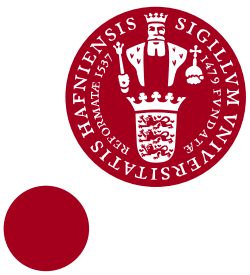
UNIVERSITY OF COPENHAGEN
FACULTY OF SCIENCE



Bachelor's Thesis

Mathematical Models of Biological Oscillators

Introduction to biological networks through a novel web app

Johan Nørregaard Andersen
Nanoscience

Supervisor

Thorsten Hansen
Department of Chemistry

Abstract

This article is a self-contained introduction to the mathematics and computation of biological networks in the lens of oscillatory behaviour. Implicit assumptions in typical models of biological networks are discussed. Oscillatory networks reviewed include the Lotka-Volterra equations and the Goodwin model. Bioscillators is a novel web app for exploring dynamics of biological networks. Many one- and two-dimensional networks can be fully analyzed on paper but most networks of three or more dimensions need computational simulation and visualization.

Contents

1 Introduction

A heart beats rhythmically and a neuron's voltage spikes in a constant interval. They both have a small pattern repeated in time with a controlled frequency. Biological oscillators are ubiquitous in nature and essential for life.

Do oscillators exist that are more important than hearts and neurons? Plants and prokaryotes don't have hearts and neurons. But they still share some biological rhythms with us. The cell cycle of a stem cell repeats oscillatory. And most organisms have self-sustained circadian[1] rhythms. In a period of 24 hours, an organism will undergo an oscillation between resting and excited. In fact, most of these organisms will continue to display their circadian behaviour even in the absense of an environment such as circadian oscillation of light or temperature. But in the absence of Zeitgebers,[2] the period drifts from 24 hours to a new constant period. So it's not just behaviour - the organism has an innate oscillator that is evolved for and entrains to Earth's spin oscillator. What's more, putting the organism in an artificial environment oscillating with 23 or 25 hours, it will entrain to that.[1]

Even single cells have a self-sustained circadian rhythm, expressed in oscillations of protein concentrations. Might the circadian oscillator happen at the scale of individual molecules? When the Belousov–Zhabotinsky reaction[2], the famous chemical oscillator, was first discovered, it was met with skepticism.[3] We will work our way towards understanding the intracellular circadian oscillator.

A historical pioneer of biological rhythm models was oscillations in populations. In environments where a predator has one main source of food, the population of both the predator and the prey will oscillate. We will see that we can write our models of population dynamics as chemical reactions. And chemical oscillations were met with skepticism 60 years ago, but harmonic oscillators are ubiquitous on the molecular level in modelling chemical bonds and rotations of molecules. So in order to understand the circadian rhythm, we will first look at population dynamics and then at the harmonic oscillator.

This article is written as a self-contained[3] introduction to biological networks and should be approachable with minimal prior knowledge on mathematical biology.

To aid the non-specialist in exploring biological networks, I have developed an accessible web application. The application is called Bioscillators and is available at `www.bioscillators.com`.

2 One-Dimensional Population Ecology

2.1 Birth is a chemical reaction

Consider the case of modelling the population size dynamics of a herd of rabbits. We classify this problem as one-dimensional as there is only one variable, the population size. The most important change the population can undergo is birth, which we write using chemical reaction notation[4]:

$$\mathrm{R} \xrightarrow{\mathrm{b}} \mathrm{R} + \mathrm{R} \qquad \{1\}$$

In this model, a rabbit R spawns a new rabbit with a birth rate b. Birth happens in a time interval given by the gestation period τ = about 31 days for rabbits. The birth rate can therefore be defined as $b = \tau^{-1}$, so b can also be thought of as a frequency (b = about once per 31 days).
If you introduce a few rabbits to a new environment with plenty of space and resources (or equivalently you might place some bacteria on a new agar plate or study virus spread in a newly infected area), Reaction 1 will be the dominating reaction determining population size in the beginning.
Other changes the population size might undergo include death by old age with rate d or death by a predator P with rate p. This can also be modelled in the language of chemical reactions:

$$\mathrm{R} \xrightarrow{\mathrm{d}}$$

$$\mathrm{R} + \mathrm{P} \xrightarrow{\mathrm{p}} \mathrm{P}$$

These reactions are surely important, and we'll return to those later. Because considering just Reaction 1 leads to essential insights about more complicated models as those models should converge to Reaction 1 in the limit of low population size in a bountiful environment.

[1] Circadian means "about a day". From Latin: circa/about + dies/day
[2] Light and temperature are examples of a "Zeitgeber" which is German for "time giver"
[3] Self-contained besides assuming some calculus and linear algebra
[4] Read Appendix I for a proper definition of how to read chemical reaction notation

The population size dynamics from Reaction 1 can be written as a differential equation. We let $R = R(t)$ denote the number of rabbits at time t. The time derivative of R is given by[5]:

$$\dot{R} = \frac{\mathrm{d}R}{\mathrm{d}t} = b \cdot R \tag{1}$$

As the rate of change of $R(t)$ is proportional to $R(t)$, the number of rabbits will grow exponentially, e.g. $R_0 = R(0) = 2 \rightarrow R(1\text{mo}) = 4 \rightarrow R(2\text{mo}) = 8 \rightarrow R(3\text{mo}) = 16 \rightarrow \ldots \rightarrow R(12\text{mo}) = 8192$.

Besides representing birth as a chemical reaction or a differential equation, it can also be represented graphically as a simple graph with just one node and one edge (Figure 1). The other biological networks discussed in this article can also be represented as graphs. Bioscillators, the web application developed for this project, uses an unambiguous graphical representation of networks as graphs.

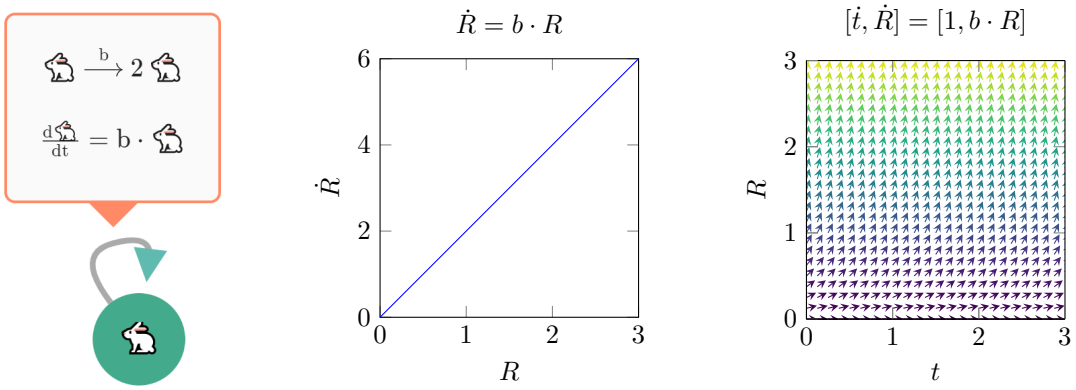


Figure 1: Different representations of exponential growth of rabbits: $\mathrm{R} \xrightarrow{\mathrm{b}} \mathrm{R} + \mathrm{R}$, $b = 2$
(Left) The representation from Bioscillators (Middle) $\dot{R} = b \cdot R$ (Right) R(t) as a vector field

2.2 Birth is not a chemical reaction

A lot of implicit assumptions is made when modelling animal birth (and death) as a chemical reaction. We'll discuss some of them explicitly here as the points extend to all models of biological networks.

According to Reaction 1 and Equation 1:

- Fractional rabbits exist.
  R is a continuous parameter, but in reality only an integer number of rabbits can exist One can restate the dynamics of a biological network to integer-valued variables if the rate constants are interpreted as probabilities that collapse stochastically.[4] This method can yield new insights for small population numbers, but at a cost of significantly increased computation time.

- Both males and females can give birth.
  This can be accommodated by assuming that the number of males equals the number of females and by letting R mean half of the real population size

- The litter size is always 1.
  In reality, a rabbit litter varies from 1-12. An easy solution to this problem is by only accounting for the average litter size, e.g. rewriting Reaction 1 to:

  $$\mathrm{R} \xrightarrow{\mathrm{b}} \mathrm{R} + 6\,\mathrm{R}$$

  This solution to the problem also encompasses miscarriage and maternal death as factors in determining the change of the population size, as those factors can be seen as merely changing the average outcome of the birth reaction.

[5] We use Newton's dot-notation for time derivatives: $\dot{x} = \frac{\mathrm{d}x}{\mathrm{d}t}$

- There is no evolution.
  Mathematically, this is incorporated in the constantness of the rate constants. Interesting phenomena occur for larger networks when letting the constants change over time.
- Rabbits are fertile their whole life.
  To accommodate this, we can adapt our model to include three types of rabbits: kittens, does and geriatrics, where only does are fertile:

$$\mathrm{R_{doe}} \xrightarrow{\mathrm{b}} \mathrm{R_{doe}} + \mathrm{R_{kit}}$$

$$\mathrm{R_{kit}} \xrightarrow{\mathrm{g_1}} \mathrm{R_{doe}} \xrightarrow{\mathrm{g_2}} \mathrm{R_{ger}}$$

  with realistic growth rates $g_1 = 6$ months and $g_2 = 4$ years.
- Birth happens instantly.
  Accommodating time delay in the outcomes of reactions is a general problem of modelling biological networks. A proposed solution[5] to this problem is rethinking Equation 1 to be a delay differential equation (where the gestation period $\tau \approx 31$ days):

$$\dot{R}(t) = b \cdot R(t - \tau)$$

  But this type of equation has a major mathematical drawback, namely that $\dot{R}$ is no longer just a function of the current state R. This means that phase plane analysis and other standard methods are out of the table. It also means that analytical solutions are pragmatically unapproachable. And in general, delay differential equations are unnecessary, as the same effect can be achieved by adding intermediate rabbit types, as we did in fixing the fertility problem (p is the pregnancy rate, and $\frac{1}{p} \approx$ a few days):

$$\mathrm{R_{doe}} \xrightarrow{\mathrm{p}} \mathrm{R_{pregnant}} \xrightarrow{\mathrm{b}} \mathrm{R_{doe}} + \mathrm{R_{kit}}$$

2.3 The only important analytical solution

We are seeking an analytical solution to Equation 1. That is, we want to determine the population size $R(t)$ as a closed-form expression without dynamics. This is easily done as Equation 1 has the form of the prototypical linear differential equation $\frac{\mathrm{d}x}{\mathrm{d}t} = x$. In fact, it is unavailing to seek a closed-form expression of more complicated biological networks than Reaction 1. Instead, we will always refer to the solution of this simple case. Start by doing a separation of variables:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = b \cdot R \tag{1}$$

$$\frac{1}{R}\,\mathrm{d}R = b\,\mathrm{d}t$$

Then integrate and rearrange:

$$\int \frac{1}{R}\,\mathrm{d}R = \int b\,\mathrm{d}t$$

$$\ln(R) = bt + c$$

$$R(t) = e^{ln(R)} = e^{bt+c} = e^c \cdot e^{bt}$$

Recognizing that $e^{bt} = 1$ for $t = 0$ we define $R_0 = R(0) = e^c$ and the final solution is

$$R(t) = R_0 \cdot e^{bt} \tag{1}$$

which is the exact form of what we qualitatively figured in subsection 2.1.

