Integrating computations, mathematics, physics and chemistry in undergraduate biology programs

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Overarching questions

Which skills are needed by MSc candidates in biology?

There is new demand for more

- quantitative methods & reasoning
- understanding data and phenomena via models
- creating *in silico* virtual labs

Challenge:

How to integrate such computing-based activities in the bachelor programs when the students are *not* interested in mathematics, physics, and programming?

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How to teach computing in biology?

Do we need to still follow the tradition and teach mathematics, physics, computations, chemistry, etc. in separate discipline-specific courses?

- Uninteresting to first study tools when you want to study biology
- Little understanding of what the tools are good for
- Minor utilization of tools later in biology

It's time for new thinking:

- Just-in-time teaching: teach tools *when needed*
- Teach tools in the *context of biology*
- Emphasize development of *intuition and understanding*
- Base learning of the students' own *explorations in biology projects*
- Integrate lab work with computing tools

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Current status: CSE is ready for biology

- CSE (*Computing in Science Education*) in life science is a faculty priority area
- Core professors in the CSE project and 5 IBV professors are dedicated to implementation
- 4 CINPLA PhD students have excellent background for and strong interests in the implementation
- Let's roll!

Suggested pilot project: Oct 2014 - Oct 2015

- Form a project team of dedicated CSE+IBV people and CINPLA PhD students
- Develop a pedagogical framework
- CSE+IBV people identify a set of possible examples
- PhD students work closely with CSE+IBV people to find data, define models, and write documents
- Spring 2015: intro course in computing and programming for IBV teachers, using selected examples
- Educational workshop at IBV:
  - Present results from the project
  - Discuss how and where to implement examples in BIOxxxx courses
- Fall 2016: First integration of computing in courses

The pedagogical framework

Aim: Develop intuition about the scientific method

- Method: case-based learning
- Coherent problem solving *in biology* by integrating mathematics, programming, physics/chemistry, ...
- Starting point: data from lab or field experiments
- Visualize data
- Derive computational models directly from mathematical/intuitive *reasoning*
- Program model(s), fit parameters, compare with data
- Develop intuition and understanding based on
  - the principles behind the model
  - exploration of the model ("what if")
  - prediction of new experiments

Example 1: ecoli lab experiment

Observations of no of bacteria vs time in seconds, stored in Excel and written to a CVS file:

```
0,100
600,140
1200,250
1800,360
2400,480
3000,820
3600,1300
4200,1700
4800,2900
5400,3900
6000,7000
```

Visualize data

- Meet a text editor and a terminal window
- Very basic Unix

First program:

```
t = [0, 600, 1200, 1800, 2400, 3000, 3600,
     4200, 4800, 5400, 6000]
N = [100, 140, 250, 360, 480, 820, 1300, 1700, 2900, 3900, 7000]
import matplotlib.pyplot as plt
plt.plot(t, N, 'ro')
plt.xlabel('t [s]')
plt.ylabel('N')
plt.show()
```

Concepts must be introduced implicitly in a structured way

Warning

- Always identify new concepts
- Train new concepts in simplified ("trivial") problems

Concepts in the previous example:

- Lists or arrays of numbers
- Plotting commands
- Curve = function of time

Notice:

The concept of a continuous function $N(t)$ is not necessary, just straight lines between discrete points on a curve.

Read data from file

```
import numpy as np
data = np.loadtxt('ecoli.csv', delimiter=',')
print data  # look at the format
t = data[:,0]
N = data[:,1]
import matplotlib.pyplot as plt
plt.plot(t, N, 'ro')
plt.xlabel('t [s]')
plt.ylabel('N')
plt.show()
```

Typical pattern:

The population grows faster and faster. Why? Is there an underlying (general) mechanism?

Lab journal

Use IPython notebook as lab journal.

How can we reason about the process?

