

# Route planning for bacteria

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Bacteria have been fascinating biologists since their discovery in the late 17th century. By analysing their movements, mathematical models have been developed as a tool to understand their behaviour. However, adapting these models to real situations can be challenging, because the model coefficients cannot be observed directly. In this snapshot, we study this question mathematically and explain how the idea of “route planning” can be used to determine these model coefficients.

## 1 Route planning

Imagine you are meeting with a friend in an hour from now. The direct path from your place to theirs takes 40min, so if you leave now, you will be early. However, the sun is shining and you do not want to wait 20min before leaving. You instead decide to go for a walk and combine that with the trip to your friend. To do so, you choose a direction and start walking. Assuming you walk at a constant speed, when do you need to change your direction towards your friend’s place to be on time?

In order to formulate this question mathematically, we first need to state assumptions and clarify notation. For simplicity, we consider your neighbourhood

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as the flat plane  $\mathbb{R}^2$  and assume that there are no obstacles (such as buildings) in your way, so you can walk in a straight line in any direction. Additionally, we suppose you walk with a constant speed of 6km/h. The set of all possible directions you can choose is the unit circle given by

$$V = \{w \in \mathbb{R}^2 \mid \|w\| = 1\}.$$

Here  $\|w\| := \sqrt{w \circ w} := \sqrt{w_1^2 + w_2^2}$  denotes the length of a vector  $w = (w_1, w_2) \in \mathbb{R}^2$  and  $x \circ y := x_1 \cdot y_1 + x_2 \cdot y_2$  denotes the *scalar product* of two vectors  $x = (x_1, x_2), y = (y_1, y_2) \in \mathbb{R}^2$ .

The reader can readily check, using only the properties of addition and multiplication, that the scalar product is symmetric and linear in each component, that is, the following calculation rules hold for all  $\lambda, \mu \in \mathbb{R}$  and  $x, y, z \in \mathbb{R}^2$ :

1. (symmetry)  $x \circ y = y \circ x$ .
2. (linearity)  $x \circ (\lambda \cdot y + \mu \cdot z) = \lambda \cdot (x \circ y) + \mu \cdot (x \circ z)$ .

Here 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, that is,  $\lambda \cdot x = (\lambda \cdot x_1, \lambda \cdot x_2)$ .

The problem may now be formulated mathematically in the following way:

**Question.** Consider a starting point  $s \in \mathbb{R}^2$  (your house) and a destination  $d \in \mathbb{R}^2$  (your friend's house) which is to be reached in time  $T = 1$  hour. Assume you walk at a constant speed of 6km/h and the distance between your house and your friend's house is  $\|d - s\| = 4$ km. If  $v \in V$  is the first direction you walk in after leaving your house, find the time  $t_c \in [0, 1]$  and the point  $c \in \mathbb{R}^2$  at which you need change direction and walk towards your friend.

When convenient, we will leave out all units to make the calculations cleaner. It is implicitly assumed that lengths and coordinates are scaled in kilometers (km), times in hours (h) and velocities in kilometers per hour (km/h).

The following observation allows us to rephrase the above problem as a purely geometrical question. In one hour, you will walk 6km in total to reach a destination that is 4 km away. Since you only change direction once, the starting point  $s$ , the destination  $d$  and the turning point  $c$  form a triangle such that your walking path coincides with the sides joining  $s$  to  $c$  and  $c$  to  $d$  (see Figure 1). We are interested in finding the turning point  $c$  or, equivalently, the time  $t_c$  at which you reach  $c$  and need to change direction. Geometrically, the task is to find the vertex  $c$  of a triangle with two other vertices,  $s$  and  $d$ , such that the length of your walking path (that is, the sum of the lengths  $l_1 = \|c - s\|$  and  $l_2 = \|d - c\|$  of the two shorter sides of the triangle) satisfies  $l_1 + l_2 = 6$ . The direction of  $c$  from  $s$  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

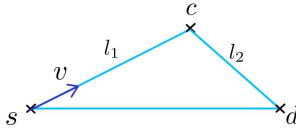


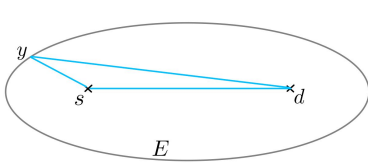
Figure 1: The triangle with vertices  $s$ ,  $c$  and  $d$ .

out, knowledge of the initial direction  $v$  and the fact that  $l_1 + l_2 = 6 \geq 4 = \|d - s\|$  guarantees a unique solution.

