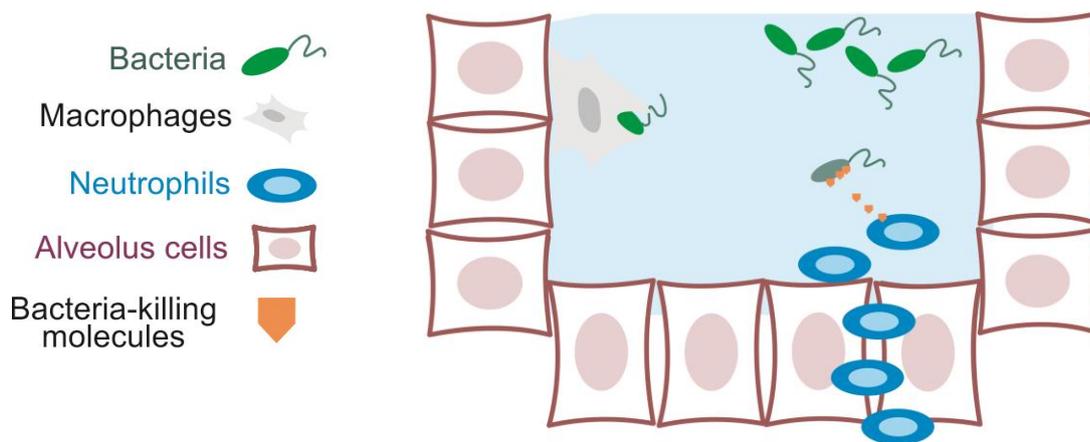




## What is pneumonia?

The most frequent cause of **pneumonia** is infection with **pathogens**, that is viruses or **bacteria** that invade and attack a zone of the body, in our case the **lung alveoli**. Lung alveoli are small air sacs. They are the building blocks of the lungs, and they are where red blood cells take up the oxygen that our cells need to work.



**Figure 1.** Sketch of an infected lung alveolus.

As a response to the attack by pathogens against the lung alveoli, the body triggers **inflammation**. This is the body's basic mechanism of defence against infections. Inflammation starts when the cells in the alveolar lining "sense" the presence of the bacteria. As a consequence, they produce and discharge molecules that act as an emergency call to the body. The body replies to this signal by sending different types of highly specialized protective cells, the so-called **immune cells**. The closest immune cells replying to the call are the **macrophages**. Macrophages can recognize the bacteria and eliminate them by simply eating and digesting them. Other immune cells that also react very quickly to the call are the **neutrophils**. Neutrophils release a lot of natural, highly

toxic molecules that are like chemical weapons that can kill the bacteria. Other types of cells also move to the site of infection, but this happens much later.

Although the aim of the immune cells when they provoke inflammation is to eliminate the threat caused by the bacteria, their work has a number of side effects. For example, during inflammation, the infected lung alveoli get filled with liquid and debris, and this makes it much more difficult for the oxygen to reach the red blood cells. Hence, **breathing can get difficult**. The molecules released by the neutrophils not only kill bacteria but also damage the neighbouring alveolar cells. Finally, if the immune cells fail to neutralize or contain the infection, pathogens can **spread with the blood to other sites in the body** and harm other very important organs like the kidney or the liver.

When detected in due time by a clinician, bacterial pneumonia can be treated with **antibiotics**. The antibiotics are molecules that target bacteria, weaken them and provoke their death. However, some times the antibiotics come too late to prevent the damage, and in severe cases pneumonia can kill weak people like elderly and children. It actually kills almost one million children annually, especially in poor countries with difficulties to access medical care and antibiotics.

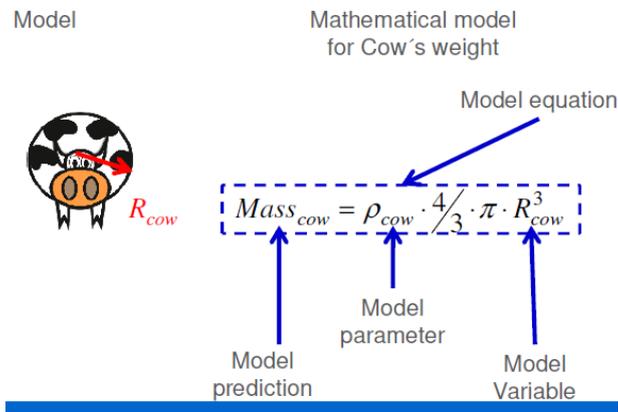
### **What is a mathematical model?**

A **model** is a simplified representation of a natural system. Models are used in science to organize knowledge, identify open questions, or simulate natural systems from atoms and molecules to galaxies. A **simulation** is the mimicking – and potentially the prediction – of a system's behavior using a model.

