

Route planning for bacteria

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Bacteria are fascinating biologists since their discovery in the late 17th century. They analysed their movement and translated it into mathematical models. Adapting these models to real situations can be challenging, because the model coefficients cannot be observed directly. We study this question mathematically and show why a simple 'route planning' consideration is of great use.

1 Route planing

Imagine you have an appointment to meet with a friend in one hour. The direct path from your place to his takes 40 min, so if you leave now, you will be early. On the other hand the sun is shining and you do not want to wait at your place for 20 min before leaving, so you decide to go for a walk and combine that with walking to your friend. You thus choose an arbitrary direction and start walking there. Say you want to walk at a constant speed, when do you need to change your direction to be at your friend's place on time?

Let us put this question in a mathematical setting:

At first, we formulate some assumptions and clarify the notation. For simplification we approximate your neighbourhood with a flat plane \mathbb{R}^2 and assume that there are no buildings etc on your way so you can walk along a straight

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line in any direction. Additionally, we suppose you walk with a constant speed of 6km/h. Then all possible directions you can choose are collected in the unit circle $V = \{w \in \mathbb{R}^2 \mid \|w\| = 1\}$. The norm $\|w\| := \sqrt{w \circ w} := \sqrt{w_1^2 + w_2^2}$ of the vector $w = (w_1, w_2) \in \mathbb{R}^2$ is the Euclidean norm and calculates the length of the vector. Here $x \circ y := x_1 \cdot y_1 + x_2 \cdot y_2$ denotes the Euclidean scalar product of two vectors $x = (x_1, x_2), y = (y_1, y_2) \in \mathbb{R}^2$ which measures the angle between x and y . One can easily check that it is linear in each component and symmetric, i.e. the following calculation rules of hold for all $\lambda_1, \lambda_2, \mu_1, \mu_2 \in \mathbb{R}, x_1, x_2, y_1, y_2 \in \mathbb{R}^2$:

$$\begin{aligned} x_1 \circ y_1 &= y_1 \circ x_1 && \text{and} \\ x_1 \circ (\mu_1 \cdot y_1 + \mu_2 \cdot y_2) &= \mu_1 \cdot (x_1 \circ y_1) + \mu_2 \cdot (x_1 \circ y_2), \end{aligned}$$

where the multiplication $\lambda \cdot x$ of a scalar $\lambda \in \mathbb{R}$ with a vector $x = (x_1, x_2) \in \mathbb{R}^2$ works componentwise $\lambda \cdot x = (\lambda \cdot x_1, \lambda \cdot x_2)$.

Then mathematically the problem can be formulated in the following way:

Question. *You have a starting point $S \in \mathbb{R}^2$ (your house) and a destination $D \in \mathbb{R}^2$ (your friend's house) to reach in time $t = 1$ hour. Say you walk at a constant speed of 6 km/h and the distance between your house and your friend's house is $\|D - S\| = 4$ km. The first direction you walk into after leaving your house will be denoted by $v \in V$. You are interested in finding the time $t_X \in [0, 1]$ and the point $X \in \mathbb{R}^2$ where you need to change direction and walk a straight line to your friend.*

Note that we leave out all units in the mathematical world to make the calculations more clean. It is implicitly assumed that lengths and coordinates are scaled in km, times in h and velocities in km/h.

The following geometrical considerations will help us solving this problem: In one hour, you will walk 6km in total to reach an aim that is 4km away. Since you want to change your direction only once, the starting point S , the destination D and the turning point X form a triangle where your walking path coincides with the sides $[S, X]$ and $[X, D]$, see figure 1. We are interested in finding X or equivalently the time t_X at which you reach X and need to change direction. That means the task is to find the vertex X of a triangle with two other vertices S and D such that the length of your walking path, i.e. the sum of the lengths $d = \|X - S\|$ and $s = \|D - X\|$ of the sides $[S, X]$ and $[X, D]$, is equal to $d + s = 6$. The direction of $[S, X]$ is your initial direction v .

At first, you can ask yourself whether this problem is solvable at all and in case it is, whether the solution is unique or if there are multiple possibilities. It turns

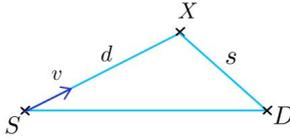


Figure 1: Triangle SDX .

out, the knowledge on the initial direction v and the choice of $d+s = t \cdot 6 \geq 4 = x$ guarantees a unique solution.

