

Biological Modeling: Research projects

At this time point in our course you have learned enough to make your first steps as a modeler in biology. You have been trained to read and formulate mathematical models, and to analyze these graphically, mathematically, and numerically. You now have a few weeks to work on a somewhat larger project by yourself. The main goal of this project is that you apply your newly acquired skills to do a piece of research of your own. Most of the projects that we propose here start with a published paper, **but we also welcome proposals to work on a project of your own** (please contact us to discuss this).

For the projects starting with a paper, you should first repeat its results by coding its model(s) into R or Grind. Next, find other papers, and define extensions of the research yourself. It is your own responsibility to study exciting new extensions of the work, and to make this a truly interesting project.

Please work in small groups of no more than three. We will have no more than 6 groups. Every project will be assigned an assistant whom you can contact for help, make an appointment by email to meet on campus or online. Make a concise “lab-journal” in which you **shortly** describe your progress every day that you worked on the project. This journal has to be handed in together with your written report.

Every group will present their work using an electronic slide show during a ‘symposium’ on Thursday 1 February 2023 in BBG-161, in the morning. Each of the participants should speak (in English) for about 5 minutes, and everybody needs to be present, and ask questions throughout the symposium. The oral presentation should be exciting for the audience. You have to make clear what questions you addressed, how this was approached, why it is interesting, and what results you obtained. Too technical details should be avoided (as these will be explained in the written report). Subdivide your presentation into natural parts such that all members of your research team get to speak! Your presentation should be enthusiastic and strongly focus on your main line of research.

The written report has to be delivered in the last week of the course (electronic submissions of PDF-files by email to r.j.deboer@uu.nl are accepted until Sunday the 4th of February). The report should have a summary, and start with an Introduction explaining the project, its context, and have a short review of the relevant literature. In the Methods section you can define and explain the mathematical model. In the Results section you can mix the results of the original paper with your own extensions of the research, and you can provide your extensions of the mathematical model. Provide the interpretation of your results in the Results section, i.e., write in a *Nature* or *Science* style. In the Discussion you describe possible problems/shortcomings, other extensions, and you provide further context of your work. Use the instructions on writing reports that you received in earlier courses (e.g., the bachelor Biology schrijfwijzer tbb.bio.uu.nl/rdb/bm/Projects/BiologieSchrijfwijzer2023.pdf, **but definitely also read the short tutorial on writing scientific reports that we provide** tbb.bio.uu.nl/rdb/bm/Projects/GuidelinesReport.pdf, which also gives the Rubrics that we use for grading the report.

We will give written feedback on your oral and written presentation later by email. Please make an appointment to discuss that feedback with us. With the project we hope to increase your experience with the techniques you have encountered so far, and to show that you have arrived at a stage where you can critically continue the work of recent papers in this field.

1 The carbon cycle

We all know that atmospheric CO₂ levels are increasing and to prevent global warming huge investments are being made to reduce the release of CO₂ by burning fossil fuels. Estimates the human CO₂ production, and of the natural flux of CO₂ between the atmosphere, the upper and deep layers of the ocean, and the vegetation are published on various websites (e.g., earthobservatory.nasa.gov/features/CarbonCycle). The current yearly human production of about 9 giga ton per year is much smaller than the natural flux from the ocean (90), vegetation (60), and soil (60) into the atmosphere. So how can such a small increase give rise to such a large increase in atmospheric CO₂ levels? This is being discussed on various websites (e.g., skepticalscience.com/co2-residence-time.htm).

Find papers on this topic and find out where the data in this NASA diagram is based upon. Study this question by making a compartment model, for the main CO₂ compartments (atmosphere, ocean, deep ocean, and vegetation (first including the soil?)). For instance, for the amount of CO₂ in the atmosphere one would write something like,

$$\frac{dA}{dt} = f_{OA}O - f_{AO}A + f_{VA}V - f_{AV}A + h ,$$

where we have four flux parameters (to and from the ocean O , and to a from the vegetation V), and the human production h (in kilo tons per year). Note that the terms like $f_{OA}O$ correspond to the total fluxes depicted in the diagrams, whereas the parameter f_{OA} of this model is therefore defined as a relative flux. Write equations for the other compartments, fill in parameters, and study what increase in atmospheric CO₂ levels one would predict if the parameter h goes from 0 to 9 kilo tons per year.

This project requires a literature search, model development, and numerical simulations.

