# Microbiology and…
# Mathematics: microbiological meaning from mathematical models

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Mathematical modelling has traditionally been a normal part of microbiological research. It was not considered to warrant any special mention in the title and abstract and then required burying in the supplementary material. Models were simply used when useful and researchers had the skills to use them. Describing the growth and death of populations is probably the first area where models were used as a matter of course; then came the molecular biology revolution. While pioneered by scientists with strong theoretical skills and mindset, experiments soon trumped theory in the elucidation of the genetic code. Moreover, molecular biology had been enormously successful in revealing the function of myriads of genes without any theory, not even statistics. This side-lined modelling and the skills it required although quantitative reasoning survived in some areas of microbial sciences such as predicting bacterial growth in foodstuffs. The effects of the molecular revolution are still felt today despite the increasing recognition that mere qualitative understanding of the interactions of genes and gene products and products of gene products cannot deal with the complexity and dynamic nature of these interactions, giving rise to systems biology and the need for biologists to have quantitative skills. As Schnell, Grima and Maini put it in 2007, 'Molecular biology took Humpty Dumpty apart; mathematical modelling is required to put him back together again'.


## What is this thing called a mathematical model?

When reading papers including mathematical models, it is empowering to understand the nature of such models, even when technical details may be beyond us non-mathematicians. In the words of Gunawardena in 2014, 'a mathematical model is a logical machine for converting assumptions into conclusions' (Figure 1). From this nature of models, everything follows:

(i) Scrutinise assumptions. Since the biology is in the assumptions, they should be scrutinised by us microbiologists and indeed that is what we are best placed to do. Developing models helps to bring such assumptions to light so they can be scrutinised more easily (Figure 1).

(ii) Assumptions simplify reality. The purpose of a model is to simplify reality, otherwise, reality would be the best model of itself. The same actually holds for experimental