Let us get an intuition why this is true: Consider the situation where you have not chosen your initial direction v yet, but still want to go from S to D on a path of total length 6 while changing the direction only once. Then the set of all possible turning points Y is an ellipse

$$E := \{Y \in \mathbb{R}^2 \mid \|Y - S\| + \|D - Y\| = 6\},$$

with foci S and D and distance 6. In this notation $\|Y - S\| = d$ gives the length of the side $[S, X]$. As you can see in figure 2a, there are multiple solutions to this problem, namely every $Y \in E$.

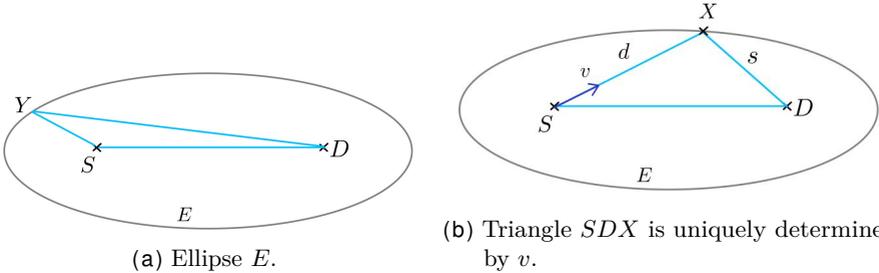


Figure 2: Geometrical intuition why X is uniquely determined.

If, however, we know the initial direction v , then the turning point X is unique: because X has to lie on the half line starting at S in direction v as well as on E , it is the intersection point of this line with the ellipse E and therefore unique, see figure 2b.

Now let us calculate X and t_X explicitly: If you arrive at D after time $t = 1$, that means

$$D = S + v \cdot 6 \cdot t_X + v' \cdot 6 \cdot (1 - t_X).$$

The factor 6 appears, because you walk with constant speed of 6 km/h and v' denotes the direction in which you walk after turning at X . Hence, v' is

the direction of $D - X$, meaning you walk straight towards D from X on. Rearranging yields

$$v' = \frac{1}{6 \cdot (1 - t_X)} \underbrace{(D - S - v \cdot 6)}_{=:b} + v.$$

Note that the vector b in the brackets is the path one would have to walk if you forgot to change direction in X and continued walking in direction v for the full 1h. Since we know that v' is a direction in V as well,

$$\begin{aligned} 1 &= \|v'\|^2 = v' \circ v' = \frac{1}{36 \cdot (1 - t_X)^2} \|b\|^2 + \frac{2}{6 \cdot (1 - t_X)} b \circ v + v \circ v \\ &= \frac{1}{36 \cdot (1 - t_X)^2} \|b\|^2 + \frac{2}{6 \cdot (1 - t_X)} b \circ v + 1^2, \end{aligned}$$

Solving this quadratic equation for $\lambda = 1/(1 - t_X)$ yields $\lambda_1 = 0$, which is impossible since $0 \leq t_X \leq 1$, or

$$\frac{1}{1 - t_X} = \lambda_2 = -\frac{2b \circ (6 \cdot v)}{\|b\|^2}$$

and thus by rearranging the upper equality and inserting b

$$\begin{aligned} t_X &= 1 + \frac{\|b\|^2}{2b \circ (6 \cdot v)} = \frac{6^2 - \|D - S\|^2}{2 \cdot (6^2 - (D - S) \circ (6 \cdot v))} \\ &= \frac{20}{2 \cdot (6^2 - (D - S) \circ (6 \cdot v))} = \frac{10}{6 \cdot (6 - (D - S) \circ v)}, \end{aligned} \quad (1)$$

as the distance from your house S and your friends house D is $\|D - S\| = x = 4(\text{km})$.

Then $X = S + t_X v = S + \frac{10}{6 \cdot (6 - (D - S) \circ v)} \cdot v$ is the location at which you arrive at time t_X and have to stop to turn into direction $v' = \frac{1}{1 - t_X} (D - S - v \cdot 6) + v$ in order to arrive at your friend's house D in exactly one hour.

We will now find out how these route planning calculations can help us with a mathematical problem. This problem arises in the study of bacterial movement.

