Mini projects
Computational Biology 2024-2025

General information

The idea of the miniprojects is to work on a small computational/modeling project in groups using the (spatial) modeling skills you have gained in this course. The expected output is a short research report, with an abstract, introduction, results, discussion, conclusions, and methods. You need to discuss your findings in the light of at least two papers. The focus should be on your own modeling efforts, with some discussion in light of recent literature so you don't work in a vacuum. We will also discuss the miniproject outcomes in a plenary session, either by every group giving short pitches about what they found, or by Paulien discussing each project and asking groups who worked on it for explanations or comments. Start simple: it is often good to think about the minimal implementation you can make that still satisfies what you're trying to model well enough. You can add more complexity as you see fit once you have something basic up and running. As for the grading of the projects, since they are on wildly different topics, in different frameworks, and you have different coding experience, we will just be grading on a scale of insufficient to exceptional. If you are unsure on how to write a research report, following the parts of this GSLS rubric (https://rubric.gsls-uu.nl/rubrics/rubricresearch-report) that are applicable (most points except for the layman's summary and appointment scheduling) should yield a good report. As a final tip, don't forget to check your results with a few seeds to make sure they are not flukes. Good luck and have fun!

Project I

Does high cost minimize the production of public good?

The potential for cooperators to establish themselves in a non-cooperative populations, or conversely for selfish individuals to invade and possibly destroy a cooperative population, has mostly been formulated in terms of relative costs and benefits of the two populations. This is true both in the context of 'group selection', 'kin selection' as well as the well-known game theoretical models of cooperation (prisoners dilemma, hawk and dove). The general model result is that cooperation should not be too costly, or it will not persist.

You will investigate these results in the context of public good production. Many micro-organisms secrete products in the medium to digest food sources and/or to enable the uptake of essential resources. Siderophores are a pre-eminent example. The production is generally costly, whereas the products and therewith benefits are shared by all in the environment.

For your model, make sure the public good decays fast, and assume the public good is *essential for growth*. Also assume that both the cost of production and the benefits are proportional to the amount produced/used. First, assume the cost of production of a unit of public good is low relative to its benefit (e.g. a ratio 1:10) and study invasion of bacteria who produce more or less public good. Then, study what increasing costs does to these invasion properties. After these ecological experiments, let production of public good evolve.

Compare your model and your results to the article by Ohtsuki et al.[1] Can you check if there is quantitative agreement under certain parameter settings?

Discuss your finding in the light of at least one relevant, recent paper.

[1]Ohtsuki, Hisashi, et al. "A simple rule for the evolution of cooperation on graphs and social networks" Nature 441.7092 (2006): 502-505.

Project II

Why do animals/cells die? Evolution of programmed death

Many organisms die because they are eaten or because of some accident. However even without such mishaps, they have a finite lifetime. The lifetime of closely related species can vary by an order of magnitude. Moreover it has been experimentally shown that simple (knockout) mutations can increase the lifespan (e.g. *Extended longevity in mice lacking the insulin receptor in adipose tissue*, M. Blüher, B. B. Kahn, C. R. Kahn - Science, 2003). In other words it is apparently possible to live longer, and we should therefore conclude that the extant lifetime of a species is an "evolutionary choice". Explanations have been sought in terms of continued evolutionary adaptability to changing environments, or in terms of trade-offs (e.g. longer lifespan implies less fecundity) but data do not support this notion.

Here we will ask if, and how, higher death-rate could give a long-term competitive advantage in a constant environment due to emergent pattern formation. You may explore this problem in a system of predators and preys.

First, study ecological dynamics between species differing in death rates, and look for example at the following:

- Who out competes whom?
- Can otherwise identical lineages with different death rates coexist? Why?
- If you find coexistence, test whether these different lineages can exist without the other? (in other words, can high or low death rate lineages be 'rescued' by lineages with other death rates?)