Consider the general case $\dot{x} = r \cdot x$. For $r > 0$ we get exponentially increasing solutions:

$$x(t) \propto e^t$$

And for $\dot{x} = r \cdot x$ with the rate $r < 0$ solutions are exponentially decreasing:

$$x(t) \propto e^{-t}$$

These general solutions are fundamental in linear stability analysis as we will see in subsection 3.2 and they can readily be generalized to higher dimensions as we see in subsection 3.4 and for complex rates in subsection 3.5.

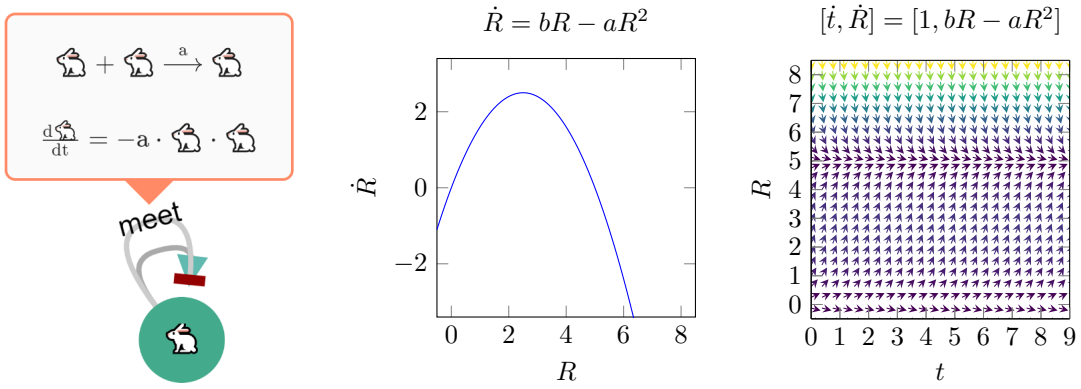


Figure 2: Different representations of logistic growth of rabbits:
$\mathrm{R} \underset{\mathrm{a}}{\overset{\mathrm{b}}{\rightleftharpoons}} 2\,\mathrm{R}\,,\ b = 2,\ C = 5 \implies a = 0.4$
(Left) Bioscillators. The edge without a chat bubble represents the edge from Figure 1
(Middle) $\dot{R} = bR(\frac{C-R}{C})$ (Right) R(t) as a vector field

2.4 Exponential population growth is unsustainable

If you enclose your rabbits on a field with a fence, they will have limited space and food. If we consider just the case of limited space, it is clear that the population will not continue growing exponentially, but eventually reach a limit determined by the area. We have now defined a different system than the pure unbounded system from Reaction 1, and this new system also has a defining reaction and dynamical equation, which are yet to be determined:

$$\mathrm{R} \longrightarrow ? \qquad \{2\}$$

$$\dot{R} = ? \qquad (2)$$

It is possible to to determine Reaction 2 and Equation 2 by just following the definitions. We call the maximum population size, permitted by the area, the carrying capacity C. If the population size reaches the carrying capacity, the population size is unchanging. We denote this $R^* = C$ and call it a fixed point of Equation 2. This fact can be stated as:

$$R = R^* = C \implies \dot{R} = 0$$

Recall Equation 1: $\dot{R} = bR$. Equation 2 should approach Equation 1 for $R \ll C$. We want to modify Equation 1 in a way that keeps $\dot{R} = bR$ for $R \ll C$ but approaches $\dot{R} = 0$ as $R \to C$. A way to accomplish this is to multiply the right hand side by a function $f(R)$ which has the properties that $f(C) = 0$ and $f(R) = 1$ for $\frac{R}{C} \to 0$. The simple difference $(C - R)$ has the property that $(C - R) = 0$ for $R = C$. We then recognize that $f(R) = \frac{C-R}{C} = 1 - \frac{R}{C} \to 1$ as $\frac{R}{C} \to 0$. We have found the simplest function that obeys our limits. In conclusion we now have a full expression for Equation 2:

$$\dot{R} = bR(\frac{C - R}{C}) \qquad (2)$$

With this equation we can also see what happens if the population size starts above the carrying capacity ($R_0 > C$). Then the change in population size $\dot{R}$ is negative as $(C - R_0)$ is negative. The system approaches $R^* = C$ for both $R_0 > C$ and $R_0 < C$.

To derive Reaction 2, we rewrite Equation 2 into a production term and a decay term.

$$\dot{R} = bR - \frac{b}{C}R^2 = bR - aR^2 \qquad (2)$$

with $a = \frac{b}{C} < b$. Equation 2 on this form gives another intuition for the system. Notice first that for sufficiently small $R \implies R^2 < R \implies aR^2 \ll bR$ as $a < b$ so the decay term is negligible and we're back at Equation 1. And as R increases, the decay term will grow until $\dot{R} = 0$ when $aR^{*2} = bR^* \implies R^* = \frac{b}{a} = C$.

We can apply the law of mass action "backwards" and write two corresponding reactions up for Equation 2. We know the production term $\dot{R} = bR$ comes from Reaction 1:

$$\mathrm{R} \xrightarrow{\mathrm{b}} \mathrm{R} + \mathrm{R}$$

The decay term $\dot{R} = -aR^2$ is proportional to R twice, which means R occurs twice as a reactant. And the stoichiometric difference is one (if it is not absorbed in a), so the decay reaction is:

$$\mathrm{R} + \mathrm{R} \xrightarrow{\mathrm{a}} \mathrm{R}$$

This reaction is intuitive if you imagine that, as R increases towards C, two individuals R have a higher chance of occupying the same space, which kills one of those individuals. We might then call a the decongestion rate. We can combine these two reactions to one single Reaction 2:

$$\mathrm{R} \underset{\mathrm{a}}{\overset{\mathrm{b}}{\rightleftharpoons}} 2\,\mathrm{R} \tag{2}$$

From this we can apply steady-state kinetics[6] to check our sanity. Reaction 2 has an equilibrium constant $K_C = \frac{b}{a} = \frac{R^2}{R}$ from which we get the expected $R^* = \frac{b}{a} = C$.

3 Theory of Dynamical Systems Analysis

3.1 First-order and autonomous

We are mainly interested in analysing first-order autonomous systems, generally written[7]:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) \tag{3}$$

where $\mathbf{x}$ is a set of dynamical variables that interacts with each other. Equation 3 means that the change of the state of the system is only dependent on the current state (autonomous or time-independent). The change of the state is not dependent on any previous state and there is no dependence on what time it is. Time dependence can be thought of as something external acting on the system. Entrainment of the intracellular circadian oscillator is an example of this. Furthermore, Equation 3 means that every variable is modelled as being localized in space or homogeneously distributed so there is no spatial dependence, i.e. the spatial derivative is zero everywhere.

But why are we restricting ourselves to first-order systems? The canonical harmonic oscillator (Equation 7: $\ddot{x} + x = 0$) is second-order and one-dimensional but not of the form of Equation 3. Why not include this in our treatment of oscillations? We will look at the harmonic oscillator shortly but justify here why we are only concerned with systems of the form of Equation 3. A mechanical system such as the harmonic oscillator has galilean relativity, i.e. positions (x) and velocities ($\dot{x}$) are dependent on your frame of reference. This is partly the reason why knowing the forces on a mechanical system yields the accelerations ($\ddot{x}$). In contrast, variables such as population size or chemical concentration has no galilean relativity. The number of rabbits is independent on your frame of reference. And chemical reactions only specify the first-order change of chemical concentrations.

3.2 Linear stability in one dimension

In subsection 2.4 we informally introduced stability analysis by showing that for Equation 2 $R = R^* = C$ is stable because $\dot{R} < 0$ for $R > C$ and $\dot{R} > 0$ for $R < C$, i.e. a perturbation from the stable point results in $R(t)$ going back towards the stable point.

We will now introduce stability analysis more generally. Consider the general one-dimensional dynamical system:

$$\dot{x} = f(x) \tag{4}$$

with fixed points x^* defined by $\dot{x} = 0$. A fixed point may be either stable or unstable and the stability can be found by considering a perturbation from the fixed point $\Delta x(t) = x(t) - x^*$. Will the perturbation grow or decay? This respectively means that the fixed point is unstable or stable. To see what happens with the perturbation we differentiate:

$$\dot{\Delta x} = \frac{\mathrm{d}}{\mathrm{d}t}(x - x^*) = \dot{x} = f(x)$$

[6] Review Appendix I for a definition of the equilibrium constant

[7] The bold font indicates a vector, i.e. $\mathbf{x} = (x_1, ..., x_n)$

because $\dot{x}^* = 0$. We can Taylor expand around the fixed point[8]:

$$f(x) = f(x^* + \Delta x) = f(x^*) + f'(x^*) \cdot \Delta x + \dots$$

where we stop the expansion here already because we're only interested in the linear stability. Linear stability is insufficient if $f'(x^*) = 0$ but we won't consider that here.

Using $f(x^*) = 0$ we get:

$$\dot{\Delta x} \approx f'(x^*) \cdot \Delta x \tag{5}$$

This is the prototypical linear differential equation and we know from subsection 2.3 that the sign of $f'(x^*)$ determines whether Δx will exponentially grow or decay.

For the sake of generalisation to higher dimensions, we define the 1D-Jacobian a to be $a = f'(x^*)$ and see that $a < 0$ means that x^* is stable and $a > 0$ means that x^* is unstable.