1. Cells divide after T seconds on average (one generation)
2. $2N$ celles divide otn twice as many new cells ΔN in a time interval Δt as N cells would: $\Delta N \propto N$
3. N cells result in twice as many new individuals ΔN in time $2\Delta t$ as in time Δt: $\Delta N \propto \Delta t$
4. Same proportionality wrt death (repeat reasoning)
5. Proposed model: $\Delta N = b\Delta t N - d\Delta t N$ for some unknown constants b (births) and d (deaths)
6. Describe evolution in discrete time: $t_n = n\Delta t$
7. Program-friendly notation: N at t_n is N^n
8. Math model: $N^{n+1} = N^n + r\Delta t\, N$ (with $r = b - d$)
9. Program model: `N[n+1] = N[n] + r*dt*N[n]`

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The first simple program

Let us solve the difference equation in as simple way as possible, just to train some programming: $r = 1.5$, $N^0 = 1$, $\Delta t = 0.5$

```
import numpy as np

t = np.linspace(0, 10, 21)  # 20 intervals in [0, 10]
dt = t[1] - t[0]
N = np.zeros(t.size)

N[0] = 1
r = 0.5

for n in range(0, N.size-1, 1):
    N[n+1] = N[n] + r*dt*N[n]
    print 'N[%d]=%.1f' % (n+1, N[n+1])
```

The output

```
N[1]=1.2
N[2]=1.6
N[3]=2.0
N[4]=2.4
N[5]=3.1
N[6]=3.8
N[7]=4.8
N[8]=6.0
N[9]=7.5
N[10]=9.3
N[11]=11.6
N[12]=14.6
N[13]=18.2
N[14]=22.7
N[15]=28.4
N[16]=35.5
N[17]=44.4
N[18]=55.5
N[19]=69.4
N[20]=86.7
```

Parameter estimation

- We do not know r
- How can we estimate r from data?

We can use the difference equation with the experimental data

$$N^{n+1} = N^n + r\Delta t N^n$$

Say N^{n+1} and N^n are known from data, solve wrt r:

$$r = \frac{N^{n+1} - N^n}{N^n \Delta t}$$

Use experimental data in the fraction, say $t_1 = 600$, $t_2 = 1200$, $N^1 = 140$, $N^2 = 250$: $r = 0.0013$.

More sophisticated methods

Can do a nonlinear least squares parameter fit, but that is too advanced at this stage.

A program relevant for the biological problem

```
import numpy as np

# Estimate r
data = np.loadtxt('ecoli.csv', delimiter=',')
t_e = data[:,0]
N_e = data[:,1]
i = 2  # Data point (i,i+1) used to estimate r
r = (N_e[i+1] - N_e[i])/(N_e[i]*(t_e[i+1] - t_e[i]))
print 'Estimated r=%.5f' % r
# Can experiment with r values and see if the model can
# match the data better

T = 1200      # cell can divide after T sec
t_max = 5*T   # 5 generations in experiment
t = np.linspace(0, t_max, 1000)
dt = t[1] - t[0]
N = np.zeros(t.size)

N[0] = 100
for n in range(0, len(t)-1, 1):
    N[n+1] = N[n] + r*dt*N[n]

import matplotlib.pyplot as plt
plt.plot(t, N, 'r-', t_e, N_e, 'bo')
plt.xlabel('time [s]');  plt.ylabel('N')
plt.legend(['model', 'experiment'], loc='upper left')
plt.show()
```

Discuss the nature of such a model

- Write up all the biological factors that influence the population size of bacteria
- Understand that all such effects are merged into one parameter r
- Understand that the reasoning must be the same whether we have bacteria, animals or humans - this is a generic model! (even the interest rate in a bank follows the same model)

Discuss the limitations of such a model

- How many bacteria in the lab after one month?
- Growth is restricted by environmental resources!
- Fix the model (logistic growth)
- Is the logistic model appropriate for a lab experiment?
- Find data to support the logistic model
  (it's a *very* simple model)

The pedagogical template (to be iterated!)