Next, study how death rates evolve (focus on the interesting cases you found from the questions above). Note: the interesting cases you should find exist in a rather narrow parameter regime. If you don't find them, then feel free to skip to the evolutionary simulations: the system might more easily evolve it than you can find it by manually trying, and you can then do ecological experiments with information from the evolved values.

Compare your results with results/discussions found in the literature, e.g. in similar models (discuss both differences in the model/experiments and in the general discussions).

Project III

Evolutionary Dynamics of Host-Endosymbiont Relationships

Endosymbiosis is a biological interaction where one organism (the endosymbiont) lives within the cells or body of another (the host). This interaction often results in a mutually beneficial relationship and has played a crucial role in shaping life on Earth. One of the most notable examples of endosymbiosis is the origin of mitochondria and chloroplasts in eukaryotic cells. In this project, you will focus on a single-celled host and its endosymbiont, aiming to understand how their relationship evolves in terms of resource consumption and growth strategies. The project consists of two parts, as described below.

Part 1: Evolution of Growth Dynamics

The first part of the project examines the evolutionary interplay between a single-cell host and its endosymbionts living within a two-dimensional grid. Symbionts divide and die inside a host. If a host loses all its symbionts, it dies. Both the host and the endosymbiont rely on externally provided nutrients to grow and divide. To reflect the early stages of endosymbiosis, let us assume:

- There are no communication mechanisms between the host and symbiont.
- Symbionts are randomly distributed to the host's offspring during division.

Growth rate (r) is determined by nutrient availability (n). You will implement a simple linear function to define this relationship:

$$r = a \cdot n - b$$

Where a, $b > 0$ are evolvable parameters that define each host and symbiont.

- The host, bearing more metabolic functions, should have growth rate constraints (for example a and b can have maximum and minimum possible values).
- The symbiont may evolve more freely

You will investigate how the host and symbiont evolve their growth parameters to survive and coordinate their dynamics. For example, how do host and symbiont manage resource consumption and division under these constraints? Are the symbiont's growth parameters limited by implicit factors in the model even without explicit constraints?

Part 2: Bi-Parental Inheritance of Endosymbionts

Most eukaryotic cells are capable of sexual reproduction. However, organelles of endosymbiotic origin are almost always inherited by one of the two parents[1]. The second part of your project will investigate one implication of bi-parental inheritance of endosymbionts. Here, two parent cells are required for reproduction; the offspring inherits its host genome and half its symbionts from one parent and half the symbionts from the other parent. How do host-symbiont relationships evolve under bi-parental

inheritance? Can you explain the changes when you compare this with the clonal reproduction you studied in Part 1?

Comment on the different levels of selection and discuss your results in the light of at least one relevant, recent paper.

[1]Breton S, Stewart DT. “Atypical mitochondrial inheritance patterns in eukaryotes” Genome. 2015; 58(10):423-431.

Project IV

Evolution of horizontally transmitted mutualists

The Hawaiian bobtail squid (*Euprymna scolopes*) has fascinated scientists for its symbiosis with the bacterium *Aliivibrio fischeri*. *A. fischeri* is a bioluminescent bacterium which makes the squid glow. When they are glowing, they have a lower the risk of predation[1]. A juvenile squid hatches un-colonised and acquires *A. fischeri* from the seawater, making it an example of horizontally transmitted symbiosis, in contrast to vertical transmission where the juvenile is born with the symbiont. Vertical transmission is classically seen as a preferred strategy for mutualistic symbionts because it helps preserve symbiont-associated lineages. In this project, you will use concepts learnt in this course to explore why horizontal transmission could be a better strategy.

Assume that horizontal acquisition of the bacteria is a primitive strategy where the symbiont is acquired by pumping seawater that is contaminated by bacteria from other squids. Let a mutant squid appear which can transmit some bacteria through the egg (vertical acquisition). Consider the following distinct reproduction strategies:
S_P: Offspring hatches un-colonised
S_M: Offspring hatches and immediately colonised by parent's symbiont.