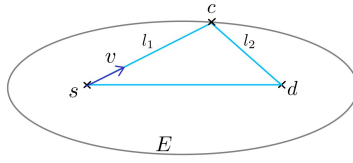
In order to get some intuition for why this is the case, consider the situation where you have not yet chosen your initial direction  $v \in V$ , but still want to go from  $s$  to  $d$  on a path of total length 6 while changing directions only once. The set of all possible turning points  $y \in \mathbb{R}^2$  is given by an ellipse  $E$  having foci  $s$  and  $d$  and major axis length 6. In mathematical notation, this is represented by the set

$$E := \{y \in \mathbb{R}^2 \mid \|y - s\| + \|d - y\| = 6\},$$

where  $\|y - s\|$  gives the length of the side joining  $s$  and  $y$ . As Figure 2a shows, there are multiple solutions to the problem when no initial direction is specified, namely every  $y \in E$ .



(a) The ellipse  $E$ .



(b) The triangle is uniquely determined by  $v$ .

Figure 2: Geometrical intuition for why  $c$  is uniquely determined.

If, however, the initial direction  $v$  is known, then the turning point  $c$  is unique. This is because  $c$  has to lie on the half line starting at  $s$  in direction  $v$  as well as on  $E$ . In other words,  $c$  is the unique intersection point of this line with the ellipse  $E$  (see Figure 2b).

Now let us solve the original problem by deriving explicit expressions for  $c$  and  $t_c$ . If you arrive at  $c$  at time  $T = 1$ , then, as illustrated in Figure 1, we must have that the displacement vector from  $s$  to  $d$  is the sum of the displacement vector from  $s$  to  $c$  and the displacement vector from  $c$  to  $d$ . Since displacement is the product of velocity and time, we know that  $c - s = v \cdot 6 \cdot t_c$  and  $d - c = v' \cdot 6 \cdot (1 - t_c)$  where  $v'$  denotes the direction in which you walk

after turning at  $c$ . Altogether,

$$d = s + (c - s) + (d - c) = s + v \cdot 6 \cdot t_c + v' \cdot 6 \cdot (1 - t_c).$$

Rearranging this equation yields

$$v' = \frac{1}{6 \cdot (1 - t_c)} \underbrace{(d - s - v \cdot 6)}_{=:b} + v. \quad (1)$$

Note that the vector  $b$  in the brackets is the path one would have to walk if you forgot to change direction in  $c$  and continued walking in direction  $v$  for the full 1h.

Since  $v'$  is a direction in  $V$ , we know that

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

Solving this quadratic equation for the variable  $\lambda = 1/(1 - t_c)$  yields two solutions:  $\lambda_1 = 0$ , which is impossible since  $0 \leq t_c \leq 1$ , and

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

Rearranging this equation, substituting  $b$  and noting that  $\|d - s\| = 4$  gives the following expression for the turning time

$$\begin{aligned} t_c &= 1 + \frac{\|b\|^2}{2b \circ (6 \cdot v)} = \frac{6^2 - \|d - s\|^2}{2 \cdot (6^2 - (d - s) \circ (6 \cdot v))} \\ &= \frac{20}{2 \cdot (6^2 - (d - s) \circ (6 \cdot v))} = \frac{10}{6 \cdot (6 - (d - s) \circ v)}. \end{aligned} \quad (2)$$

From this, we can compute the location of the turning point  $c$  using

$$c = s + t_c \cdot v = s + \frac{10}{6 \cdot (6 - (d - s) \circ v)} \cdot v.$$

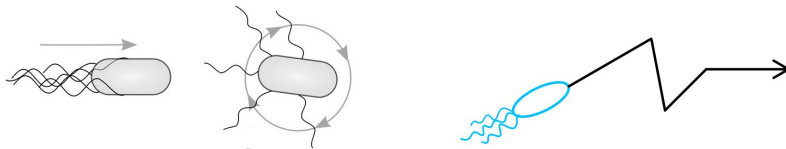
Substituting this back into (1) shows that the direction in which you must turn at  $c$  is given by

$$v' = \frac{1}{1 - t_c} (d - s - v \cdot 6) + v.$$

In the next section, we will investigate how the above route planning calculation is used in the study of bacterial movement.

## 2 Bacterial movement

Bacteria such as *Escherichia coli* (*E. coli*) move autonomously by moving whip-like structures called flagella. Flagella can be considered a miniature “motor” with two gears: one moves clockwise and the other moves counter-clockwise (see Figure 3a). Counter-clockwise movement makes the flagella form a bundle that works like a rotor propelling the bacterium forward. Clockwise movement untangles the bundle making the bacterium stop and “tumble” around. In this tumbling process, the bacterium chooses the next direction in which to run. The movement of bacteria consists of alternating phases of running in a direction and then tumbling to find a new one (see Figure 3b).



