Snapshots of modern mathematics
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The mystery of sleeping sickness – why does it keep waking up?

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Sleeping sickness is a neglected tropical disease that affects rural populations in Africa. Deadly when untreated, it is being targeted for elimination through case finding and treatment. Yet, fundamental questions about its transmission cycle remain unanswered. One of them is whether transmission is limited to humans, or whether other species play a role in maintaining circulation of the disease. In this snapshot, we introduce a mathematical model for the spread of *Trypanosoma brucei*, the parasite responsible for causing sleeping sickness, and present some results based on data collected in Cameroon. Understanding how important animals are in harbouring Trypanosoma brucei that can infect humans is important for assessing whether the disease could be reintroduced in human populations even after all infected people have been successfully treated.

It all begins with a small insect, called *tsetse* after the Tswana word for fly. Apart from delivering a painful bite, the tsetse fly is mostly known for transmitting a parasite that causes a deadly disease: sleeping sickness. This parasite, called *Trypanosoma brucei* after the Scotsman David Bruce who

discovered it in 1903, existed long before humans. Over millenia of co-evolution, it has developed to infect humans and animals alike. A major scourge of African populations in the 20th century, its case numbers have now been reduced to less than 10,000 annual cases through extensive control and treatment of infected cases. In spite of these successes, sleeping sickness has proven frustratingly hard to eliminate, as cases seem to occur in places which have not seen a case for years or even decades [6].

A number of hypotheses have been brought forward for this mysterious reappearance. Could it be the movement of people that brings the infection back to places? This is possible, but does not explain why it always appears in the same places. Could it be that some people do not develop symptoms and maintain the infection in a community when there are no apparent cases of the disease? There is some, but overall relatively little evidence for this phenomenon to occur. Or could it be that the infection keeps being transmitted in animal populations, possibly in the rainforest and far from human habitations? Animal infections have been reported since the early 20th century, yet, conventionally, West African sleeping sickness has been thought to be mainly a human disease that only rarely jumps to animals. In the early 2000s, triggered by the discovery of more than 40 human cases of sleeping sickness in the area of Bipindi in central Cameroon, a group of French researchers have decided to investigate this hypothesis. By testing the blood of a number of wild and domestic animal species using modern genetic methods, they have, for the first time, been able to pinpoint whether the same parasites that infect humans can be found in other species [3, 4].

Surprisingly, the researchers found that a whole range of animal species seemed to be infected by the same type of parasite that infects humans: monkeys, antilopes, rodents, even rats. A clear indication that animals might play a role in transmission, but not evidence for this possibility — they could still be so-called accidental hosts, that only occasionally get an infection from humans, the main host. To link the observed infections in animals and humans to the question of transmission, one needs to link the observed data to our mechanistic understanding of how transmission happens in a (human or animal) population. This is where mathematics can play an important role. A mathematical model of infectious disease dynamics allows to encode our biological knowledge into mathematical theory, and use this to interpret data with the use of statistics. In a sense, this is not too different from the development of a theory in physics — we try to make sense of what we observe (in the universe, say, or in an experiment) using a consistent set of mathematical relations, say, Newton's laws of motion. The difference is that in Mathematical Epidemiology[1], observations can usually

[1] Epidemiology is the science studying patterns, causes, and effects of health and disease.

not be reproduced, and certainly never so under exactly the same conditions. Yet, using careful inference we can use mathematical models to find patterns in data and learn something about the underlying biological processes [5].

To model the spread of sleeping sickness, we encoded our biological knowledge into a system of *ordinary differential equations* (so-called ODEs, i.e., equations relating the derivative of a function to the function itself)[2]. The number I_a of infected hosts of species a, for example, behaves as

$$\frac{dI_a}{dt} = \lambda_a(N_a - I_a) - (\mu_a + \gamma_a)I_a$$

where

- λ_a is the force of infection that a susceptible host experiences
- N_a is the population size of species a,
- μ_a is the natural mortality rate of species a, and
- γ_a is the rate at which a host of the species loses infectiousness (through recovery or death due to disease).