2 Bacterial movement

Certain bacteria, e.g. Escherichia coli (E. coli), have the possibility to move autonomously by moving so called flagella. This 'motor' has two gears: either it moves clockwise or counter-clockwise. Counter-clockwise movement makes the single flagella form a bundle that works like a rotor and moves the bacteria

forward in a certain direction. Clockwise movement however untangles this bundle and makes the bacteria stop and 'tumble' around, compare figure 3a. In this process, they choose a new direction to run into. The movement of bacteria thus consists of alternating phases of running in one direction and then tumbling to find a new direction as displayed in figure 3b.

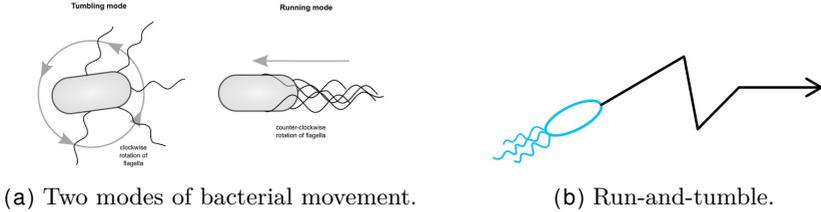


Figure 3: Bacterial movement

If the bacterium now wants to reach an aim like a food source, it cannot simply run there. At first, bacteria cannot 'see' very good, they only sense the environment very close to them. Hence, it cannot pick the right direction to run towards the food in a straight line. Bacteria solved this by developing a 'memory': instead of looking at locations they could go to, they look at the places they were. If the place the bacterium is now provides more food than the places it was before, it might be a good choice to keep going in this direction and hope to come even closer to the food source. The bacterium thus tumbles less frequently and keeps its direction for longer times. If the place it is now however offers less food than the places before, it moves away from the food source and thus change the direction more often.

This behaviour can be summarized by a mathematical model. For example a classical kinetic partial differential equation can be used for the description [1, 7]:

$$\underbrace{\partial_t f(x, t, v) + v \circ \nabla_x f(x, t, v)}_{\text{run}} \quad (2)$$

$$= \underbrace{\int_V K(x, t, v, v') f(x, t, v') - K(x, t, v', v) f(x, t, v) dv'}_{\text{tumble}}.$$

In this equation, the movement of bacteria is characterized by the evolution of the bacteria density f for a full bacteria population instead of single bacteria. This f is a function of space $x \in \mathbb{R}^2$, time t and direction $v \in V$ on the unit circle and $f(x, t, v)$ denotes the part of the bacteria population which is at location x at time t and runs into direction v . By relating the partial derivative in time

$\partial_t f$ and the gradient $\nabla_x f$, a derivative in space, the movement is characterized: The left hand side describes a movement along a straight line into direction v - this corresponds to the 'run'- phase. The integral on the right hand side, instead, describes the tumbling. The tumbling coefficient $K(x, t, v, v')$ stands for the probability of bacteria changing their direction from v' into v at time t at location x . The first term in the integral thus explains a gain in the bacteria density $f(x, t, v)$ by bacteria $f(x, t, v')$ that originally ran into another direction v' but at point (x, t) change their direction to v . The second term is a loss of bacteria from $f(x, t, v)$ that tumble into another velocity v' at the point (x, t) . In order to consider all possible other directions v' , the integral is drawn.

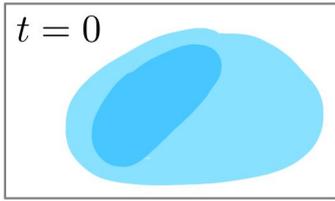
We refer the interested reader to [10], chapter 3, for a more detailed explanation of partial derivatives and the gradient and to [14], chapter 1.3, for an explanation of the transport characteristics of the right hand side of (2). For further information on the model, the interested reader is referred to Chapter 5 in [12]. However, we point out that in our case, we did not use the more complicated coupled system presented there but solely the equation for the bacterial movement with an independent chemoattractant.

We stress that there are various other possibilities to model bacterial movement. E.g. one can consider a random walk of single bacteria on the microscopic level [5, 2] or the Keller-Segel model [8, 11] on the macroscopic level, where the information on the direction of movement is lost. Also on the kinetic scale, more refined models were developed [13, 4].