(a) Two modes: running (left) and tumbling (right).

(b) Path of a single bacterium.

**Figure 3:** Bacterial movement by run-and-tumble.

When a bacterium attempts to reach a destination, such as a food source, it is not able to run directly there. Bacteria cannot “see” well and so only sense the environment very close to them. To overcome this, bacteria develop a kind of “memory”. Instead of looking at locations they could go to in the future, they look at the places they have been in the past. If the place where the bacterium is now provides more food than where it was before, it might be a good choice to keep going in this direction with the hope of coming even closer to the food source. In this case, the bacterium would tumble less frequently and continue in its current direction for a longer period of time. Conversely, if the place where it is now offers less food, the bacteria would tumble more frequently and thus change direction more often.

This behaviour can be modelled mathematically as the following *classical kinetic partial differential equation* [1, 7]:

$$\begin{aligned}
 \partial_t f(x, t, v) + \underbrace{v \circ \nabla_x f(x, t, v)}_{\text{run}} \\
 = \underbrace{\int_V K(x, v, v') f(x, t, v') - K(x, v', v) f(x, t, v) dv'}_{\text{tumble}}. \quad (3)
 \end{aligned}$$

In this equation, the movement of bacteria is described in terms of the *bacteria density function*, denoted  $f$ , which represents the full bacteria population rather than just a single bacterium. The bacteria density is a function of space  $x \in \mathbb{R}^2$ , time  $t$  and direction  $v \in V$  on the unit circle with  $f(x, t, v)$  being the proportion of the bacteria population located at  $x$  at time  $t$  which is running in direction  $v$ .

Let us now take a closer look at each term in the partial differential equation (3) so as to see how it provides a mathematical description of bacterial movement.

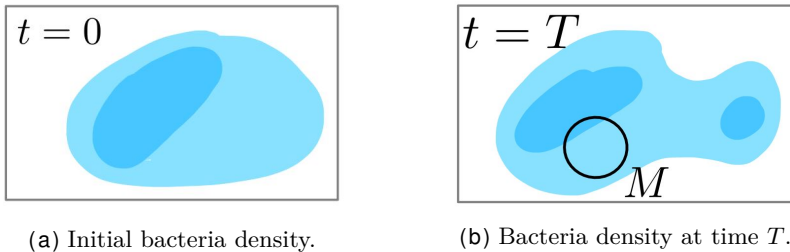
- *Time derivative:* The first term,  $\partial_t f(x, t, v)$ , is the derivative of the bacterial density function with respect to time. It represents the change in bacterial density (over time) for bacteria at location  $x$  who are running in direction  $v$ .
- *Run component:* The second term,  $v \circ \nabla_x f(x, t, v)$ , represents the change in bacterial density at location  $x$  due to bacteria running in direction  $v$ . Mathematically, this term can be interpreted as the (directional) derivative of the bacterial function with respect to location at the point  $x$  in the direction  $v$ . Note that, if moved to the right-hand-side of eqrefchemotaxis, this term has a negative coefficient representing the fact that bacteria at location  $x$  who are running in direction  $v$  contribute a decrease to bacterial density at  $x$ .
- *Tumble component:* The integral on the right-hand-side of eqrefchemotaxis represents the total change in bacterial density at location  $x$  due to tumbling that occurs at the point  $x$ . Here the *tumbling coefficient*,  $K(x, v, v')$ , stands for the probability of bacteria changing their running direction from  $v' \in V$  to  $v \in V$  at location  $x$ . Thus, the first term in the integral thus represents a gain in the bacteria density  $f(x, t, v)$  due to bacteria originally running in direction  $v'$  that change their running direction to  $v$  at  $(x, t)$ . Similarly, the second term in the integral represents a loss in the bacteria density  $f(x, t, v)$  due to bacteria that run in direction  $v'$  after tumbling at  $(x, t)$ . In order to consider contributions from all possible tumble directions, the integral is taken over all directions  $v' \in V$ .

Altogether, we see that (3) expresses the idea that the evolution of bacterial density at  $(x, t, v)$  is given by the sum of two components: the change in bacteria density due to bacteria running in direction  $v$  at  $(x, t)$ , and the change in bacteria density due to bacteria tumbling at  $(x, t)$ .

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 (3). For further information on the model, the interested reader is referred to [12, Chapter 5]. However, we point out that this work does not use the more complex coupled system model presented there, but rather a simpler model based solely on the equation for the bacterial movement with an independent

chemoattractant. We stress that there are also various other possibilities to model bacterial movement. For example, one can consider a random walk of single bacterium 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].