- Start with a real biological problem
- Be careful with too many new concepts
- Workflow:
  - data
  - visualization
  - patterns
  - modeling (*discrete*)
  - programming
  - testing
  - parameter estimation (difficult)
  - validation
  - prediction
- Make many small exercises that train the new concepts
- Repeat the case in a way that makes a complete understanding

Technology for documenting cases

- Documentation: slides in the doconce format with extra notes (can compile with/without notes)
- Realistic goal: write out the slides for a gentle book on biocomputing examples
- The biological case is in a separate file that the students can work with as an IPython notebook
- Problem: not much basic literature exists
- Cases must be linked in a learning graph:
  I want to do nerve cell modeling, but how to progress to this stage?
- Make a list of concepts and where concepts are trained
- Think of each case as a *separate module*

Immediate tasks

- Find a good bacteria growth lab example - do the first example
- Alternative model: random 2D walk, people meet and make new individuals
- Predator-pray model: any field experiment to build?
- Experiments based on technology: imaging, sensors, ...
- Disease modeling coupled to data
- Predator-pray with disease
- Bioinformatics cases and programming
- ...

Adding model complexity: Predator-Prey model from ecology

The population dynamics of a simple predator-prey system is a classical example shown in many biology textbooks when ecological systems are discussed. The system contains all elements of the scientific method:

- The set up of a specific hypothesis combined with
- the experimental methods needed (one can study existing data or perform experiments)
- analyzing and interpreting the data and performing further experiments if needed
- trying to extract general behaviors and extract eventual laws or patterns
- develop mathematical relations for the uncovered regularities/laws and test these by performing new experiments

Case study from Hudson bay

Lots of data about populations of hares and lynx collected from furs in Hudson Bay, Canada, are available. It is known that the populations oscillate. Why? We shall demonstrate the scientific method by

1. plotting the data
2. derive a simple model for the population dynamics
3. (fitting parameters in the model to the data)
4. using the model predict the evolution other predator-pray systems

Hudson bay data

Year	Hares (x1000)	Lynx (x1000)
1900	30.0	4.0
1901	47.2	6.1
1902	70.2	9.8
1903	77.4	35.2
1904	36.3	59.4
1905	20.6	41.7
1906	18.1	19.0
1907	21.4	13.0
1908	22.0	8.3
1909	25.4	9.1
1910	27.1	7.4
1911	40.3	8.0
1912	57	12.3
1913	76.6	19.5
1914	52.3	45.7
1915	19.5	51.1
1916	11.2	29.7
1917	7.6	15.8
1918	14.6	9.7
1919	16.2	10.1
1920	24.7	8.6