2 COVID-19 herd immunity in the Brazilian Amazon

Manaus in Brazil was one of the cities that was hit very hard by the first wave of the COVID-19 epidemic, and on top of that it suffered from two large infection waves (Buss *et al.*, 2021; Sabino *et al.*, 2021). Detailed data on the daily number of people dying from the disease is available online (compiled by Bruce Nelson from the Instituto Nacional de Pesquisas da Amazonia on t.co/6g4HHEAuNY). We ask you to study whether this data can be modeled with classic SIR models of the form,

$$\frac{dS}{dt} = wR - \beta S \frac{I}{N} , \quad \frac{dI}{dt} = \beta S \frac{I}{N} - (d+r)I \quad \text{and} \quad \frac{dR}{dt} = rI - wR ,$$

with susceptible individuals, S , infected individuals, I , and recovered individuals, R . Here $N = S + I + R$ is the total number of individuals, β the infection rate, r the recovery rate, d the death rate due to COVID-19, and w is rate at which immunity wanes. The daily number of deaths is defined as dI in this model. In the R-script this is added as an extra column to the output of the model (using Grind's `tweak` option).

We provide the data and the R-script in the subdirectory [models/manaus](#) on the website of the course. Because the model may have more parameters than can be estimated from the data we start with using their estimates on the $R_0 = \frac{\beta}{r+d} \simeq \frac{\beta}{r} = 2.5$, and the estimated time to recovery of 10 days, and we fix the death rate using their estimate that the disease fatality is 0.2%.

First try to fit the first wave, i.e., the data until day 200. Do you obtain a good description of this data, and do you obtain realistic parameter values? Change the number of free parameters to study which parameters are identifiable. Can the first wave be described when immunity does not wane?

Since equilibrium was approached after the first wave, the second wave can only occur if the level of immunity wanes, and/or if second wave is due a new strain to which the recovered individuals are poorly protected (Buss *et al.*, 2021; Sabino *et al.*, 2021). Can this model also describe both waves? Modify the model to allowing for a second strain that can also infected recovered individuals (at a rate β_R). Can this model describe both waves and does this require that immune wanes?

Read the commentary on www.reuters.com/article/us-health-coronavirus-brazil-manaus/in-brazils-amazon-a-covid-19-resurgence-dashes-herd-immunity-hopes-idUSKBN2610I4 to put your results in perspective.

The fitting of this model to the data is quite complicated and will quite some time on a slow computer.

3 Co-existence by trade-offs?

Posfai *et al.* (2017) study the “Paradox of the plankton” by modeling resource competition between a large number of consumers. Their major idea is that consumers are expected to specialize on a subset of the resources, and therefore they introduce trade-offs among the consumption rates when parametrizing their model. Surprisingly, they find that an unlimited number of species can coexist, and that their model reproduces several features of natural ecosystems, including keystone species and population dynamics characteristic of neutral theory. The consumer equation of their model takes the following form:

$$\frac{dN_i}{dt} = \left(\sum_j \frac{\beta_{ij} c_{ij} R_j}{h_{ij} + c_{ij} R_j} - \delta_i \right) N_i ,$$

where each additional resource increases the maximum birth rate, $\beta_i = \sum_j \beta_{ij}$, that is approached when all resources are available at large densities, i.e., when $R_j \gg h_{ij}$ for all j (which would be the natural situation when all consumer densities are low).

This project appears in the book as Question 9.8: to get started on the project make sure you first complete this question. Discuss whether or not you find this a proper model for substitutable resources or for essential resources. Second, use Grind to study the idea of a trade-off in our own models for competition for substitutable resources. Simplify their analysis by considering just two resources. Do you find similar results, and –if so– what is actually required to repeat these results? Do you expect different results when there are three (or more) resources? Third, try the same trade-off in our models for essential resources. Do obtain the same results? What do you think of this paper: is this indeed resolving the Paradox of the plankton?

Note that the same group has another paper on this model (Erez *et al.* (2020)), which was praised in the Princeton UU news bulletin: www.princeton.edu/news/2020/09/18/princeton-scientists-explain-how-diverse-species-coexist-microbial-communities.

Good for students liking Tilman diagrams. Parts of the papers are somewhat mathematical, the main idea is explained above, however.