This can also be seen in Figure 2, that the stable point $R^* = C$ has a negative slope. We can also now see that $R^* = 0$ has a positive slope and is an unstable point which means that introducing just a few rabbits in an empty field (perturbation from $R^* = 0$) gives exponential growth.

3.3 Oscillations are impossible in one dimension

We are still considering the general dynamical system of Equation 4: $\dot{x} = f(x)$. An oscillatory solution has the property that for some period $T > 0$: $x(t + T) = x(t)$ and $x(t + s) \neq x(t)$ for all $0 < s < T$. Assuming existence and uniqueness of solutions, oscillatory solutions are impossible for a first-order autonomous system.[6] We will not prove this rigorously here though refer to topological arguments. As we just saw, fixed points in one dimension can either be stable or unstable. That is, a perturbation from a fixed point ($\Delta x(t) = x(t) - x^*$) will either grow exponentially for unstable points or decrease exponentially for stable points. So as $t \to \infty$, $x \to \pm\infty$ or $x \to x^*$ for some stable fixed point x^*. This can be seen in the phase plots of Figure 1, Figure 2 and any other system you can imagine complying to Equation 3. Uniqueness of $\dot{x}$ given x means trajectories does not reverse direction. This is opposed to higher dimensions where $\dot{x}_i$ given x_i can take different values given different x_j, $j \neq i$.

3.4 Linear stability in two dimensions

In two dimensions Equation 3 can be represented as:

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y) \end{aligned}$$

Generalizing the arguments from subsection 3.2, a perturbation

$$\mathbf{\Delta x} = \mathbf{x}(t) - \mathbf{x}^* = \begin{pmatrix} \Delta x \\ \Delta y \end{pmatrix}$$

from a fixed point $\mathbf{x}^* = (x^*, y^*)$ has the linear stability:

$$\begin{aligned} \dot{\Delta x} &= \frac{\partial f(x^*, y^*)}{\partial x} \Delta x + \frac{\partial f(x^*, y^*)}{\partial y} \Delta y \\ \dot{\Delta y} &= \frac{\partial g(x^*, y^*)}{\partial x} \Delta x + \frac{\partial g(x^*, y^*)}{\partial y} \Delta y \end{aligned}$$

where $\dot{\Delta x}$ reduces to Equation 5 if the perturbation only has an x-component. It can be written in matrix notation as

$$\dot{\mathbf{\Delta x}} = \underline{A} \cdot \mathbf{\Delta x} \tag{6}$$

with the 2D-Jacobian

$$\underline{A} = \left[\begin{matrix} \frac{\partial f(x,y)}{\partial x} & \frac{\partial f(x,y)}{\partial y} \\ \frac{\partial g(x,y)}{\partial x} & \frac{\partial g(x,y)}{\partial y} \end{matrix} \right] \Bigg|_{\substack{x = x^* \\ y = y^*}}$$

[8] We use dot-notation for time derivatives and $f'(x) = \frac{\mathrm{d}f}{\mathrm{d}x}$

The type of the fixed point is now determined by the eigenvalues of $\underline{A}$ which luckily reduces to just the sign in 1D. Generalizing from one dimension: If both eigenvalues are negative, the fixed point is stable and if both eigenvalues are positive, the fixed point is unstable. But there are even more options in 2D. For a complete review of these options, [6] is referred to.

If $\underline{A}$ has eigenvectors $\mathbf{v}_i$ with corresponding eigenvalues λ_i, as Equation 6 is linear, we can generalize the analysis from subsection 2.3 to get

$$\mathbf{\Delta x(t)} = c_1\mathbf{v_1}e^{\lambda_1 t} + c_2\mathbf{v_2}e^{\lambda_2 t}$$

with c_i to be determined on a case by case basis.

The eigenvalues in 2D can have an imaginary component even though x, y, f and g are all real. We will now look at what this means.

3.5 The harmonic oscillator

Newton's second law states that the forces acting on an object determines the object's acceleration ($m \cdot a = F,\ a = \ddot{x}$). Hooke's law states that a perturbation from the equilibrium position of a spring will be counteracted by a force proportional to the perturbation ($F = -k \cdot x$ if the equilibrium is at $x^* = 0$). Combining this we have:

$$m \cdot a = F = -k \cdot x$$

It is called the harmonic oscillator because every perturbation $x_0 = x(0) \neq 0$ will direct the system back towards equilibrium, but overshoot, thereby directing the system the other way, ad infinitum. This model of a spring (most often with damping) is used for all sorts of other problems in physics and biology. This is fundamentally because it is a model of a quadratic potential, and every equilibrium potential is locally quadratic. It has the well-known textbook solution:

$$x(t) = x_0 \cdot cos(\omega t)$$

with $\dot{x}_0 = 0$, frequency $\omega = \sqrt{\frac{k}{m}}$ and an oscillation period of $T = \frac{2\pi}{\omega}$.
We will just analyze the general version of this problem so we let $\frac{k}{m} = 1$ and now have the canonical harmonic oscillator:

$$\ddot{x} + x = 0 \tag{7}$$

with the solution $x(t) = x_0 \cos(t)$ for a starting position x_0 and no starting velocity $\dot{x}_0 = 0$. This can actually be put on the form of Equation 3.[6] Let $x_1 = x$ and $x_2 = v = \dot{x}$. We have $\dot{x} = v$ and $\dot{v} = \ddot{x}$. And $\ddot{x} = -x$ by Equation 7 so therefore we have:

$$\begin{pmatrix}\dot{x}\\ \dot{v}\end{pmatrix} = \begin{pmatrix} v \\ -x\end{pmatrix} = \begin{bmatrix}0 & 1\\ -1 & 0\end{bmatrix} \cdot \begin{pmatrix}x\\ v\end{pmatrix} \tag{8}$$

Even though the harmonic oscillator is second-order one-dimensional, we now have it on the form of first-order two-dimensional (and linear). We can now analyze this problem with linear stability analysis and phase plot analysis.

How can we understand in this framework that this system yields oscillatory behaviour?
The only fixed point of Equation 8 is $x = v = 0$. As the system is linear, the Jacobian $\underline{A}$ is simply the matrix in Equation 8. Recognize this Jacobian as the rotation matrix for a clockwise rotation of $\frac{\pi}{2}$ radians or 90 degrees.[9] The eigenvalues of the Jacobian are $\lambda = \pm i$.[10] And recall that multiplying by $-i$ means rotating by $\frac{-\pi}{2}$ in the complex plane.[11] This means that we can imagine the x-v-plane (Figure 4.1) to be the complex plane by letting $z = x + iv$ and write

$$\dot{z} = -i \cdot z \implies z(t) = z_0 e^{-it}$$

[9] If you're not convinced, sketch first the vector $v = (a, b)$ and then $u = (b, -a)$ and see that u is v rotated
[10] $\underline{A}\mathbf{v} = \lambda\mathbf{v} \implies (\underline{A} - \lambda\underline{I})\mathbf{v} = 0 \implies |\underline{A} - \lambda\underline{I}| = 0 \implies \lambda^2 + 1 = 0 \implies \lambda = \pm i$
[11] Let $z = a + ib$ and the rotated point is $w = b - ia$, then $-iz = -ia + b = w$

where we've used the analytical solution from subsection 2.3 and $z_0 = x_0 + iv_0$ is the starting point. By Euler's theorem[12]:

$$\begin{aligned} z_0 e^{-it} &= z_0(\cos(-t) + i\sin(-t)) \\ &= (x_0 + iv_0)(\cos(-t) + i\sin(-t)) \\ &= x_0\cos(-t) - v_0\sin(-t) + i(x_0\sin(-t) + v_0\cos(-t)) \end{aligned}$$

Now equate this with $z(t) = x(t) + iv(t)$ and use $\sin(-t) = -\sin(t)$ and $\cos(-t) = \cos(t)$ to get back to the real phase plane:

$$\begin{pmatrix} x(t) \\ v(t) \end{pmatrix} = \begin{bmatrix} \cos(t) & \sin(t) \\ -\sin(t) & \cos(t) \end{bmatrix} \cdot \begin{pmatrix} x_0 \\ v_0 \end{pmatrix}$$

where the matrix is the standard clockwise rotation matrix. It means that any starting point will oscillate with a period of $T = 2\pi$. With $v_0 = 0$ this reduces to the classical textbook solution: $x(t) = x_0\cos(t)$. We now have an intuition for why imaginary eigenvalues of the Jacobian evaluated at a fixed point leads to oscillatory solutions around that point. For any system more complicated than the harmonic oscillator, but with a fixed point with imaginary Jacobian eigenvalues, the system will behave approximately as the harmonic oscillator for small $\mathbf{\Delta x} = [x_0,\ v_0]$.

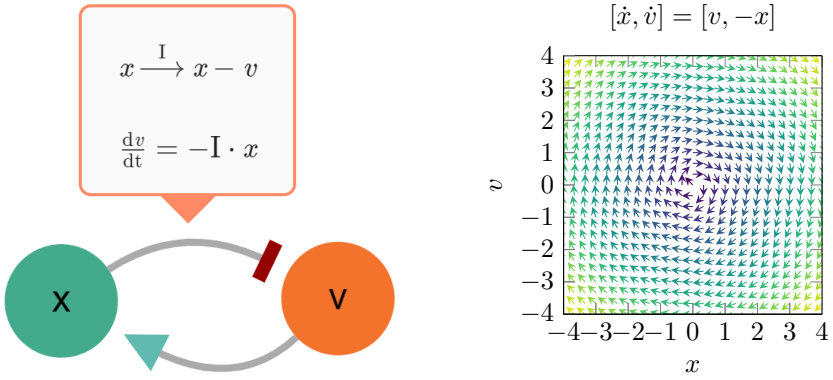


Figure 3: Different representations of the harmonic oscillator: $\ddot{x} + x = 0$
$\mathrm{v} \rightleftharpoons \mathrm{v} + \mathrm{x}$ $\qquad \mathrm{x} \rightleftharpoons \mathrm{x} - \mathrm{v}$ $\qquad v = \dot{x}$ $\qquad I = 1$
(Left) Bioscillators. Only $\dot{v}$ is shown. (Right) The (complex) x-v plane