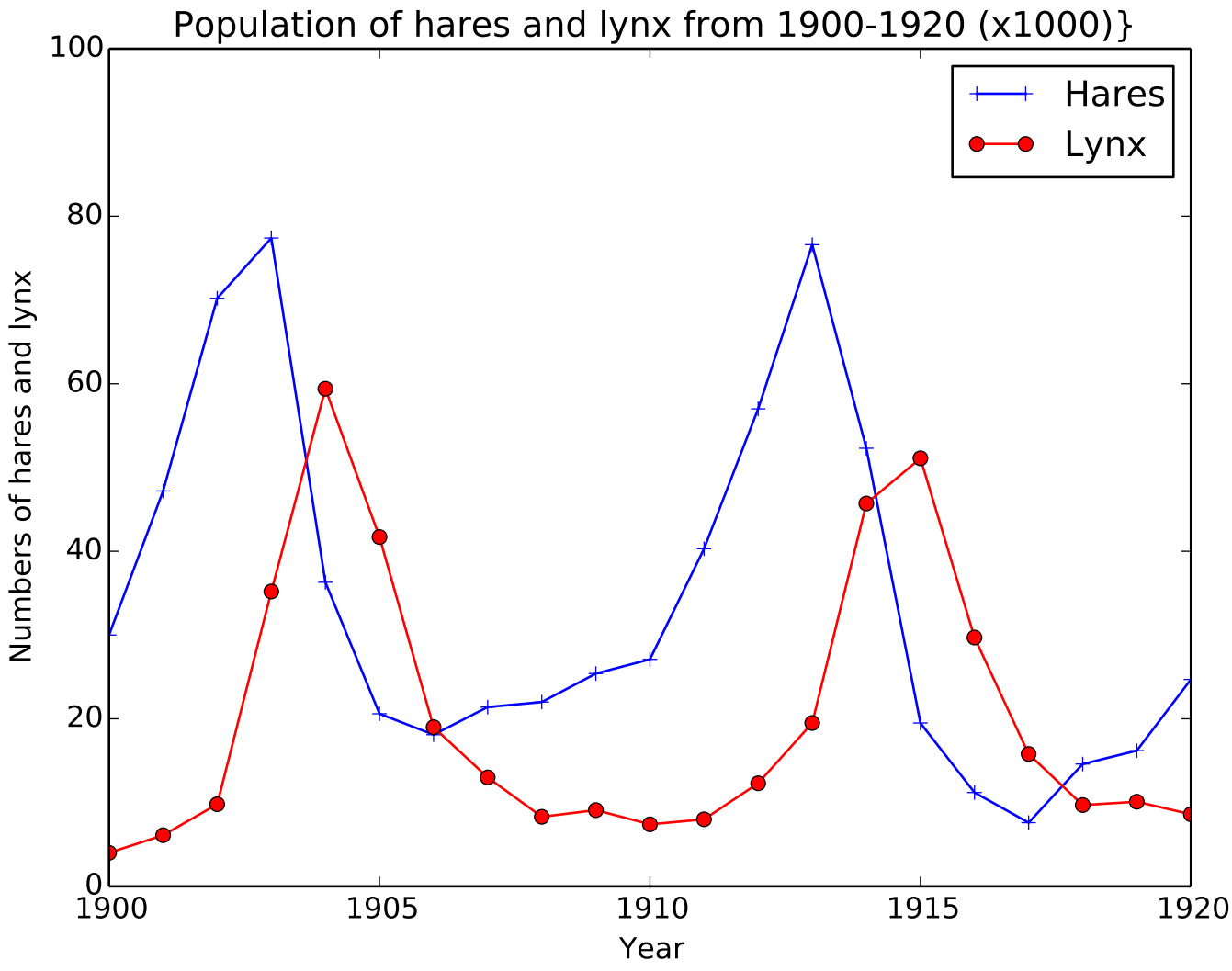
Plotting the data

```
import numpy as np
from  matplotlib import pyplot as plt

# Load in data file
data = np.loadtxt('Hudson_Bay.dat', delimiter=',', skiprows=1)
# Make arrays containing x-axis and hares and lynx populations
year = data[:,0]
hares = data[:,1]
lynx = data[:,2]

plt.plot(year, hares ,'b-+', year, lynx, 'r-o')
plt.axis([1900,1920,0, 100.0])
plt.xlabel(r'Year')
plt.ylabel(r'Numbers of hares and lynx ')
plt.legend(('Hares','Lynx'), loc='upper right')
plt.title(r'Population of hares and lynx from 1900-1920 (x1000)}')
plt.savefig('Hudson_Bay_data.pdf')
plt.savefig('Hudson_Bay_data.png')
plt.show()
```

Hares and lynx in Hudson bay from 1900 to 1920



Why now create a computer model for the hare and lynx populations?

- We see oscillations in the data
- What causes cycles to slow or speed up?
- What affects the amplitude of the oscillation or do you expect to see the oscillations damp to a stable equilibrium?
- With a model we can better *understand the data*
- More important: we can understand the ecology dynamics of predator-pray populations

The traditional (top-down) approach

The classical way (in all books) is to present the Lotka-Volterra equations:

$$\frac{dH}{dt} = H(a - bL)$$
$$\frac{dL}{dt} = -L(d - cH)$$

Here,

- H is the number of preys
- L the number of predators
- a, b, d, c are parameters

Most books quickly establish the model and then use considerable space on discussing the qualitative properties of this *nonlinear system of ODEs* (which cannot be solved)

The "new" discrete bottom-up approach

The bottom-up approach

- Start with experimental data and discuss the methods which have been used to collect the data, the assumptions, the electronic devices, the aims etc. That is, expose the students to the theory and assumptions behind the data that have been collected and motivate for the scientific method.
- Where appropriate the students should do the experiment(s) needed to collect the data.
- The first programming tasks are to read and visualize the data to see if there are patterns or regularities. This strengthens a research-driven intuition.
- Now we want to increase the understanding through modeling.
- Most of the biology lies in the *derivation* of the model. We shall focus on an intuitive discrete approach that leads to difference equations that can be programmed *and solved* directly.

