$ is a parameter $[-1 \leq \alpha \leq 1]$ that gives the mother's influence on the daughter's cycle time, $0 < k < 1$ scales the strength of the periodic input. $T_{osc}$ is the period of the periodic input. When $\alpha = 0$ this is the degree 1 sine circle map as discussed for example in [4]. When $\alpha = 1$, the map is called the "standard map" which has been studied so much by physicists that it rates Wikipedia and Scholarpedia articles. Your job is to analyze the bifurcations in this map as a function of $T_0$, $k$ and $\alpha$. You might start with $\alpha = \pm 0.5$ and assume $T_{osc} = 24$ hours. The long-range goal would be to derive an analysis of the dynamics that takes into account the continuous changes in the locking zones and bifurcations in the space of 3 parameters similar to the type of analysis done for the problem in the first project [9].

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