4 Two-Dimensional Population Ecology

4.1 Predator-Prey modelling

Let's look at a classical biological network. Back in 1910, a simple model for a predator-prey relationship was proposed.[7] The classical Lotka-Volterra equations has the form:

$$\begin{aligned} \dot{R} &= bR - pFR \\ \dot{F} &= -dF + rRF \end{aligned} \tag{9}$$

where R is the number of rabbits and F is the number of foxes. From our discussion in subsection 2.4 we can write these equations as chemical reactions:

$$\begin{aligned} \mathrm{R} &\xrightarrow{\mathrm{b}} \mathrm{R} + \mathrm{R} \\ \mathrm{F} &\xrightarrow{\mathrm{d}} \\ \mathrm{F} + \mathrm{R} &\xrightarrow{\mathrm{p}} \mathrm{F} \\ \mathrm{F} + \mathrm{R} &\xrightarrow{\mathrm{r}} 2\,\mathrm{F} + \mathrm{R} \end{aligned}$$

[12] $e^{i\theta} = \cos\theta + i\sin\theta$

and we can call b the rabbit birth rate, d the fox death rate, p the predation rate and r the fox reproduction rate. The equations assume that predation is the major death factor for rabbits and the foxes only have one food source, making their reproduction proportional to the number of rabbits. The first two reactions make sense, they are simple birth and death reactions. The third reaction also makes intuitive sense, as it says that when a fox and a rabbit meet, the rabbit has a chance of being eaten. The last equation is harder to make intuitive sense of. This is an artifact of the simple equations that were not made for being interpreted as chemical reactions. But it is correct in the sense that the reproduction of foxes must be proportional to both the number of foxes and the number of rabbits if that's their only food source. A way to rethink the system so the semantics are better might be:

$$\begin{aligned} \mathrm{R} &\xrightarrow{\mathrm{b}} \mathrm{R} + \mathrm{R} \\ \mathrm{F}_h &\xrightarrow{\mathrm{d}} \\ \mathrm{F}_h + \mathrm{R} &\xrightarrow{\mathrm{p}} \mathrm{F}_f \\ \mathrm{F}_h \xleftarrow{\mathrm{s}} \mathrm{F}_f &\xrightarrow{\mathrm{r}} \mathrm{F}_f + \mathrm{F}_h \end{aligned}$$

where F_h are hungry foxes, F_f are full foxes and s is the starvation rate. This keeps the proportionalities and adds nice semantics. But it is easier to mathematically analyse Equation 9, and the net result is for our intents and purposes the same.

We'll now use our newfound techniques from section 3.

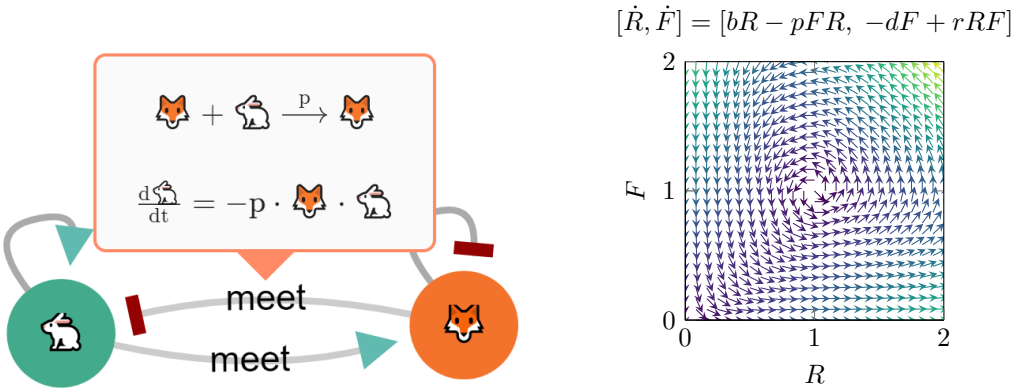


Figure 4: Different representations of the Lotka-Volterra equations: $b = p = d = r = 1$
(Left) Bioscillators. Only the predation edge has a chat bubble. (Right) The R-F phase plot

4.2 Analysis of the Lotka-Volterra equations

Equation 9 is non-linear so can't be put on matrix form like the harmonic oscillator. But we can calculate the Jacobian:

$$\underline{A} = \begin{bmatrix} \frac{\partial \dot{R}}{\partial R} & \frac{\partial \dot{R}}{\partial F} \\ \frac{\partial \dot{F}}{\partial R} & \frac{\partial \dot{F}}{\partial F} \end{bmatrix} = \begin{bmatrix} b - pF & -pR \\ -d + rF & -d + rR \end{bmatrix}$$

We define the nullcline of R to be the line on the R-F-plane where $\dot{R} = 0$. This happens at $F = \frac{b}{p}$. Similarly, the nullcline of F defines the line $R = \frac{d}{r}$. The fixed points of the system are therefore:

$$\begin{pmatrix} R^* \\ F^* \end{pmatrix} \in \left\{ \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} d/r \\ b/p \end{pmatrix} \right\}$$

We are mainly interested in analysing what happens around the last fixed points as we always start at some $R_0 > 0$, $F_0 > 0$. The Jacobian evaluated there is

$$\begin{bmatrix} b - pF & -pR \\ -d + rF & -d + rR \end{bmatrix}\Bigg|_{\substack{R^* = d/r \\ F^* = b/p}} = \begin{bmatrix} 0 & \frac{-pd}{r} \\ \frac{rb}{p} & 0 \end{bmatrix}$$

Comparing with the matrix in Equation 8 we see that this yields counter-clockwise rotation on the R-F-plane. To verify this we can also calculate the eigenvalues λ_i and see that they are imaginary:

$$\underline{A}\mathbf{v} = \lambda\mathbf{v} \implies (\underline{A} - \lambda\underline{I})\mathbf{v} = 0 \implies 0 = |\underline{A} - \lambda\underline{I}| = \begin{vmatrix} -\lambda & \frac{-pd}{r} \\ \frac{rb}{p} & -\lambda \end{vmatrix} = \lambda^2 + bd \implies \lambda = \pm i\sqrt{bd}$$

The oscillatory solutions for the harmonic oscillator and the Lotka-Volterra equations are called orbits. Orbits have the property that every starting condition will return to itself after the period. They are called orbits because they all look like they orbit the center fixed point in the phase plot. A perturbation from an orbit results in a new orbit. Orbits are also called closed trajectories as different trajectories never touch in the phase plane. Orbits as oscillatory solutions are in contrast to limit cycles for which a perturbation will be directed back to the cycle. Limit cycle solutions can occur in gene regulatory networks which we'll introduce now.

5 Intracellular Rhythms

To understand the terms inherent in the circadian and other intracellular oscillators, we must first discuss some dynamics of biomolecules.

5.1 Enzyme kinetics

An enzyme is a protein that catalyzes a chemical reaction. Let the reaction be the conversion of a substrate S to a product P. In 1913 L. Michaelis and M. Menten proposed[8] a mathematical model of how this could work that fit some of the data available at the time. It starts out by assuming that the enzyme E forms a reversible complex with the substrate before irreversibly converting it into the product.

$$\mathrm{E} + \mathrm{S} \underset{\mathrm{k}_r}{\overset{\mathrm{k}_f}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{\mathrm{k}_c} \mathrm{E} + \mathrm{P}$$

We will denote the concentration of the lone enzyme E as e, [S] = s, the complex [ES] as c and [P] = p. We are interested in finding $v = \frac{\mathrm{d}p}{\mathrm{d}t}$ = the rate of production of P given the concentrations of the substrate and the enzyme. The total concentration of enzyme $e_0 = e + c$ is assumed constant ($\frac{\mathrm{d}e_0}{\mathrm{d}t} = 0$). In order to get a useful equation out of this reaction, k_f and k_r are assumed to be so fast that the reversible reaction is in chemical equilibrium. This means that $k_f es = k_r c$. As the production of P is proportional to c, let's find an expression for that. Using our enzyme conservation and the dissociation constant $K_D = \frac{1}{K_C} = \frac{k_r}{k_f}$ we get:

$$\begin{aligned} k_f es &= k_r c \\ k_f(e_0 - c)s &= k_r c \implies \\ k_f e_0 s &= (k_r + k_f s)c \implies \\ c = e_0\frac{k_f s}{k_r + k_f s} &= e_0\frac{s}{K_D + s} = e_0\frac{1}{\frac{K_D}{s} + 1} \end{aligned}$$

We can now write the common expression for the rate of production of P:

$$v = \frac{\mathrm{d}p}{\mathrm{d}t} = v_{max}\frac{s}{K_D + s}$$

with the maxmimum efficiency $v_{max} = k_c e_0$.

The equation implies first-order kinetics for small substrate concentrations ($s \ll K_D \implies \frac{s}{K_D+s} \approx sK_D^{-1}$) and diminishing returns for higher substrate concentrations ($s \gg K_D \implies \frac{s}{K_D+s} \approx 1$). Normally, K_D is not understood as the diffusion constant. Letting $s = K_D \implies \frac{s}{K_D+s} = \frac{1}{2}$ we see that K_D denotes the concentration of s for which $v = \frac{v_{max}}{2}$. v_{max} and K_D are fitted to data.

5.2 Cooperative ligand binding

We can generalise the Michaelis-Menten equation. Consider the case of a protein P that have multiple binding sites for a ligand L. The ligands act cooperatively in the sense that the more ligands are bound already, the easier it is to bind another ligans, up to a point. Famously, A. Hill discovered that O_2 binds cooperatively to hemoglobin.[9] The heme iron has four binding sites but an effective Hill coefficient of 2.8[10]. The general cooperative ligand binding reaction is:

$$\mathrm{P} + \mathrm{nL} \underset{\mathrm{k}_r}{\overset{\mathrm{k}_f}{\rightleftharpoons}} \mathrm{PL}_n$$

This model forgets that P has n (the Hill coefficient) binding sites that work separately and only accounts for binding of all of them at the same time. As the binding work cooperatively, this is a reasonable assumption to to have given the need to compromise with the number of free parameters.