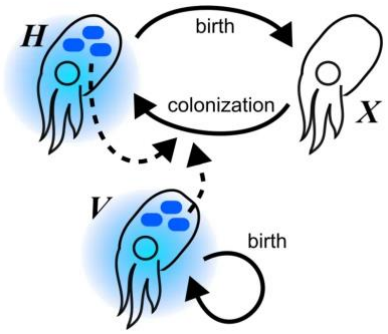
(1) Consider the given system of ODEs:

$$\frac{dH}{dt} = \beta X(H + V) - \delta H$$

$$\frac{dX}{dt} = bH(1 - N) - \beta X(H + V) - (\delta + s)X$$

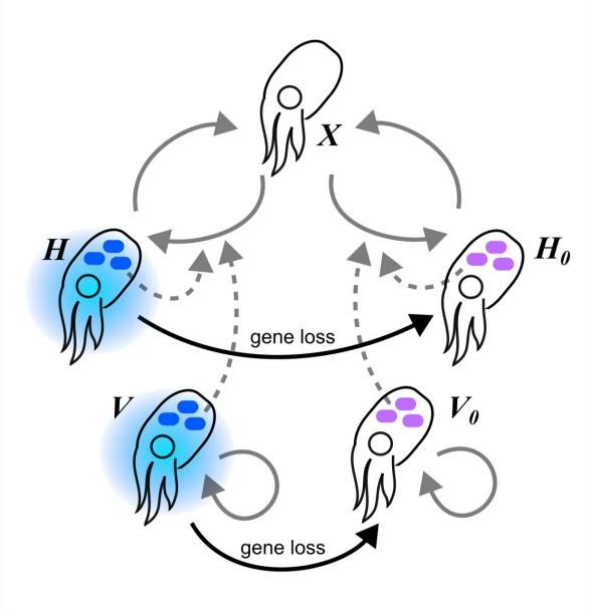
$$\frac{dV}{dt} = bV(1 - N) - \delta V$$

Here, species H reproduces with an intrinsic birth rate b to create un-colonised juveniles X. Without the mutualist, the squid dies at a higher rate due to predation. These un-colonised squids can be colonised by symbionts from other squids at rate β. Assume a mutant squid species V emerges that colonises their juveniles with their symbiont at birth.



Using grind.R, find whether strategy S_M invades. Give reasons to your observations.

(2) Assume that *A. fischeri* can mutate and lose its ability to produce bioluminescence (but gaining bioluminescence through mutation is negligibly rare). We can expect this non-mutualist to outcompete the mutualist within a squid as the former does not bear the metabolic cost of bioluminescence. Then, every H and V squid can be converted into a H_0 or V_0 squid respectively at a certain rate and they cannot evade predation anymore. Note that the juveniles can also be colonised by these non-mutualists now. Extend the ODE model to incorporate the occurrence of these non-mutualists and answer whether strategy S_M invades. Discuss the error threshold.



(3) Compose a CA of the squid population (with species H and V) and check again whether strategy S_M invades. Does spatial structure influence the outcome? If so, how?

Comment on how the studied mechanism can be extended to other host-symbiont systems and compare your results with similar models in recent literature.

Optional questions

(A) Extend the model to include the mode of symbiont transmission as an evolvable parameter.

(B) Does it matter if the mutualist increases the birth rate of its host (fecundity advantage) instead of decreasing its death rate (lifespan advantage)?