All these quantities can be related to observations made by field epidemiologists.

The ODE can be interpreted as follows: the change in the number I_a of infected individuals of species a (human or animal) is given by an increase proportional to the the force of infection λ_a (which will depend on the number of infections in other species and the rate at which individuals of species a come in contact with these), and the number of individuals of species a that can be infected; this is balanced by a decrease in proportion to the mortality rate μ_a and the rate of losing infectiousness γ_a.

To relate transmission between different species (via bites from tsetse flies), we use the concept of the *next-generation matrix* which describes how many new infections in another species hosts of one species will cause on average [1]. For species 1, 2 and 3, for example, this would be written as

$$\mathbf{K} = \begin{pmatrix} K_{11} & K_{12} & K_{13} \\ K_{21} & K_{22} & K_{23} \\ K_{31} & K_{32} & K_{33} \end{pmatrix}$$

where each entry K_{ij} represents the average number of infections caused by an infected individual of species j in a completely susceptible population of species i. These enter the calculations of the forces of infection λ_a in specifying the influence of different species on generating infections in the same and other

[2] An example for a mathematical model using partial differential equations (PDEs) instead of ODEs can found in Snapshot 10/2014: *Drugs, herbicides, and numerical simulations* by Benner et al.

species. Using inference on field data, we can fill the different components of this matrix. By then projecting onto sub-matrices, we can evaluate how much transmission there would be if, say, infection would be eliminated from one of the species. In other words, we can tell if transmission would continue in animals if all humans were treated.

Applying this theory to the data collected in Bipindi yields a surprising result: it looks like animals play a stronger role in transmitting the parasite than humans [2]. In fact, it seems like cycles could continue in the rainforest separately from humans. At the same time, none of the animal species appears solely responsible for transmission — it is almost as if the whole ecosystem was infected by the parasite, rather than an individual species (Fig. 1).

These results, obtained using a combination of data collection and mathematical theory, provide a possible explanation as to why sleeping sickness keeps coming back. Even when all human cases are treated, the parasite could be circulating far from human habitations, and there remains a risk that the disease could come back to humans. In spite of these new insights, many questions about sleeping sickness and the link to potential animal reservoirs remain. Could it be that the infection lingers in some animal that was not even tested? Could human immunity play a stronger role than suspected? These issues would change the results of the study. Plans for new field studies are underway to better inform the mathematical models developed for this study. Using a combination of epidemiological detective work and mathematical theory, we can hope to help finally solve the mystery of sleeping sickness.

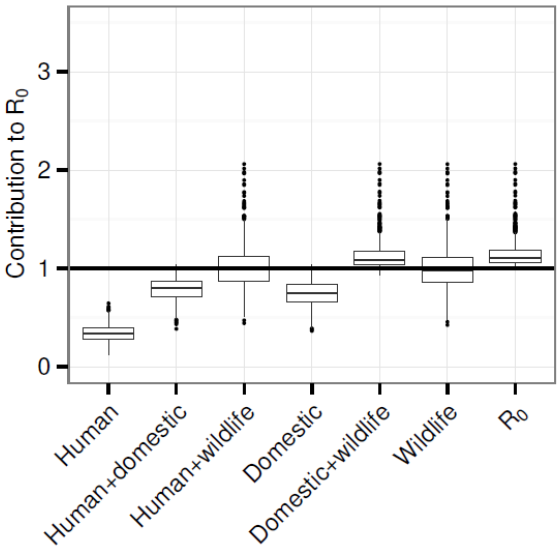

Figure 1: The contribution of each different groups of species to transmission in Bipindi. Above the line, species can transmit the parasite between themselves without involvement of any other species [2]. The horizontal line corresponds to the median, the upper and lower "hinges" to the interquartile range. The dots denote outliers.

Image credits

Fig. 1 is taken from [2].

References

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Mathematical subjects
Numerics and Scientific Computing

Connections to other fields
Life Science

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