By the same line of argument as in subsection 5.1 we can calculate the proportion $\theta_b = \frac{c}{p+c}$ of proteins P with bound ligands. We let p denote the concentration of P, l of L and c of the complex PL_n. Using

$$K_D = \frac{k_r}{k_f} = \frac{pl^n}{c}$$

we get

$$\begin{aligned}\theta_b &= \frac{c}{p+c} = \frac{\frac{pl^n}{K_D}}{p + \frac{pl^n}{K_D}} \\ &= \frac{l^n}{K_D + l^n} = \frac{1}{1 + \frac{K_D}{l^n}}\end{aligned}$$

If instead the ligands deactivate the protein, we are interested in the proportion of unbound proteins $\theta_u = \frac{p}{p+c}$ given by

$$\theta_u = 1 - \theta_b = \frac{K_D}{K_D + l^n} = \frac{1}{1 + \frac{l^n}{K_D}}$$

We can now write a rate $v = k\theta_b$ or $v = k\theta_u$ where the rate constant k absorbs the true total protein concentration $p_0 = p + c = 1$. We call these rates respectively Hill activation and Hill repression. An example of this is DNA transcription. Here P is a gene and PL_n is a gene with n transcription factors L bound. If they are positive transcription factors (PTF), the gene expression is proportional to θ_b, and if they're negative transcription factors (NTF), the gene expression is proportional to θ_u.

The Hill equation is used to model many things in biology.[11] But it is most often used phenomenologically, fitting the parameters k and K_D because detailed molecular mechanisms are generally not known. Most often, the real response curve does not fit the Hill equation, but has the same sigmoidal quality of approaching a step function, acting as a biological soft on/off switch. Different biochemical processes yields a sigmoidal function qualitatively like the Hill equation. You may imagine a ligand polymer forming, one ligand at a time, before collectively binding to P, or the ligands binding to P in turn with PL_n being more active than PL_{n-1}. Either way, you don't get precisely the Hill equation, but the Hill equation is exact enough assuming fast reaction times for the intermediates.

5.3 The central dogma

The central dogma of molecular biology, first stated in 1957 by the co-discoverer of the double-helix structure Francis Crick,[12] states that the constant and persistent DNA is transcribed into temporary strings of RNA which gets translated into strings of amino acids. It is called the central dogma because every living organism has it in common. The nucleotides and amino acids are even chemically the exact same for all organisms.

If the piece of DNA being transcribed is a gene, the corresponding RNA-string is called a messenger RNA (mRNA). The protein complex RNA polymerase handles the transcription and ribosomes mediate translation. Transcription takes 10 minutes for a typical gene in human cells and translation takes about one minute.[13] Transcription and translation occur at rates comparable between different organisms at respectively 10-100 $\frac{bp}{s}$ and 10 $\frac{aa}{s}$.

The amino acid strings, peptides, fold and combine to form proteins. Proteins are actively degraded and replaced all the time as the cell has changing needs. Human proteins typically have

half-lives on the order of hours but varies from minutes to days depending on the protein and the half-lives change in response to different kinds of stimuli.[14]

Likewise, the mRNA molecules also get actively degraded. The gene regulation typically happens at the DNA-level so the translation of a gene is linearly proportional to the concentration of corresponding mRNA molecules. So the mRNA has to be actively degraded in order for the gene regulation at the DNA-level to have an effect. Average mRNA half-lives range from about 5min in E. coli to about 10 hours in humans.[15]

In principle, the mRNA transcription rate of a gene should be proportional to $\theta(t - 10\text{min})$ and translation be proportional to $\text{mRNA}(t - 1\text{min})$ as the polymerase and ribosomes should have time to work. Because the cell is a stochastic system, there is also a variable time delay before the transcription and translation happens. There are also other time delays, e.g. in eukaryotes for transporting the mRNA out of the nuclues. But because the rate of protein and mRNA degradation happens on the order of hours in humans we can often disregard the few minutes delay in order to make our models manageable.

As the degradation times are on the order of hours, one can imagine a gene regulatory negative feedback loop with circadian or ultradian[13] periods, as the feedback takes long to fully propagate.

5.4 The Goodwin model

Feedback inhibition is an important regulatory principle in cells. A product of an enzyme can e.g. stimulate a kinase to deactive the enzyme when there is enough product. Or a protein might stimulate a negative transcription factor for its own gene when enough of the protein has been translated. Goodwin in the 1960's was the first to properly study mathematical models of these biological negative feedback loops[16] and show that such biological networks may lead to oscillatory behaviour. He first considered a simple model for feedback inhibition, because there was new experimental data showing metabolic products inhibiting their own synthesis proteins.[17] He was not looking for oscillatory behaviour at first. The simple model he conjured is a two-dimensional system which account just for the concentration of mRNA (X) and the concentration of the gene product (Y), justified by the DNA concentration being constant and that the other timescales involved are small.

$$\begin{aligned} X &= a_1 \frac{K}{K+Y} - d_x \\ Y &= a_2 X - d_y \end{aligned}$$

where Y inhibits production of X with a Hill coefficient of 1 and d_i are constant degradation terms following zero-order kinetics. In the absense of Y, X is transcribed with a rate a_1. Y is translated in proportion to the concentration of X, i.e. no regulation occurs post-transcriptionally. Time evolution of this system leads to closed trajectory oscillations which was surprising at the time because it was commonly thought that concentrations would stabilize at some equilibrium. But the model has one major drawback making it too unrealistic. As the degradation is zero-order, the concentrations in the model can become negative. This can be accomodated by letting the degradations be linear ($X = -d_x X$), as most authors do, or by Michaelis-Menten kinetics ($X = -d_x \frac{X}{K+X}$). With either degradation, the oscillations become damped, i.e. go towards 0. So it seems that for a two-variable negative gene regulation network, the oscillations will either become closed or damped.

Circadian oscillators are neither closed nor damped but have robust oscillations called limit cycles. Goodwin is most famous for his three-dimensional model from 1965[18]:

$$\begin{aligned} X &= a_1 \frac{K^n}{K^n + Z^n} - d_1 X \\ Y &= a_2 X - d_2 Y \\ Z &= a_3 Y - d_3 Z \end{aligned}$$

where X is mRNA, Y is the gene product and Z is the negative transcription factor. The linear degradation rates ensure the concentrations are always positive. The third variable acts like a time delay in the negative feedback. Delay in negative feedback loops makes it easier to overshoot the regulation, resulting in oscillatory behaviour. The Goodwin model doesn't exhibit oscillations if you skip this extra variable, unless you make the model time-delayed.[19] You can think of Z as being the phosphorylated version of Y or as merely the concentration of Y in the nucleus. Griffith in 1968[20]

[13] Ultradian means faster than once per day

gave an analytical proof that only $n > 8$ yields limit cycle solutions. A Hill coefficient of such large degree is unrealistic if you imagine cooperativity,[21] but may represent e.g. a protein with multi-site phosphorylation where only the n-phosphorylated protein is active.[22]

Griffith's proof was not trivial and should not be seen as an example of how to analyze nonlinear biological networks of three dimensions or more. We have to rely on computational methods. At www.bioscillators.com/goodwin the model is implemented with $a_1 = a_2 = a_3 = k_u$ and $d_1 = d_2 = d_3 = k_d$ as inspired by [22]. It is readily seen that n has to be larger than 8 for the oscillations not to be damped. Simply drag the logarithmic n-slider and observe the change in the plot. Granted, it is not entirely convincing as there might've been other values for the other parameters for which $n < 8$ yields undamped oscillations. But we're not in the business of rigorous pure mathematics. In mathematical modelling, you don't have to take all fringe cases into account. This computational approach is necessary for analyzing larger biological networks. By playing around with the other parameters in Bioscillators, it is seen that k_u has to be larger than k_d for oscillations to occur and that k_d is the greatest factor determing the period. K controls the average concentrations and $n > 8$ controls the amplitudes.

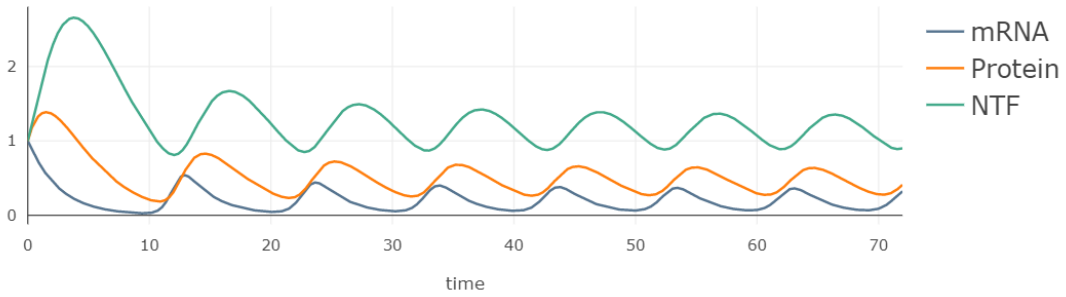


Figure 5: Time evolution of the Goodwin model plotted with Bioscillators
$k_u = 1 \quad k_d = 0.4 \quad K = 0.8 \quad n = 10$
X is messenger RNA (mRNA), Y is the protein and Z is negative transcription factor (NTF)

5.5 Beyond the Goodwin model

The Goodwin model is used as the basis for most models of circadian oscillators.[23][24] In reality, circadian oscillators are networks of many genes regulating each other.[25][26] But the molecular interactions are modelled in ways we have discussed here.

Intracellular cicadian oscillators are self-sustaining. They will continue running in the absense of any cues about the environment. If the period of the circadian oscillator is just slightly off 24 hours, the phase compared to the earth day will drift over time, making the oscillator worse than redundant. So the cell has to be entrained to the phase and period of the real day. In fact, the free-running circadian period of clocks in humans and other organisms vary greatly from 24 hours.[27] Entrainment happens mainly by input of light. It basically works by a phase response curve, i.e., the oscillator interprets differently at different times in the day. Regulating the period can happen by regulating the degradation rate k_d of different species in the network. Different light-sensitive (by proxy) proteins are abundant at different times a day, making the phase response curve possible. Unfortunately, we won't go further into entrainment here. It is reviewed in other sources.[1]

As it takes about 10 minutes to transcribe a gene, the maximum number of a protein with a circadian rhythm is on the order of 100. This means that gene regulatory networks are of a very stochastic nature. The high diffusion constant of proteins in cells at 1-100 $\frac{\mu m^2}{s}$ [28] makes deterministic models worth discussing anyway. But generalizing a deterministic model to a stochastic one[29] can lead to some species oscillating that didn't before. Stochastic modelling are also important for analysing the robustness of gene regulatory networks.[30] The stochastic nature of the circadian

clock also makes the individual cell's clock too unreliable which is why the suprachiasmatic nucleus contains thousands of cells that synchronize with each other.[31]

Circadian oscillators do not have to be based on a gene regulatory network. In human red blood cells[32] and cyanobacteria[33] the clock works by posttranslational modifications. The cyanobacteria circadian clock has been replicated in vitro.