A **computational model** is a set of rules that encode the behavior of the natural system that we want to investigate. A mathematical model can be used to mimic or predict the behavior of the system modelled by making **computational simulations**. A computational simulation can be used as a tool to formulate scientific hypotheses and design experiments. This is common practice for example in physics: mathematical modeling has been used to formulate hypotheses on the structure of the atom, or the movement of the planets in the solar system.

Further, computational simulations can be used to make **predictions**. For example, computational simulations are used to predict the weather, storms or heat periods, with moderate to high accuracy for the immediate future. What we know about climate change is based on predictions of very advanced computational models. Computational

simulations are also used in technology, to design planes or cars in a way they consume less fuel, or to select the best routes for trains and buses.



**Figure 2. A mathematical model** is a set of parametric equations or other mathematical entities encoding the basic properties of the investigated biological system. For example, when calculating the mass of a cow, one can derive a simplified mathematical model like the one proposed. In the model, we assume that the average cow has a spherical shape. We distinguish the **model variable** that can be measured (here the radius of the cow,  $R_{cow}$ ), the **model prediction** or quantity that can be inferred from the model using the value for the model variable (here the mass of the cow,  $Mass_{cow}$ ), and the **model parameter**, a fixed quantity that has to be known to apply the model for prediction (here the expected density of the cow,  $\rho_{cow}$ ).

Over the last decades, we have obtained sufficient knowledge, technology and computers to construct also mathematical models that can predict the behavior of biological systems. For example, the appropriate dose range of new drugs is established using simulations of mathematical models. In the Gaminfection Hackathon, we are using computational modelling to play, simulate and learn about pneumonia.

Mathematical models are constructed, characterized and simulated following a well-established procedure. Most of the elements of the workflow are common to the use of computational models in any area of natural sciences or engineering. The workflow is composed of the following steps, represented in Figure 2:

1. **Model derivation.** We use the available knowledge to identify the relevant compounds and interactions of our observed system. Here in our pneumonia model, we identify the cell types that play a role during infection and the interaction and processes they undergo. This information is transformed via rules into the equations of the computational model.

2. **Model calibration and validation.** We iteratively improve the computational model until the model perfectly reproduces all the available observations. When the model fails initially, we refine it by modifying its equations.
3. **Predictive simulations.** Once we have a model that can mimic perfectly all the observations, we run simulations with the model for new scenarios, in this case for different infection conditions. To make a simulation, one has to setup the model by giving **initial values** to some of the variables in the model, for example the initial amount of bacteria in the alveolus. Once this is done, the simulation can be run in the computer, and we get a prediction of how the inflammation would evolve over time, i.e. a prediction for the growth of bacterial and of the time in which all bacteria are removed by the immune cells. Running simulations with systematically randomized initial values can give a lot of insights into the behaviour of the modelled system.