A closer look at equation (3) shows that bacterial movement, represented by its density  $f$ , is completely characterized if the tumbling coefficient  $K$  is known. Thus, the problem of understanding bacterial movement amounts to determining the unknown coefficient  $K$ , and it is for this reason that biologist are very interested in determining it. Because the coefficient cannot be observed directly, biologists perform experiments which measure it indirectly. First, they place bacteria on a plate (see Figure 4a) and take a picture of the initial density. Then they wait for some time, before taking a second picture to see where the bacteria are now (see Figure 4b). By counting bacteria in certain regions of the second picture, it is possible to determine the tumbling coefficient using the mathematical theory of *inverse problems*.



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

In mathematical language, problems in which a quantity is to be reconstructed from measurements are known as *inverse problems*. Usually mathematical models are used in a “forward” way. In the context of bacterial movement, this means that knowing the tumbling coefficients as well as the initial configuration of the bacteria, the location of bacteria at a later time  $T$  can be computed by evolving the initial configuration with respect to the model (3) (see Figure 5a). In contrast, the inverse problem observes the map of initial configuration to the measurements (containing the unknown model) and tries to infer the model parameter  $K$  from these observations (see Figure 5b).

In our research, we considered the inverse problem of determining the tumbling coefficient  $K$  from measurements of the bacteria density. In a first study

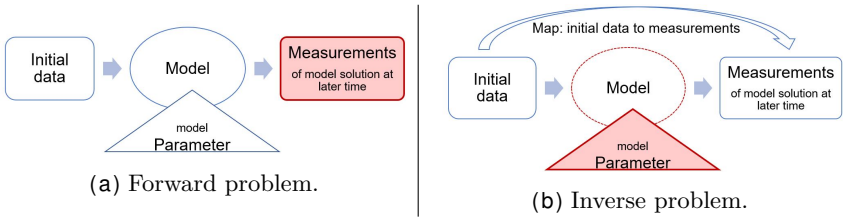


Figure 5: Setup of forward and inverse problem. The aim is to determine the red quantity.

[6], we proved that this is theoretically possible.

As inverse problems are usually difficult, mathematicians have developed a range of techniques to solve them. An additional difficulty in our setting is that we aim to reconstruct  $K(x, v, v')$  as a function of incoming direction  $v'$  and outgoing direction  $v$  from direction-independent measurements. To overcome this, we applied a technique known as *singular decomposition*, which proved helpful in similar situations [9, 3]. Assuming certain initiations, this technique requires measurement of only the proportion of the bacteria that tumbled precisely once between time 0 and the time of measurement  $T$ . An explicit formula relating the density measurement to the tumbling coefficient can then be used to reconstruct  $K$  at the tumbling point.

To be precise, this technique requires that all bacteria start at the same point  $x_i$  in space and run in the same initial direction  $v_i$ . After a short time  $T$ , another measurement is taken at another point in space  $x_m$ . As bacteria run at constant speed  $s_b$ , this setup is just the setting of our path finding problem from Section 1: The bacteria start at point  $s = x_i$  and have to reach point  $d = x_m$  in time  $T$ . The initial direction is  $v_i$  and bacteria run with constant speed. Figure 6 illustrates the geometrical setup.

When done appropriately, all bacteria counted at time  $T$  are bacteria that tumbled exactly once at a unique tumbling point  $c$  and chose the same direc-

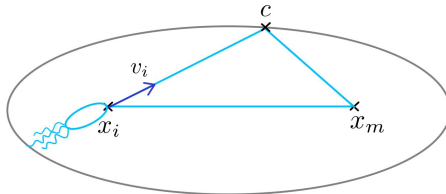


Figure 6: Bacterium in the route planning setting.



tion  $v'$  before heading directly towards  $x_m$ . From the definition of the tumbling coefficient, we see that this measurement can be used to determine  $K(c, v', v_i)$ .

Putting everything together, we can adapt formula (2) by replacing 6km/h with the bacterial speed  $s_b$  and calculating the time of tumbling  $t_c$  as well as the tumbling point  $c = x_i + v_i t_c s_b$  and the direction after tumbling  $v' = (x_m - x_i - v_i \cdot s_b)/(1 - t_c) + v_i$ . This is important for the inverse problem because it tells us the point at which we observed the tumbling coefficient  $K(c, v', v_i)$ . This crucial step in our research allowed us to show that it is possible to determine the tumbling coefficient from indirect experimental measurements.

## 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](https://www.researchgate.net/publication/49694912_A_Minimal_Model_of_Metabolism-Based_Chemotaxis/figures), visited on March 28, 2022.

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