Many other intracellular reactions exhibit oscillations. With periods of seconds, there are glycolytic oscillators and oscillations in the concentrations of cAMP and Ca^{2+}. Studying these reactions inspire to create synthetic biocompatible nanoparticles with timekeeping.[34]

Misregulation of the protein complex NF-B, an oscillator present in most animal cell types, can result in cancer, inflammatory diseases and more. A lot of research is currently looking at how to model and manipulate this regulation. The Goodwin model is used as a starting point for the core feedback loop.[35]

Mathematical models of gene regulatory networks have also made it possible to design and create synthetic oscillators that are not present in nature. Famously, in 2000 the repressilator was implemented in E. coli.[36] Recently, a temperature-robust synthetic circadian oscillator was also created.[37] These synthetic networks have given new insights into the workings of gene repression[38] and give hope to future medicines for NF-B misregulation, circadian mutants and other diseases of gene regulation.

6 Methods

6.1 Numerical solutions of dynamical systems

An initial value problem is to find $x(t) = x(t_0 + \tau)$ given a function for the slope and an initial value:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x,t)\ , \quad x_0 = x(t_0) \tag{10}$$

This is the more general version of the time-independent Equation 3. We know that $x(t)$ is given by:

$$x(t_0+\tau) = x_0 + \int_{t_0}^{t_0+\tau} f(x,t)\,\mathrm{d}t = x_0 + F(x,t)\big|_{t_0+\tau} - F(x,t)\big|_{t_0} \tag{11}$$

But the problem is that we want a dumb computer to calculate it. A dumb computer cannot find the antiderivative $F(x,t)$ given $f(x,t)$. It is possible with a computationally expensive computer algebra system. But even then, F cannot be easily found for all well-defined f, and for some elementary functions, an elementary antiderivative doesn't even exist. So we have to approximate. The naive way to begin is to note that Equation 10 implies $\mathrm{d}x = f(x,t)\,\mathrm{d}t$ which gives $x(t+dt) = x(t) + f(x,t)\,\mathrm{d}t$, so:

$$x(t_0+\tau) \approx x_0 + f(x_0,t_0)\tau \quad \text{for small } \tau \tag{12}$$

This is called the Euler method. It has the issue that it converges too slow for practical purposes. Most notably, it consistently underestimates $x(t)$ for $\frac{\mathrm{d}^2x}{\mathrm{d}t^2} > 0$ and overestimates for $\frac{\mathrm{d}^2x}{\mathrm{d}t^2} < 0$. To find a better method than the Euler method, we start by recognizing that Equation 12 is merely the first two terms of the Taylor expansion of $x(t)$ around $t = t_0$:

$$x(t_0+\tau) = x_0 + f(x_0,t_0)\tau + \tfrac{1}{2}\dot{f}(x_0,t_0)\tau^2 + \tfrac{1}{3!}\ddot{f}(x_0,t_0)\tau^3 + \tfrac{1}{4!}\dddot{f}(x_0,t_0)\tau^4 + \dots \tag{13}$$

The derivatives seem offset by one to the exponent of τ because we've defined $\frac{\mathrm{d}x}{\mathrm{d}t} = f(x,t)$.
This continued expansion does not immediately help us further as we still cannot algebraically find the derivatives $\frac{\mathrm{d}^n f(x,t)}{\mathrm{d}t^n}$.

The Runge-Kutta method uses the trick of estimating $x(t)$ by using a weighted average of $f(x,t)$ at different places in the interval $t = t_0$ to $t = t_0 + \tau$. With this method, no calculus or algebraic manipulation is required after deriving it generally. The Euler method can be understood as a first-order Runge-Kutta. We will derive here the general second-order Runge-Kutta, which has the form:

$$x(t_0+\tau) = x_0 + (a_1k_1 + a_2k_2)\tau \tag{14}$$

with

$$k_1 = f(x_0,\ t_0)$$
$$k_2 = f(x_0 + qk_1\tau,\ t_0 + p\tau)$$

There are four unknowns: a_1, a_2, q and p for which we seek some constraints. We get these constraints by comparing with the first three terms of Equation 13 using $\dot{f}(x,t) = \frac{\partial f}{\partial t} + \frac{\partial f}{\partial x}\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\partial f}{\partial t} + \frac{\partial f}{\partial x}f(x,t)$:

$$x(t_0+\tau) = x_0 + f(x_0,t_0)\tau + \frac{1}{2}\frac{\partial f(x_0,t_0)}{\partial t}\tau^2 + \frac{1}{2}\frac{\partial f(x_0,t_0)}{\partial x}f(x_0,t_0)\tau^2 + \dots \tag{15}$$

$k2$ can also be expanded as a Taylor series of two variables:

$$k_2 = f(x_0 + qk_1\tau,\ t_0 + p\tau) = f(x_0,t_0) + \frac{\partial f(x_0,t_0)}{\partial t}p\tau + \frac{\partial f(x_0,t_0)}{\partial x}qk_1\tau\dots$$

Using this expansion and $k_1 = f(x_0,t_0)$ in Equation 14 and comparing with Equation 15:

$$\begin{aligned}
x(t_0+\tau) &= x_0 + (a_1k_1 + a_2k_2)\tau && && && (14)\\
&= x_0 + a_1f(x_0,t_0)\tau + a_2f(x_0,t_0)\tau && + a_2\tfrac{\partial f(x_0,t_0)}{\partial t}p\tau^2 && + a_2\tfrac{\partial f(x_0,t_0)}{\partial x}qf(x_0,t_0)\tau^2 + \dots\\
&= x_0 + (a_1+a_2)f(x_0,t_0)\tau && + a_2p\tfrac{\partial f(x_0,t_0)}{\partial t}\tau^2 && + a_2q\tfrac{\partial f(x_0,t_0)}{\partial x}f(x_0,t_0)\tau^2 + \dots\\
x(t_0+\tau) &= x_0 + f(x_0,t_0)\tau && + \tfrac{1}{2}\tfrac{\partial f(x_0,t_0)}{\partial t}\tau^2 && + \tfrac{1}{2}\tfrac{\partial f(x_0,t_0)}{\partial x}f(x_0,t_0)\tau^2 + \dots && (15)
\end{aligned}$$

The constraints are therefore:

$$\begin{aligned}
a_1 + a_2 &= 1\\
a_2p &= \tfrac{1}{2}\\
a_2q &= \tfrac{1}{2}
\end{aligned}$$

We now have 3 equations with 4 unknowns which means we have a free parameter. A popular choice is $a_2 = \frac{1}{2} \implies p = q = 1$ yielding

$$x(t_0+\tau) = x_0 + \tfrac{1}{2}(f(x_0,t_0) + f(x_0 + f(x_0,t_0)\tau,\ t_0+\tau))\tau$$

which is known as Heun's method or the improved Euler's method.[39] This can now be readily implemented in a dumb computer given just the function $f(x,t)$ and a time step τ. In this notation, when $x(t_0+\tau)$ has been calculated, we let $t_0 \leftarrow t_0 + \tau$ and run the method again and continue like this.

The most used classical Runge-Kutta method is not a second-order but a fourth-order. Going higher than fourth-order, there is diminishing returns of accuracy per compuation.[6] The constraints will not be derived here but are available in other sources.[40] With the classical choice of parameters, and written in a manner that is closer to the computational implementation:

$$\begin{aligned}
k_1 &= f(x_n,\ t_n)\\
k_2 &= f(x_n + k_1\tfrac{\tau}{2},\ t_n + \tfrac{\tau}{2})\\
k_3 &= f(x_n + k_2\tfrac{\tau}{2},\ t_n + \tfrac{\tau}{2})\\
k_4 &= f(x_n + k_3\tau,\ t_n + \tau)\\
t_{n+1} &= t_n + \tau\\
x_{n+1} &= x_n + \tfrac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)\tau
\end{aligned}$$

This method is used in Bioscillators. One can improve on this method without going to higher orders by having a variable time step τ. This is called adaptive Runge-Kutta methods.[41] These methods don't change the order of the truncation error but approaches the optimal time step that saves computation time. For the models discussed in this thesis, it has been necessary to use RK4 instead of Euler's method but the efficiency has been high enough without adaptive methods. For the sake of notation, we have discussed Runge-Kutta in one dimension. It is readily generalised to more dimensions just by letting x, f and k_i be vector quantities.

6.2 Software dependencies

Bioscillators is built on top of React, a javascript library developed by Facebook. Besides performance issues, javascript was not made for large apps, but for small scripts. Basically, classical web programming is global and event-based, which quickly makes the code inscrutable. React makes separation of concerns easy with encapsulated components and provides a framework for state-based logic. React also encompasses JSX syntax, which extends the classical markup-language HTML to be dynamic. Most logic which was classically handled server-side (backend) can be handled client-side (frontend) with React. This makes it possible to effectively do more advanced dynamics as the client doesn't have to wait for a server response. A React app is a single page application, i.e. the website doesn't reload when changing URL. React was chosen over its top competitors: Google's Angular and the third-party Vue.

On top of React, Gatsby is used. As React is dynamic state-based on the client side, there is no static HTML generated. This makes pages built with React unfriendly for search engines and link sharing services. Gatsby fixes this problem by compiling static HTML for every page. The browser then loads the static content first, and then downloads the dynamics and preloads the other pages. The server used for Bioscillators doesn't have any backend scripts. It merely serves static files to the browser. Gatsby also has immediate support for making the website into a Progressive Web App which can be installed to look native.

A UI Framework embedded in React and Gatsby is used. It is called Material UI and gives fancy components for layout and form elements. For displaying LaTeX on the site, KaTeX is used over its competitor MathJax because it renders much faster. The plotting library Plotly was used which makes it easy to quickly make an interactive plot with a lot of points. But it has the disadvantage of a large size and it can't draw vector fields. For handling the core logic of rendering an interactive graph, Cytoscape with Edgehandles and Popper was used.

6.3 Bioscillators design choices

The goal of Bioscillators was to make a piece of software that makes biological networks comprehensible and approachable. It should intuitively display biological networks, and people should be able to play with and simulate networks without understanding the math behind.