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Basic (computer-friendly) mathematics notation

- Time points: $t_0, t_1, \ldots, t_m$
- Uniform distribution of time points: $t_n = n\Delta t$
- H^n: population of hares at time t_n
- L^n: population of lynx at time t_n
- We want to model the changes in populations, $\Delta H = H^{n+1} - H^n$ and $\Delta L = L^{n+1} - L^n$ during a general time interval $[t_{n+1}, t_n]$ of length $\Delta t = t_{n+1} - t_n$

Basic dynamics of the population of hares

The population of hares evolves due to births and deaths exactly as a bacteria population:

$$\Delta H = a\Delta t H^n$$

However, hares have an additional loss in the population because they are eaten by lynx. All the hares and lynx can form $H \cdot L$ pairs in total. When such pairs meet during a time interval Δt, there is some small probablity that the lynx will eat the hare. So in fraction $b\Delta t HL$, the lynx eat hares. This loss of hares and must be accounted for: subtracted in the equation for hares:

$$\Delta H = a\Delta t H^n - b\Delta t H^n L^n$$

Basic dynamics of the population of lynx

We assume that the primary growth for the lynx population depends on sufficient food for raising lynx kittens, which implies an adequate source of nutrients from predation on hares. Thus, the growth of the lynx population does not only depend of how many lynx there are, but on how many hares they can eat. In a time interval ΔtHL hares and lynx can meet, and in a fraction $b\Delta tHL$ the lynx eats the hare. All of this does not contribute to the growth of lynx, again just a fraction of $b\Delta tHL$ that we write as $d\Delta tHL$. In addition, lynx die just as in the population dynamics with one isolated animal population, leading to a loss $-c\Delta tL$.

The accounting of lynx then looks like

$$\Delta L = d\Delta t H^n L^n - c\Delta t L^n$$

Evolution equations

By writing up the definition of ΔH and ΔL, and putting all assumed known terms H^n and L^n on the right-hand side, we have

$$H^{n+1} = H^n + a\Delta t H^n - b\Delta t H^n L^n$$

$$L^{n+1} = L^n + d\Delta t H^n L^n - c\Delta t L^n$$

Note:

- These equations are ready to be implemented!
- But to start, we need H^0 and L^0 (which we can get from the data)
- We also need values for a, b, d, c