4 Temperate phages

Generally, bacteriophages infect bacterial cells by injecting their DNA into them. The viral DNA is transcribed to make many copies of viral proteins, such that numerous copies of the infecting particle are assembled. After a while the bacterial cell bursts and releases viral particles. This is the lytic life-cycle of the bacteriophage. Temperate bacteriophages can choose a different life-cycle, where they

integrate into the DNA of the host cell. This “prophage” remains dormant and is passed on with every bacterial division. This is called the lysogenic life cycle. At some point the prophage can be induced to resume the lytic form of the life cycle, and start to produce proteins and burst the cell. The evolutionary difference between these two life cycles has been studied extensively (Gandon, 2016; Berngruber *et al.*, 2013). A recent twist to the decision between lysis and lysogeny is a paper by Erez *et al.* (2017) demonstrating that $\phi 3T$ phages “communicate” by producing a signal peptide upon infecting a cell (see Hynes & Moineau (2017) for a commentary). The concentration of this peptide increases the propensity for the lysogenic life-cycle of subsequent infections. Two recent papers studied the evolution of this (Maldonado-Barragán & West, 2020; Doekes *et al.*, 2021).

In the course we have used chemostat equations to model bacterial growth. To simplify we first follow Berngruber *et al.* (2013) and use Logistic growth to formulate a simple mathematical model for temperate phages:

$$\begin{aligned}\frac{dS}{dt} &= rS(1 - S - L) - mS - \beta SV, \\ \frac{dL}{dt} &= rL(1 - S - L) - mL + \phi\beta SV - \alpha L, \\ \frac{dV}{dt} &= \alpha L + (1 - \phi)\beta SV - mV,\end{aligned}$$

where S is the density of uninfected bacteria, L the density of lysogens (i.e., bacteria with a prophage), and V the density of the phages. The parameter r denotes the replication rate of the bacteria, and m (for mortality) is the loss of bacteria and phages (that is largely due to wash-out from the chemostat). We have simplified the model by ignoring the loss of phages by absorption to bacteria (you may want to put this back). Thus, β is the mass-action infection rate, a fraction ϕ of the infections is lysogenic, and α is the induction rate. A second simplification is that we have scaled the density of the phages by their burst rate.

First use this model to study the lysis-lysogeny decision. Can you find an “optimal” value of ϕ ? One approach to study this is to write a model for two strains of the virus, that differ in ϕ , while assuming that lysogens cannot be super-infected (see Berngruber *et al.* (2013)). Second, extend the model with an equation for the peptide and make ϕ a function depending on its concentration. Do phages responding to this peptide outcompete phages that don’t? Would it make a difference to model this as a chemostat (rather than by logistic growth)?

This is a fairly numerical project, Grinding various different models.

5 Competitive exclusion and parasitism

Many species suffer from a heavy burden with pathogens (Dobson *et al.*, 2008). If pathogens truly control population densities, this may increase ecosystem diversity by reducing competitive exclusion. This is often referred to as the Janzen-Connell hypothesis, e.g., in Sedio & Ostling (2013) and Bagchi *et al.* (2014). In the course we considered several populations of bird species with a birth rate declining linearly with the population size, and with a death rate that is independent of the population density. We let the individuals be susceptible to an infection with a parasite that increases the death rate somewhat, but hardly affects the birth rate. We assumed that transmission of parasites occurs upon contacts between infected and susceptible individuals of the same species, and obeys mass action kinetics. Further there was no vertical transmission, i.e., the parasite is not transmitted to eggs. Thus, we let $N_j = S_j + I_j$ be the total number of birds, S_j be the susceptible non-infected birds, and I_j be the infected birds of the j^{th} species:

$$\frac{dS_j}{dt} = bN_j(1 - \sum N_i/k) - d_j S_j - \beta_j S_j I_j \quad \text{and} \quad \frac{dI_j}{dt} = \beta_j S_j I_j - (d_j + \delta_j) I_j,$$

where δ_j reflects the deleterious effect of the infection. Note that one can reduce the number of parameters by defining an infection rate increasing with the virulence, $\beta_j = \frac{\delta_j}{h+\delta_j}$.

First analyze a 2-dimensional system, i.e., let $j = 1$ and consider one species. Next, study how many new species you can add to this one-species ecosystem assuming that (1) all bird species occupy the same niche, and (2) every new species has a faster death rate, i.e., a lower fitness, than the previous one ($d_{j+1} > d_j$). Make a simple function describing how d_j depends on j . Note that you can define vectors of equations in Grind (see the tutorial).