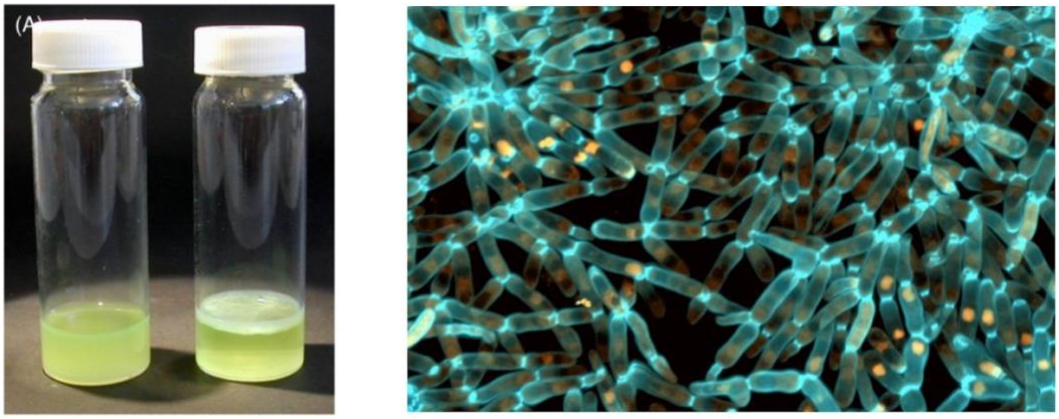
[1]Jones, B.W., Nishiguchi, M.K. "Counterillumination in the Hawaiian bobtail squid, *Euprymna scolopes* Berry (Mollusca: Cephalopoda)" Marine Biology 144, 1151–1155 (2004).

Project V

Sticking together

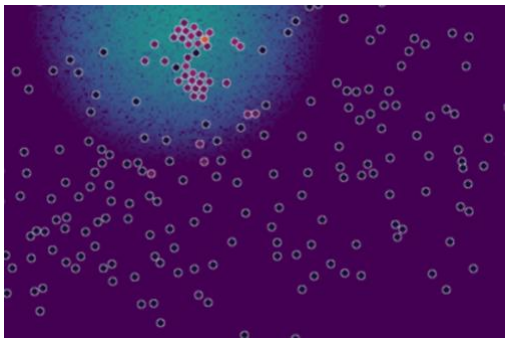
While simple unicellular life forms appeared relatively early on the planet Earth, complex multicellular life only emerged after a few billion years of evolution. Nevertheless, multicellular life has emerged more than once, and can take many different forms — from simple branching structures, to slime mold aggregates, to fully developed tissues with distinct cells types performing specific functions.

While selection pressures that favour multicellular life in bacteria may not be identical to the selection pressures identified for eukaryotic organisms, there may be generic principles at play. One of the most primitive forms of multicellularity is "sticking together", which has indeed been experimentally observed for both kingdoms. Lab experiments show that bacterial cells (*Pseudomonas fluorescens* SBW25) evolve to stick together to form a floating mat at the liquid-air interface, where oxygen is available[1]. Similarly, when yeast in a flask is repeatedly selected for size (as a proxy for predation), cells are shown to not fully separate after division, forming "snowflake"-like structures[2].



Experimentally evolved multicellular aggregates in prokaryotes (left) and eukaryotes (right).