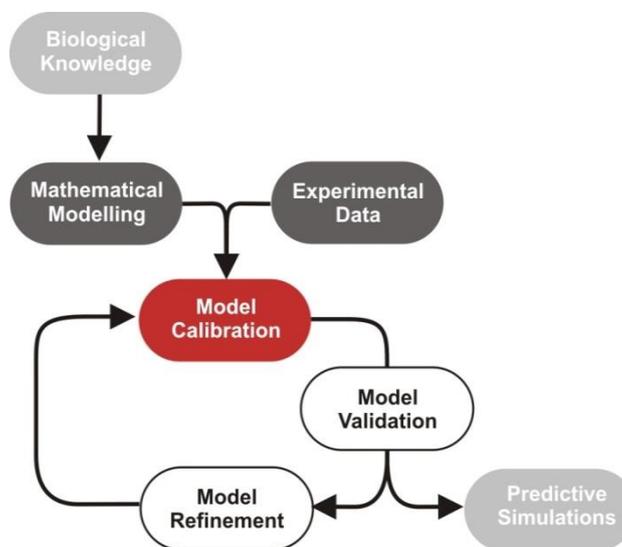
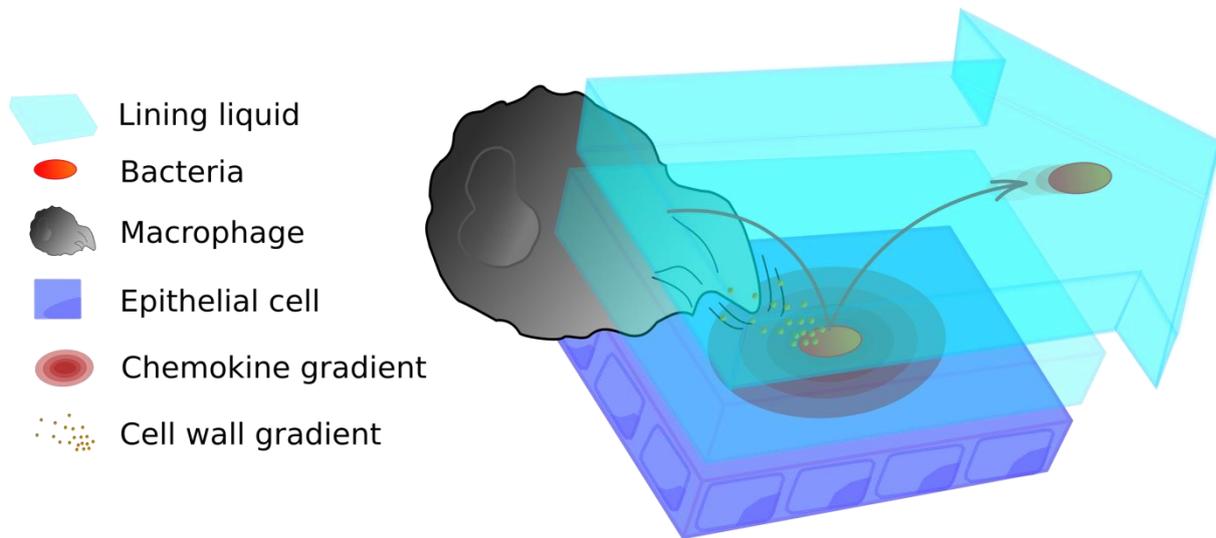


Figure 2. The mathematical modelling workflow

### Our lung infection mathematical model

The mathematical model behind the Unity code that we have developed for the Gaminflection Hackathon is supposed to reproduce the first 24 hours after the arrival of the bacteria in the alveolus. In these 24 hours, the decision is made whether the infection fails or succeeds. The model represents a single alveolus composed of 121 (11x11) **lung epithelial cells**.



**Figure 3.** Sketch of the lung infection mathematical model.

In **Error! Reference source not found.** the mathematical model is explained using a very simple sketch. In the model the inner alveolar surface is modelled as a two-dimensional square-shaped landscape with layers of lining liquid on top. The model includes equations that mimic the following processes:

- a) The movement of the bacteria in the alveolar lining liquid.
- b) The **proliferation** (cell division) of the bacteria.
- c) The movement of macrophages tracing the bacteria and their ability to kill the bacteria.
- d) The death of “exhausted” macrophages that have eaten too many bacteria in a short time.

Bacteria are immersed in the alveolar **lining liquid**. This lining liquid is composed of two separated layers, one static layer attached to the epithelial cells and another flowing layer above the previous one. If bacteria jump from the static to the flowing layer, they can be washed out from the alveolus. If bacteria stay in the static layer, they are recognized by the epithelial cells and signal molecules are released (named **chemokines**) to attract **macrophages**. Macrophages are like Pac-Man: they pursue the bacteria and eat them. In the model, bacteria can divide every 200 minutes producing two bacteria out of one. Macrophages can die if they eat too many bacteria at once.

## **Glossary**

Lung alveolus: the place in the lungs in which the gas exchange with the red blood cells happens. They are formed by a single layer of epithelial cells through which the gas passes.

Epithelial cells: the cells through which the gas exchange happens in the lungs. They form a barrier, protecting the body from entry of microorganisms to the blood, and also they are able to recognize the pathogens and release chemicals that activate the immune system and recruit cells to kill the pathogens.

Chemokines: chemicals released by the lung epithelial cells to attract other cells like macrophages to a specific position in the alveolus.

Lining liquid: a very thin layer of liquid that covers the inner part of the alveolus. Its function is to protect the epithelium from pathogens and to keep the alveolar surface slippery.

Macrophages: immune cells present in the lungs that are able to pursue and eat bacteria. They are also able to follow the gradient of chemokines created by the epithelial cells in response to bacteria.