Finally, one can also play with the virulence of the parasites. Does it help if the dominant species are infected with more virulent parasites? The Janzen-Connell hypothesis typically states that pathogens are expected to evolve towards infecting the most abundant species, which is called negative density dependence (Bagchi *et al.*, 2014). Do you expect this to evolve in this model? Remember that for this definition of the infection rate the R_0 is an optimum function of the virulence.

This is a nice project requiring a clever design of the various death rates, nullclines and numerical simulations.

6 Ontogenetic development for dummies

Persson & De Roos (2013) and De Roos & Persson (2013) summarize their extensive work on the effects of having juveniles and adults with different energetic requirements. These surprising effects include increases of the population size when the death rate increases, implicit Allee effects, and several more. They use both ODEs and PDEs for the modeling of the age dependent growth of the biomass of adults and juveniles, and these models are fairly complicated.

The aim of this project is to see whether their interesting effects can also be found in more simple (phenomenological) models, e.g.,

$$R = K - c_1J - c_2A, \quad \frac{dJ}{dt} = \frac{eAR}{h_2 + R} - \frac{mJR}{h_1 + R} - \mu d_1J \quad \text{and} \quad \frac{dA}{dt} = \frac{mJR}{h_1 + R} - \mu d_2A$$

where R is the available amount of resource, K the total, and c_1 and c_2 determine how much stored in juveniles, J , and adults, A . The rates at which juveniles mature, and the rate at which adults produce juveniles, depend on the availability of the resource. With the two h_i parameters one can change the symmetry of this dependence on the resource ($h_1 = h_2$ would be a conventional symmetric system). With the parameter μ one can increase the death rate of both juveniles and adults simultaneously.

Read their paper and try to repeat as much of their results with this toy model. You may also enjoy watching these lectures: staff.fnwi.uva.nl/a.m.deroos/Research/Webinars/.

This is a somewhat numerical project, introducing you to quite a different class of models for population dynamics.

7 Early warning signals in the Sahel

The notion that we might be able to observe “early warning” signals in time series data of systems that are about to collapse is receiving a lot of attention recently (Scheffer *et al.*, 2009; Veraart *et al.*, 2012; Scheffer *et al.*, 2012). This theory is based upon the simple fact that when a system approaches a catastrophic bifurcation (like a saddle-node bifurcation) the dominant eigenvalue is approaching

zero, implying that the return time of the system to its steady state is becoming very long. Thus, an increasing return time of a system under slowly changing environmental conditions could provide a warning signal for an upcoming catastrophe. It would be extremely important if one could indeed detect such early warning signals in the time series of any particular system, because one could change the environmental conditions to prevent a future disaster. Long return times should be associated with more variation in the data, and to a better correlation between subsequent data points. The review paper by Scheffer *et al.* (2009) provides interesting examples of early warning signals in biological data, and clearly explains the underlying theory in several boxes. Read this paper before you embark on this exercise. In the book this project was introduced as Question 11.2, where you may have repeated their analysis using a logistically growing resource harvested according to a sigmoid functional response, i.e., $dX/dt = X(1 - X/K) - cX^2/(1 + X^2)$.

Now we ask you to consider a more real-world example. Start with a model describing the dynamics of water uptake in arid zones (Rietkerk & Van de Koppel, 1997; HilleRisLambers *et al.*, 2001), that you may have seen in the first year course. Overgrazing by cattle in arid areas is known to lead to desertification. In the Sahel zone one may find both barren areas and vegetated areas in the same region. This bistability has been studied with models having saddle-node bifurcations (Noy-Meir, 1975; Rietkerk & Van de Koppel, 1997; HilleRisLambers *et al.*, 2001). The main idea is that in areas with little vegetation coverage most of the (sometimes heavy) rainfall fails to penetrate into the soil, and is rapidly washed off into rivers and disappears. In areas with somewhat more vegetation water is better captured, but vegetation also consumes water by growth. Models for vegetation growth in arid areas can remain simple because the availability of water in the soil is typically the major limiting factor. This main idea is translated into the following model:

$$\frac{dW}{dt} = R\left(w_0 + \frac{V}{k_2 + V}\right) - r_W W - \frac{gVW}{k_1 + W},$$