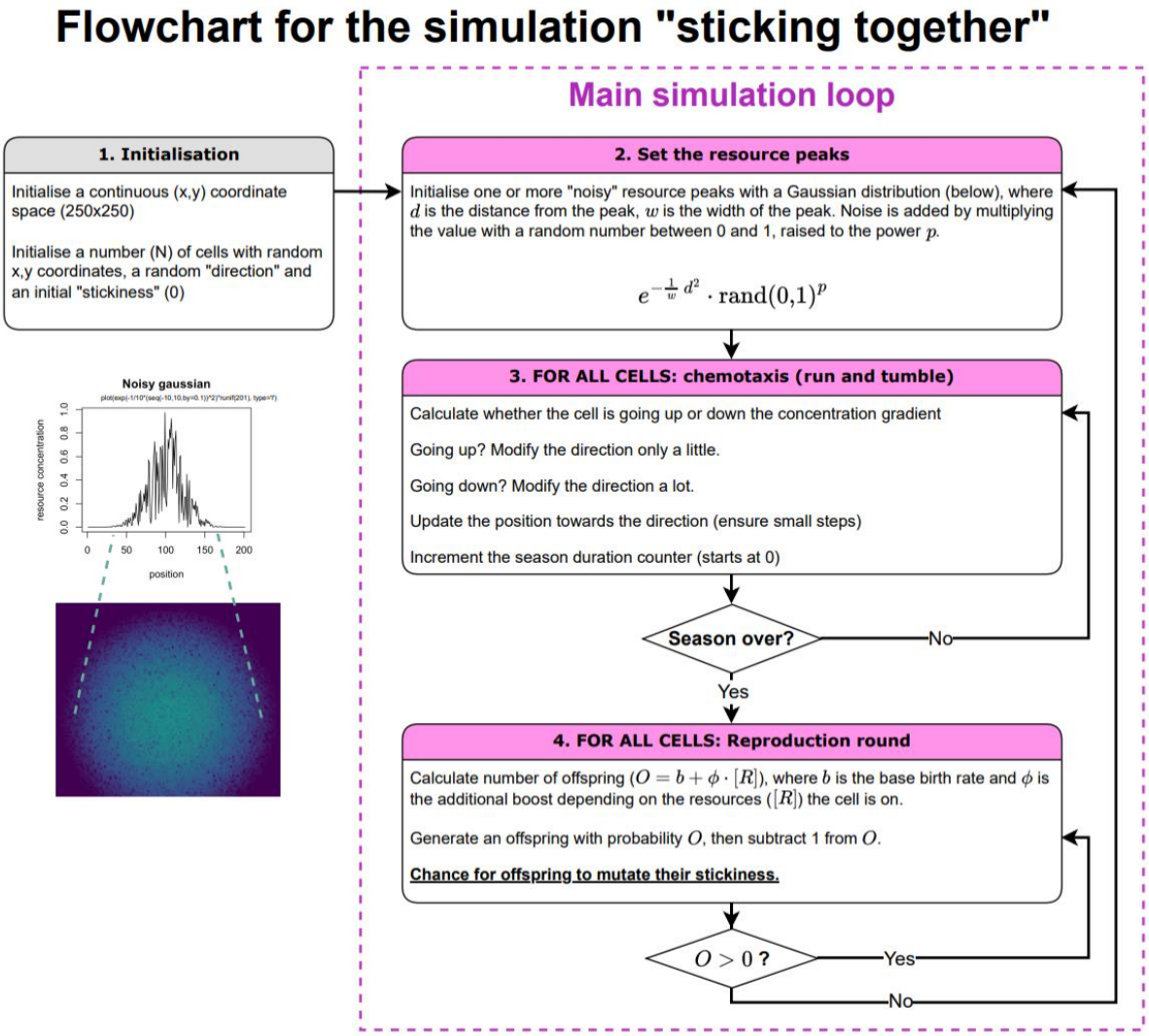
For the latter example, called “snowflake yeast”, continued selection experiments gave rise to more complex functions, such as programmed cell death to more efficiently fragment the clusters of cells into propagules (“baby snowflakes”) or increase the flow of nutrients into the aggregate. Clearly, sticking together appears to be an easy stepping stone towards multicellularity and subsequent complexity.



In this mini project, you will explore a computational model to investigate why cells would want to stick to one another when foraging for resources (screenshot above). The base Cacatoo code for this project is provided here (jsfiddle.net/bramvandijk88/j1rLwdq0/).

First, it is advised to read the code and inspect the flowchart below; ensure you conceptually understand what the simulation does. Then, explore the model as given and hypothesise about the various benefits of cells sticking together, and explore how these mechanisms change with the parameters of the model. Can you also identify disadvantages to sticking together?

For the research part of this mini-project, extend the model to enable cells to be even "smarter" as they try to improve their ability to find resources. For this, you can think about environmental sensing, timed regulation, or other concepts that you've learned about in this course.



[1]Hammerschmidt, K., Rose, C., Kerr, B. et al. "Life cycles, fitness decoupling and the evolution of multicellularity" Nature 515, 75–79 (2014).
[2]Ratcliff, W., Fankhauser, J., Rogers, D. et al. "Origins of multicellular evolvability in snowflake yeast" Nat Commun 6, 6102 (2015).