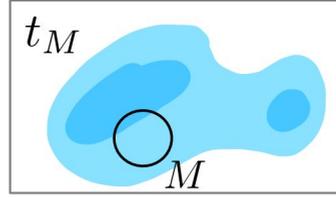
Contemplating equation (2), one observes that the movement is characterized only by one coefficient K describing the tumbling, since this is the only coefficient appearing in the model.

This tumbling coefficient therefore seems to be important and biologists are very interested in determining it. Because they cannot simply observe it, they do experiments: First, they place bacteria on a plate, see figure 4a, then they wait for some time, before they take a picture to see where the bacteria are now, compare figure 4b. From counting the bacteria at certain points of the picture, they would like to determine this tumbling coefficient.

In the mathematical language, this problem is called an inverse problem. Usually models are used in a 'forward' way, i.e., knowing the full model with all coefficients as well as the initial configuration of the bacteria, they solve for the location of bacteria at a later time T by evolving the initial configuration w.r.t. the model (2), see figure 5a (left). In contrast, inverse problems aim to determine e.g. a model coefficient by observing real experiments. They

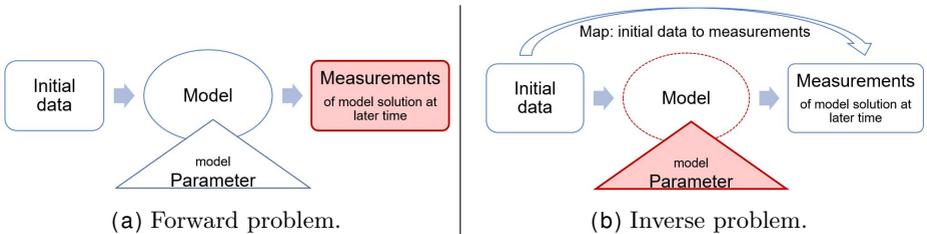


(a) Initial bacteria density.



(b) Bacteria density at time t_M .

Figure 4: Experiment: Bacteria are placed on a plate at time $t = 0$, then they run for some time until at time t_M the measurement M is taken by counting all bacteria inside the circle. Darker blue stands for a higher bacteria density.



(a) Forward problem.

(b) Inverse problem.

Figure 5: Setup of forward and inverse problem. The aim is to determine the red quantity.

thus observe the map of initial configuration to the measurements (containing the unknown model) and try to infer a model parameter, here K , from these observations, compare figure 5b (right).

In our research, we are considering the inverse problem of determining the tumbling coefficient K from such measurements of the bacteria density in space and time. At first, we studied whether this is theoretically possible at all [6]. This is where our above route planning considerations come into play. Because inverse problems are usually hard to solve, mathematicians have developed different techniques to help them. In our case, the so called singular decomposition technique, which proved helpful in similar situations [9, 3], can be applied. It tells us, that by a certain choice of initial data and measurement method, we are able to observe only that part of all bacteria that tumbled exactly once until time T . To be precise, for this technique it is crucial, that all bacteria start at the same point x_i in space running in the same initial direction v_i . Then the measurement is taken at a point x_m in space after time T . As it is observed in experiments that bacteria run at constant speed, this is just the

setting of our path finding problem in the first section 1: The bacteria start at point $S = x_i$ and have to reach point $D = x_m$ in time T . Their initial direction is v_i and they run with constant speed. Figure 6 illustrates the geometrical setup.

Hence, we can adapt formula (1) by exchanging the 6 (km/h) by the bacterial speed and calculate the time t_X of tumbling as well as the tumbling point $x_i + v_i t_X$. This is important for the inverse problem, because it tells us the point at which we observed the tumbling coefficient. It was a crucial step in our research where we showed that it is possible to determine the tumbling coefficient from experimental measurements.

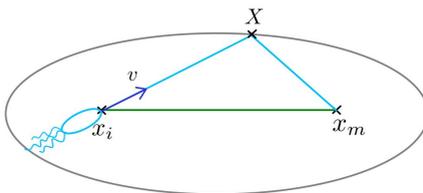


Figure 6: Bacterium in the route planning setting.

Image credits

Figure 3a “Two modes of bacterial movement.”. Authors: Matthew D Egbert, Xabier E. Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons Attribution 4.0 International via Researchgate, https://www.researchgate.net/publication/49694912_A_Minimal_Model_of_Metabolism-Based_Chemotaxis/figures, visited on March 28, 2022.

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