$$\frac{dV}{dt} = i + \frac{cgVW}{k_1 + W} - dV - hV,$$

where R is the rainfall (in mm d^{-1}), V is the vegetation biomass (in g m^{-2}), and W is the amount of water in the soil (mm). The model has two saturation constants, k_1 (mm) defines the amount of water at which the vegetation grows at half its maximal rate, and k_2 (g m^{-2}) is the vegetation cover at which the penetration of water into the soil is $R(w_0 + 1/2) = 1.4 \text{ mm d}^{-1}$. The parameter h denotes the grazing by cattle, which depends on the herd size that is set by people buying and selling cattle. Parameters of this model have been estimated by Rietkerk & Van de Koppel (1997) and HilleRisLambers *et al.* (2001):

Name	interpretation	value	dimension
R	rainfall	2	mm d^{-1}
c	conversion of water to plant biomass	10	$\text{g mm}^{-1}\text{m}^{-2}$
d	death rate of vegetation	0.05	d^{-1}
g	maximum water uptake	0.05	$\text{mm g}^{-1} \text{m}^2 \text{d}^{-1}$
k_1	half saturation constant	5	mm
k_2	half saturation constant	5	g m^{-2}
r_W	soil water loss due to evaporation	0.2	d^{-1}
w_0	water infiltration in absence of vegetation	0.2	—
i	immigration of seeds/plants	0.01	$\text{g m}^{-2} \text{d}^{-1}$

In the absence of a vegetation there is about 2 mm water in the soil. The death rate of the vegetation is partly due to normal turnover and partly due to grazing by cattle. Assume that in the absence of cattle the vegetation turnover is about $d = 0.05 \text{ d}^{-1}$, resulting in a carrying capacity of approximately 450 g m^{-2} . Study the effect of increasing the herd size, c , starting with just a small herd. The model is available on the website under the name `sahel.R`: Suppose the local community has decided on a

safe and stable herd size, c , and that the environment is faced with a few years of declining rainfall. Can you predict when they should start decreasing the herd size?

Finally, compare your results to those of Boerlijst *et al.* (2013): do the variables in this model differ in the early warning signals they provide?

8 Influenza infections

Every year many people become vaccinated with a current influenza vaccine. It is a major challenge to design such a vaccine because influenza is evolving, and differs from year to year. It has been described that if a major fraction of the population is immune to the currently dominant strain, a new strain may evolve during the season (as most of the population would have no immunity to such a new strain). This is called “strain replacement”. People may even be infected with both strains during a season because the crossreactive immunity for both strains is short-lived. See Furuse & Oshitani (2016) for a recent paper on this topic.

Zarnitsyna *et al.* (2018) write an SIR model allowing for strain replacement and surprisingly conclude that intermediate levels of vaccination coverage may minimize seasonal influenza outbreaks. Repeat their results and study how the size of the total epidemic depends on the fraction of people that are vaccinated before the season starts. Martcheva *et al.* (2008) wrote an earlier review on strain replacement. A cool paper to discuss during your presentation is Smith *et al.* (2004), who depict the evolution of influenza in a 2-dimensional antigenic map.

This is an interesting project given the recent COVID-19 pandemic.

9 How can ecosystems be diverse and stable?

In the last chapter of the BM-book we discussed several models investigating the relationship between diversity and stability. One approach is to fill Jacobi matrices or interaction matrices by randomly drawn parameters and study whether or not such a random system is expected to be stable (i.e., have negative largest eigenvalue). The matrices were typically filled with randomly chosen positive and negative values, such that the interaction between any pair of species could be competitive, mutualistic, or predator-prey like. Nevertheless all species were also given a logistic growth term to model their own expansion, suggesting that each species is also being maintained by some other resource that is absent from the model.

There are several exercises in the chapter filling Jacobi matrices or interaction matrices in different ways. Only the ‘Huisman’ and ‘Scheffer’ exercises distinguished between resources and consumers, and did not allow for a default self-limiting interaction of consumers. To see that this question is still open we refer you to the recent Gellner *et al.* (2023) paper.

Another potential direction of this project is to also study the paper of Cui *et al.* (2021) who repeated the classic analysis of random Jacobi matrices, while keeping the total interaction strength per species the same when they increased the connectivity of the matrix. Highly connected systems would then have smaller off-diagonal elements than lowly connected systems. Code for this model is provided at the end of the `gardner.R` script. These authors also keep the diagonal elements at $A_{ii} = -1$, however.

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