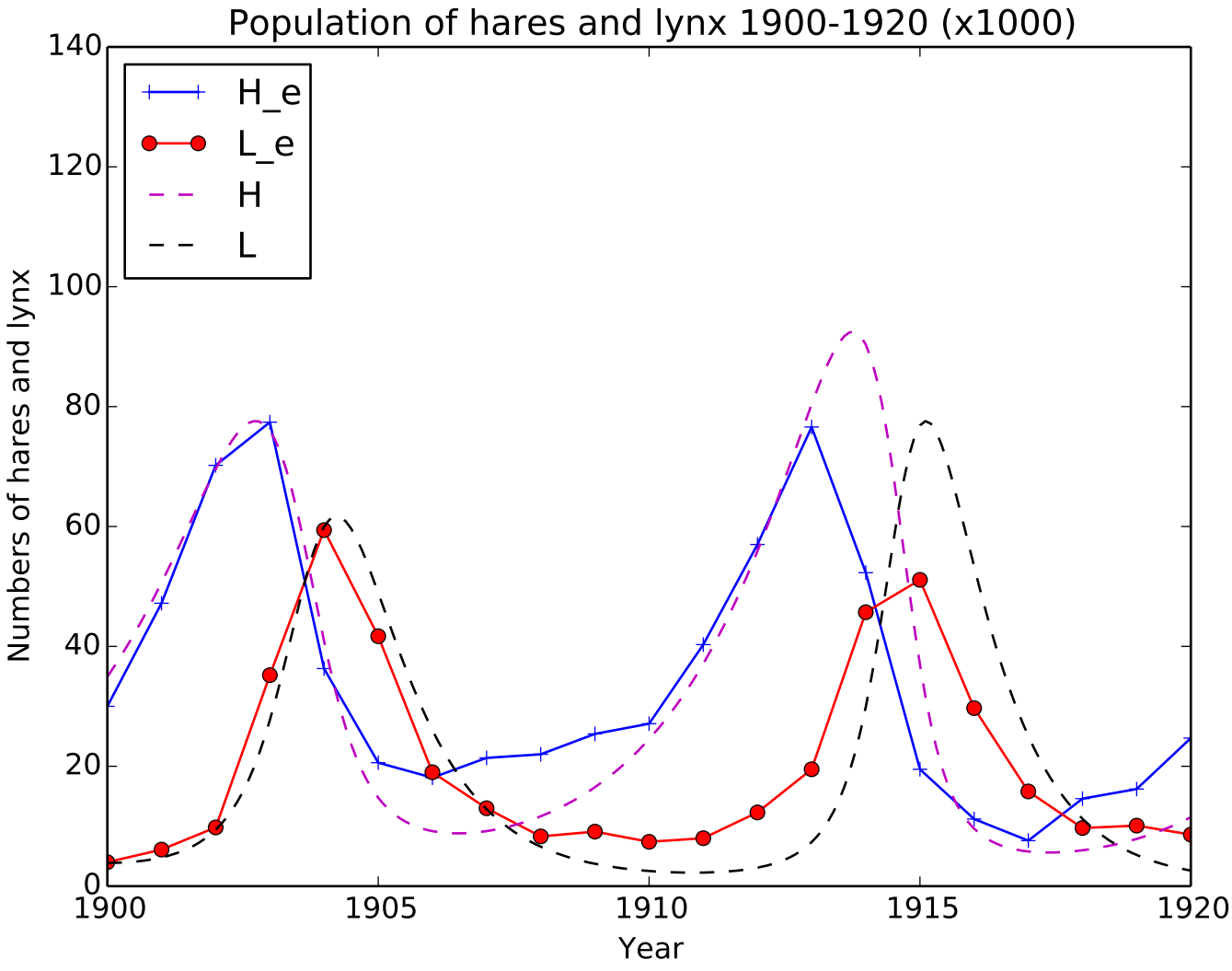
Adapt the model to the Hudson Bay case

- As always, models tend to be general - as here, applicable to "all" predator-pray systems
- The critical issue is whether the *interaction* between hares and lynx is sufficiently well modeled by constHL
- The parameters a, b, d, and c must be estimated from data
- Measure time in years
- $t_0 = 1900$, $t_m = 1920$

The program

```
import numpy as np
import matplotlib.pyplot as plt

def solver(m, H0, L0, dt, a, b, c, d, t0):
    """Solve the difference equations for H and L over m years
    with time step dt (measured in years."""

    num_intervals = int(m/float(dt))
    t = np.linspace(t0, t0 + m, num_intervals+1)
    H = np.zeros(t.size)
    L = np.zeros(t.size)

    print 'Init:', H0, L0, dt
    H[0] = H0
    L[0] = L0

    for n in range(0, len(t)-1):
        H[n+1] = H[n] + a*dt*H[n] - b*dt*H[n]*L[n]
        L[n+1] = L[n] + d*dt*H[n]*L[n] - c*dt*L[n]
    return H, L, t

# Load in data file
data = np.loadtxt('Hudson_Bay.csv', delimiter=',', skiprows=1)
# Make arrays containing x-axis and hares and lynx populations
t_e = data[:,0]
H_e = data[:,1]
L_e = data[:,2]
```

The plot


Population of hares and lynx 1900-1920 (x1000)
H_e
L_e
H
L
Numbers of hares and lynx
Year
0
20
40
60
80
100
120
140
1900
1905
1910
1915
1920

Other examples

- Disease modeling
- Predator-pray with disease
- Bioinformatics: searching in strings
- Move from difference equations to differential equations, would this be meaningful? Probably not - it does not give anything in biology before the models are so complex that one needs other things than Forward Euler...