Other software exist that can represent a biological network as a graph and simulate a time series from it. These include Copasi, CellDesigner, Systrip and PathVisio. They all have more functionality than Bioscillators, but none of them are web-based and therefore has a barrier of entering. With these, you can't just share a link to a dynamic representation of your favorite biological network to your non-specialist friend. Furthermore, small networks such as the Goodwin model are more intuitively represented in Bioscillators. I hope that a future version of Bioscillators will aid in teaching mathematical biology at the undergraduate level.

Bioscillators uses an unambiguous representation of biological networks as graphs. That is, the graph can always uniquely be translated into a set of chemical reactions and a set of differential equations. A node always represents a variable (e.g. R) and en edge represents a term in the change of the variable (e.g. $\dot{R} = b \cdot R$). The edge/term is always dependent on the node/variable at the start of the edge, and the term always applies to the change of the variable at the end of the edge.

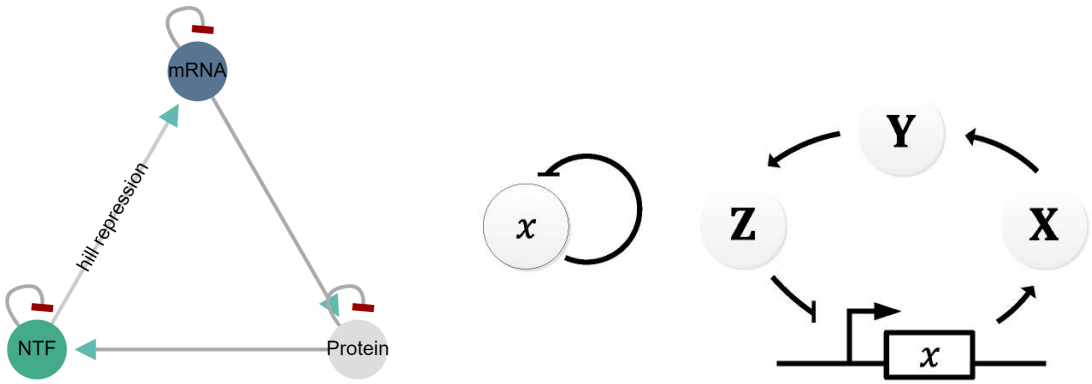


Figure 6: Different representations of the Goodwin model
(Left) Bioscillators (Right) Examples of other graph notation for the Goodwin model. In the literature, graphs are typically just for illustration and therefore ambiguous. Reprinted from [34]

Bioscillators totals about 2000 lines of novel code. The modular nature of the code makes it possible for another developer to extend the functionality. You can add new edge types[14] or edit the Plot-component without understanding the rest of the code.

The code is available open-source at `www.github.com/norregaarden/bioscillators.com`

6.4 Further development

Bioscillators is a demo application but lays the groundwork for further development on the same codebase. Possible extended functionality includes, but is not limited to:

- Vector field plots with trajectories
- Units and unit conversion instead of dimensionless parameters
- Fitting of parameters to real data
- Search in parameter space for oscillatory behaviour
- Intermediate nodes for making more complex chemical reactions
- Plotting nullclines using numerical methods for implicit plots
- Plotting previous time series behind the current
- Down- and uploading of network states
- Time-dependent factors such as temperature cycles for entrainment
- Choice of different numerical solvers

6.5 Web technologies for scientific computing

The web has great potential for being the future of scientific computing across disciplines. A web app requires no installation for the end user and the same codebase is used across all platforms, even including mobile. For developers, web apps are also preferrable, as the (processed) code is inspectable. Any web site you visit can be locally manipulated to your needs, in contrast with native applications.

There are good historical reasons for scientific software not being web-based. Javacsript, the only programming language running on websites until recently, has three main issues as a programming language explaining why it hasn't been used professionally for scientific computing.

First of all, classical web sites had to refresh the whole page when changing state. Modern frameworks such as React fixes this problem.

Secondly, javascript is made to be friendly for new programmers. This results in it not being typesafe, not having efficient variable scope handling and no proper class-based objects. All of this has recently been fixed with the introduction of Typescript which is already widely adopted. Typescript compiles to javascript, so is still compatible with all browsers. The introduction of safe types makes development much easier, as the IDE can read the code to display function definitions and find errors pre-compilation across files.

[14] See where to add new edge types in subsection II.1

Finally, javascript is compiled client-side. The browser downloads the javascript code in plaintext and then compiles it as needed. This is the main reason for javascript running slow. This has recently been fixed with the introduction of WebAssembly, for which support in browsers was widely added in 2017. WebAssembly runs as efficiently as C-languages, and C-languages can be compiled to WebAssembly. So web apps now have the capability to compute heavy numerical solutions of differential equations. Furthermore, WebGL is a new high-performance graphics API that efficiently uses the computer's GPU. This makes it possible to create stunning interactive 3D applications on websites. three.js is currently the main library for WebGL. WebAssembly and WebGL are not plugins, as Flash was, but are natively supported by browsers, making it hassle-free for the end user.

7 Conclusions

We can model some biological networks with comprehensible mathematics. All linear models are fully understood, and most models in one and two dimensions can be understood by linearizing. In molecular biology, you need three dimensions for a realistic model yielding oscillatory behaviour. All these models have a catalogue of implicit assumptions which primarily comes from the fact that the models are deterministic with continuous variables and that the number of dimensions is lowered as much as possible.

A biological network can be represented as a graph, as reactions, as time plots, phase plots and more. Every representation is equivalent to the same set of first-order differential equations. The harmonic oscillator, population ecology and molecular biology can be modelled by sets of first-order differential equations. Some types of biological rhythms outside the scope of the methods in this article include Turing patterns[42] and biological tissues as excitable media.[43]

The web app developed for this project is a proof-of-concept of interactive visualization of scientific computing. It is developed for the web because the time is ripe for doing heavy simulation and data processing with universal and accessible web technologies.

References

[1] Grigory Bordyugov et al. “Tuning the phase of circadian entrainment”. In: Journal of The Royal Society Interface 12.108 (July 2015), p. 20150282. ISSN: 1742-5689. DOI: 10.1098/rsif.2015.0282.

[2] Atchara Sirimungkala et al. “Bromination Reactions Important in the Mechanism of the Belousov-Zhabotinsky System”. In: Journal of Physical Chemistry A 103.8 (1999), pp. 1038–1043. ISSN: 10895639. DOI: 10.1021/jp9825213.

[3] A. T. Winfree. “The prehistory of the Belousov-Zhabotinsky oscillator”. In: Journal of Chemical Education 61.8 (1984), pp. 661–663. ISSN: 00219584. DOI: 10.1021/ed061p661.

[4] Daniel T. Gillespie. “Stochastic simulation of chemical kinetics”. In: Annual Review of Physical Chemistry 58 (Apr. 2007), pp. 35–55. ISSN: 0066426X. DOI: 10.1146/annurev.physchem.58.032806.104637.

[5] K. Gopalsamy. Stability and Oscillations in Delay Differential Equations of Population Dynamics. Springer Netherlands, 1992. DOI: 10.1007/978-94-015-7920-9.

[6] H. Steven Strogatz. Nonlinear Dynamics and Chaos. With Applications to Physics, Biology, Chemistry, and Engineering. Westview Press, 2001. ISBN: 9780738204536.

[7] Alfred J. Lotka. “Contribution to the Theory of Periodic Reactions”. In: The Journal of Physical Chemistry 14.3 (Mar. 1910), pp. 271–274. ISSN: 0092-7325. DOI: 10.1021/j150111a004.

[8] Kenneth A. Johnson and Roger S. Goody. “The original Michaelis constant: Translation of the 1913 Michaelis-Menten Paper”. In: Biochemistry 50.39 (Oct. 2011), pp. 8264–8269. ISSN: 00062960. DOI: 10.1021/bi201284u.

[9] HILL and AV. “The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves”. In: J Physiol (Lond) 40 (1910), pp. 4–7.

[10] Stuart J. Edelstein. “Extensions of the allosteric model for haemoglobin”. In: Nature 230.5291 (1971), pp. 224–227. ISSN: 00280836. DOI: 10.1038/230224a0.

[11] Rudolf Gesztelyi et al. The Hill equation and the origin of quantitative pharmacology. July 2012. DOI: 10.1007/s00407-012-0098-5.

[12] Matthew Cobb. “60 years ago, Francis Crick changed the logic of biology”. In: PLoS Biology 15.9 (Sept. 2017). ISSN: 15457885. DOI: 10.1371/journal.pbio.2003243.

[13] Maya Shamir et al. “Characteristic rates and timescales in cell biology”. In: Cell 164 (2016), 1302–1302.e1. DOI: 10.1016/j.cell.2016.02.058.

[14] Lijuan Zhang et al. “Method for real-time monitoring of protein degradation at the single cell level”. In: BioTechniques 42.4 (Apr. 2007), pp. 446–450. ISSN: 0736-6205. DOI: 10.2144/000112453.

[15] Jonathan A. Bernstein et al. “Global analysis of mRNA decay and abundance in Escherichia coli at single-gene resolution using two-color fluorescent DNA microarrays”. In: Proceedings of the National Academy of Sciences of the United States of America 99.15 (July 2002), pp. 9697–9702. ISSN: 00278424. DOI: 10.1073/pnas.112318199.

[16] Didier Gonze and Peter Ruoff. “The Goodwin Oscillator and its Legacy”. In: Acta Biotheoretica (Mar. 2020), pp. 1–18. ISSN: 15728358. DOI: 10.1007/s10441-020-09379-8.

[17] Brian C. Goodwin. Temporal organization in cells; a dynamic theory of cellular control processes. London, Academic Press, Nov. 1963, pp. 1–184. DOI: 10.5962/bhl.title.6268.

[18] Brian C. Goodwin. “Oscillatory behavior in enzymatic control processes”. In: Advances in Enzyme Regulation 3.C (Jan. 1965), pp. 425–437. ISSN: 00652571. DOI: 10.1016/0065-2571(65)90067-1.

[19] M H Jensen, K Sneppen, and G Tiana. “Sustained oscillations and time delays in gene expression of protein Hes1”. In: (2003). DOI: 10.1016/S0014-5793(03)00279-5.

[20] J. S. Griffith. “Mathematics of cellular control processes I. Negative feedback to one gene”. In: Journal of Theoretical Biology 20.2 (1968), pp. 202–208. ISSN: 10958541. DOI: 10.1016/0022-5193(68)90189-6.

[21] Andrew D. Keller. “Model genetic circuits encoding autoregulatory transcription factors”. In: Journal of Theoretical Biology 172.2 (Jan. 1995), pp. 169–185. ISSN: 00225193. DOI: 10.1006/jtbi.1995.0014.

[22] Didier Gonze and Wassim Abou-Jaoudé. “The Goodwin Model: Behind the Hill Function”. In: PLoS ONE (2013). ISSN: 19326203. DOI: 10.1371/journal.pone.0069573.

[23] Jean Christophe Leloup, Didier Gonze, and Albert Goldbeter. “Limit cycle models for circadian rhythms based on transcriptional regulation in Drosophila and Neurospora”. In: Journal of Biological Rhythms. Vol. 14. 6. SAGE Publications Inc., 1999, pp. 433–448. DOI: 10.1177/074873099129000948.

[24] Treenut Saithong, Kevin J. Painter, and Andrew J. Millar. “The Contributions of Interlocking Loops and Extensive Nonlinearity to the Properties of Circadian Clock Models”. In: PLoS ONE 5.11 (Nov. 2010). Ed. by Nick Monk, e13867. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0013867.

[25] Daniel B. Forger and Charles S. Peskin. “A detailed predictive model of the mammalian circadian clock”. In: Proceedings of the National Academy of Sciences of the United States of America 100.25 (Dec. 2003), pp. 14806–14811. ISSN: 00278424. DOI: 10.1073/pnas.2036281100.

[26] John B. Hogenesch and Hiroki R. Ueda. Understanding systems-level properties: Timely stories from the study of clocks. June 2011. DOI: 10.1038/nrg2972.

[27] Jürgen Aschoff. “Temporal orientation: circadian clocks in animals and humans”. In: Animal Behaviour 37.PART 6 (June 1989), pp. 881–896. ISSN: 00033472. DOI: 10.1016/0003-3472(89)90132-2.

[28] Thomas Kühn et al. “Protein diffusion in mammalian cell cytoplasm”. In: PLoS ONE 6.8 (2011), p. 22962. ISSN: 19326203. DOI: 10.1371/journal.pone.0022962.

[29] Daniel B. Forger and Charles S. Peskin. “Stochastic simulation of the mammalian circadian clock”. In: Proceedings of the National Academy of Sciences of the United States of America 102.2 (Jan. 2005), pp. 321–324. ISSN: 00278424. DOI: 10.1073/pnas.0408465102.

[30] Mae L. Woods et al. “A statistical approach reveals designs for the most robust stochastic gene oscillators”. In: ACS Synthetic Biology 5.6 (Feb. 2016), pp. 459–470. ISSN: 21615063. DOI: 10.1021/acssynbio.5b00179.

[31] Andrew C. Liu et al. “Intercellular Coupling Confers Robustness against Mutations in the SCN Circadian Clock Network”. In: Cell 129.3 (May 2007), pp. 605–616. ISSN: 00928674. DOI: 10.1016/j.cell.2007.02.047.

[32] John S. O-Neill and Akhilesh B. Reddy. “Circadian clocks in human red blood cells”. In: Nature 469.7331 (Jan. 2011), pp. 498–504. ISSN: 00280836. DOI: 10.1038/nature09702.

[33] Carl Hirschie Johnson, Phoebe L. Stewart, and Martin Egli. “The cyanobacterial circadian system: From biophysics to bioevolution”. In: Annual Review of Biophysics 40.1 (June 2011), pp. 143–167. ISSN: 1936122X. DOI: 10.1146/annurev-biophys-042910-155317.

[34] Ethungshan Shitiri, Athanasios V. Vasilakos, and Ho Shin Cho. Biological oscillators in nanonetworks—opportunities and challenges. May 2018. DOI: 10.3390/s18051544.

[35] Sandeep Krishna, Mogens H Jensen, and Kim Sneppen. Minimal model of spiky oscillations in NF-B signaling. Tech. rep. 29. 2006.

[36] Michael B. Elowitz and Stanislas Leibier. “A synthetic oscillatory network of transcriptional regulators”. In: Nature 403.6767 (Jan. 2000), pp. 335–338. ISSN: 00280836. DOI: 10.1038/35002125.

[37] Lili Wu, Qi Ouyang, and Hongli Wang. “Robust network topologies for generating oscillations with temperature-independent periods”. In: PLoS ONE 12.2 (Feb. 2017). ISSN: 19326203. DOI: 10.1371/journal.pone.0171263.

[38] Jonathan Tyler, Anne Shiu, and Jay Walton. “Revisiting a synthetic intracellular regulatory network that exhibits oscillations”. In: Journal of Mathematical Biology 78.7 (Mar. 2019), pp. 2341–2368. ISSN: 14321416. DOI: 10.1007/s00285-019-01346-3. arXiv: 1808.00595.

[39] Endre Süli and David F. Mayers. An Introduction to Numerical Analysis. Cambridge University Press, Aug. 2003. DOI: 10.1017/cbo9780511801181.

[40] W.H. Press et al. Numerical Recipes: The Art of Scientific Computing. 3rd. New York: Cambridge University Press, 2007. ISBN: 978-0-521-88068-8.

[41] William H Press and Saul A Teukolsky. “Adaptive Stepsize Runge-Kutta Integration”. In: Citation: Computers in Physics 6 (1992), p. 188. DOI: 10.1063/1.4823060.

[42] David Karig et al. “Stochastic Turing patterns in a synthetic bacterial population”. In: Proceedings of the National Academy of Sciences of the United States of America 115.26 (June 2018), pp. 6572–6577. ISSN: 10916490. DOI: 10.1073/pnas.1720770115.

[43] Cyrill B. Muratov, Eric Vanden-Eijnden, and Weinan E. “Noise can play an organizing role for the recurrent dynamics in excitable media”. In: Proceedings of the National Academy of Sciences of the United States of America 104.3 (Jan. 2007), pp. 702–707. ISSN: 00278424. DOI: 10.1073/pnas.0607433104.

Appendices

I Chemical Reaction Kinetics

Consider an exemplary chemical reaction with substances X, Y and Z, concentrations denoted by X, Y and Z, stoichiometric coefficients x, p, z, q, and forward/reverse rate constants k_f/k_r:

$$x\,\mathrm{X} + p\,\mathrm{Y} \underset{\mathrm{k}_r}{\overset{\mathrm{k}_f}{\rightleftharpoons}} z\,\mathrm{Z} + q\,\mathrm{Y}$$

From this reaction scheme it can be deduced how the substance concentrations change over time given initial concentrations. The reaction runs forward with speed v_f proportional to the reactants and in reverse with speed v_r proportional to the products:

$$v_f = k_f X^x Y^p$$
$$v_r = k_r Z^z Y^q$$

$v_f = k_f X^x Y^p$. This is called the law of mass action. You can convince yourself that this is true for the forward reaction with first-order kinetics $x = p = 1$ (which is typically true for genuine reactions). If you then double the concentration of X, the rate of X bumping into Y in the solution also doubles.
The kinetics of the reaction can be written as differentials:

$$\begin{aligned} v_f - v_r = k_f X^x Y^p - k_r Z^z Y^q &= -\frac{1}{x}\frac{\mathrm{d}X}{\mathrm{d}t} \\ &= \frac{1}{z}\frac{\mathrm{d}Z}{\mathrm{d}t} \\ &= \frac{1}{q-p}\frac{\mathrm{d}Y}{\mathrm{d}t} \end{aligned}$$

For every x molecules of X that perishes, z molecules of Z emerges. Likewise, $(q - p)$ molecules of species Y will have emerged in that reaction.
The reaction is in steady state when $\frac{\mathrm{d}X}{\mathrm{d}t} = \frac{\mathrm{d}Z}{\mathrm{d}t} = \frac{\mathrm{d}Y}{\mathrm{d}t} = 0$. This implies that $k_f X^x Y^p = k_r Z^z Y^q$ at steady state, which defines the equilibrium constant K_C for the reaction:

$$K_C = \frac{k_f}{k_r} = \frac{Z^z Y^q}{X^x Y^p}$$

From this we can apply Le Châtelier's principle: If an reaction in equilibrium is perturbed (e.g. by adding more of one of the substances), the reaction will occur in the direction that gets $\frac{Z^z Y^q}{X^x Y^p}$ back to being equal to K_C.

II Supplementary Figures

II.1 Extending Bioscillators

Below is printed lines 43-74 from file
www.github.com/norregaarden/bioscillators.com/blob/master/src/utils/edgeTypes.js
Here you can add a new edge type with a definition of how to translate into LaTeX. Read the rest of the file for more information.

```
const edgeTypes = [
  {
        // network:     (X)->(Y)
        // reaction:    X => X + Y
        // dynamics:    dY/dt     X
        name: 'linear',
        termMain: texplate`${'source'}`,    // dY/dt     |X|       change of Y is proportional to X
        preReaction: texplate`${'source'}`, // |X| => X + Y     left side of chemical reaction
  },
  {
        // network:     (X)->(Y)
        // reaction:    X + Y => X + 2Y
        // dynamics:    dY/dt     X * Y
        name: 'meet',
        termMain: texplate`${'source'} \\cdot ${'target'}`,
        preReaction: texplate`${'source'} + ${'target'}`
    },
  {
        name: 'hill activation',
        parameters: hillParameters,
        termMain: texplate`\\frac{ ${'source'} }{ ${'half'} + ${'source'} }`,
        nullaryReaction: texplate`\\ce{ E + ${'hill'} ${'source'} <=>[][{${'half'}}^{${'hill'}}] E ${'source'}_{${'hill'}} }`,
        preReaction: texplate`E ${'source'}_{${'hill'}}` // 'E' because an enzyme is imagined (constant concentration)
  },
  {
        name: 'hill repression',
        parameters: hillParameters,
        termMain: texplate`\\frac{ ${'half'} }{ ${'half'} + ${'source'} }`,
        nullaryReaction: texplate`\\ce{ D ${'source'}_{${'hill'}} <=>[{${'half'}}^{${'hill'}}][] D + ${'hill'} ${'source'} }`,
        preReaction: texplate`D ${'source'}_{${'hill'}}` // 'D' because DNA is imagined (constant concentration)
  },
]
```

II.2 The SIR model in epidemiology

Bioscillators can do more than visualize oscillators. Below is the "Suspected-Infected-Recovered" model from epidemiology implemented at `www.bioscillators.com/SIR` with infection = 1 and recovery = 0.1