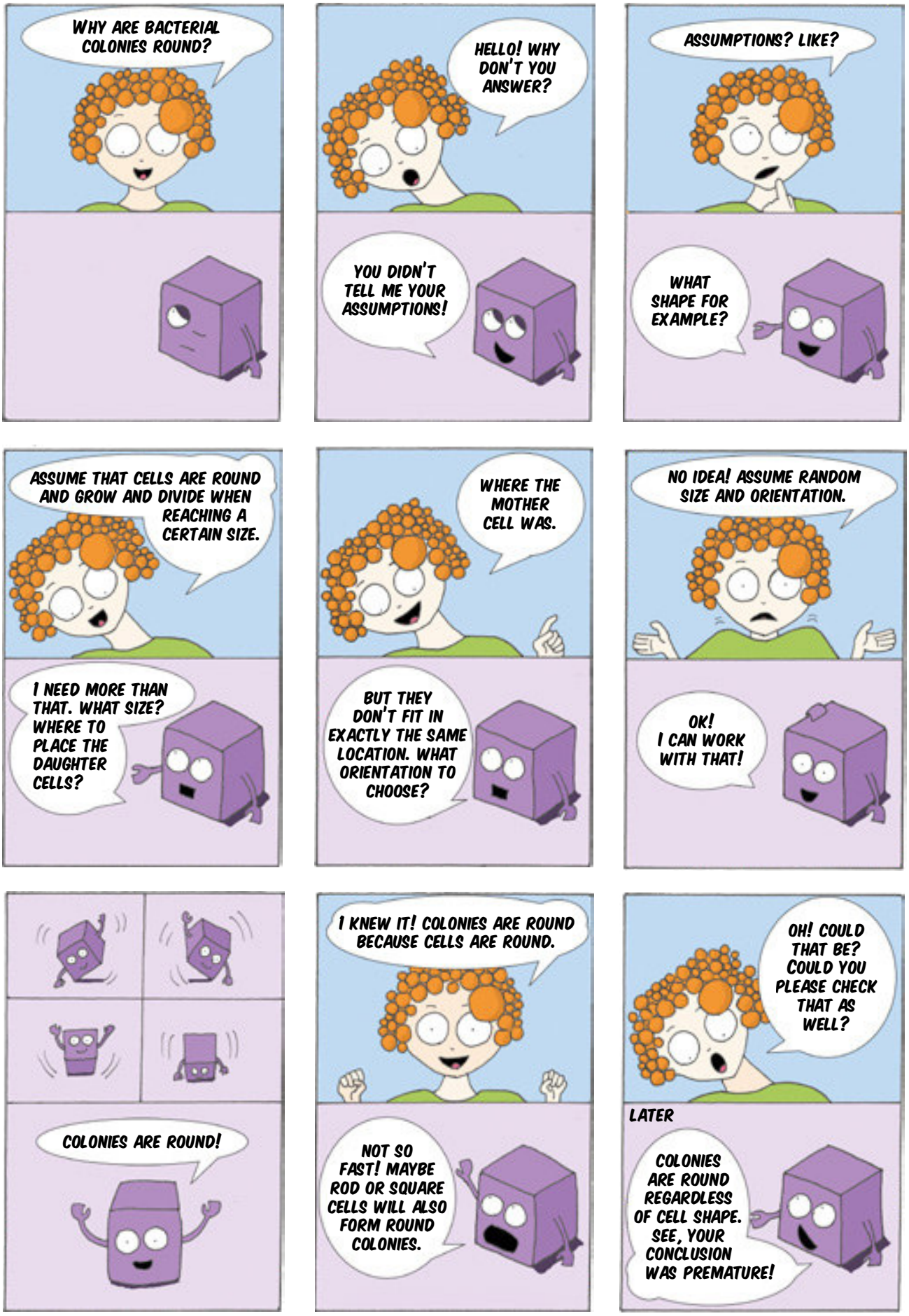


***Figure 1*** *Logic machine and microbiologist*

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# Mathematical models are not useful because they are wrong, but they are useful due to the extent to which they are not wrong

models; for example, laboratory models, insect models or mouse models of the human gut simplify reality to various degrees like different mathematical models do. Although assumptions should simplify reality, they should not distort reality. It is here that modelling of any kind is more an art than a science. As Sober and Wilson put it in 1999, 'simplifying assumptions are both the soul and Achilles' heel of mathematical models' (Figure 2).

(iii) Predictions are predictions. Even when predictions follow from empirically supported assumptions, predictions should never be given the same status as empirical truth. Since a model will predict what would happen if the assumptions were true, we can merely rule out sets of assumptions that are wrong (Figure 2). However, there might be alternative assumptions that generate similar predictions so one should test various assumptions with a family of related models (Figure 1).

(iv) A model can give the right answer for the wrong reasons (Figure 1). Even if the predictions of a model match experimental data, it can still be wrong if its assumptions are wrong. Claudius Ptolemy's geocentric astronomical model predicted the planets' positions but it is wrong because its geocentric assumptions are wrong.

## A tale of neglect

The importance of scrutinising assumptions as well as predictions can be illustrated by mathematical models of ageing in unicellular organisms. Neglecting processes of damage repair and cellular growth led to the prediction that damage segregation is beneficial but not damage repair, despite the fact that all known organisms evolved to repair damage (Figure 2).

## Chance behaviours

We evolved to recognise patterns and find regularities in natural events and predict future events. Thus, we find it hard to imagine and accept that chance, the unavoidable and uncontrollable, plays an important role in many fundamental life processes. For example, (i) chance is necessary for the formation of spatial patterns from initially uniform conditions (Turing patterns or biofilm formation), (ii) stochastic gene expression generates individual differences and (iii) evolution arises from natural selection of random mutations. Stochastic processes on a microscopic level can make systems behave predictably on a macroscopic level.

## Feedback

Logical machines have also been essential in understanding the role of positive and negative feedback in a wide range of biological processes. In quorum sensing, positive feedback in signal production amplifies the response to the signal, particularly in clusters of cells, so quorum sensing is also the sensing of clustering rather than just cell density. The positive feedback also leads to hysteresis, where down-regulation of cells occurs at an autoinducer level much below the level required for up-regulation. Such hysteresis is hard to understand without a model demonstrating how it can emerge from known non-linearities in signal production and response.

## Bistability

Another example of feedback leading to the emergence of surprising macroscale behaviour is bistability, where a cell can switch between two different but stable states, such as growing or persister states or other types of cellular differentiation. The difficulty is understanding that both states are stable to a degree but switching between them is possible. Again, logical machines help by showing that double-negative feedback or positive feedback can turn a stochastic perturbation in a molecular process into a switch on the macroscopic scale of the cell. Similarly, switching between multiple stable states on the level of microbial communities may explain the existence of enterotypes, which are stable associations of microbial populations in the gut that can differ between individuals.

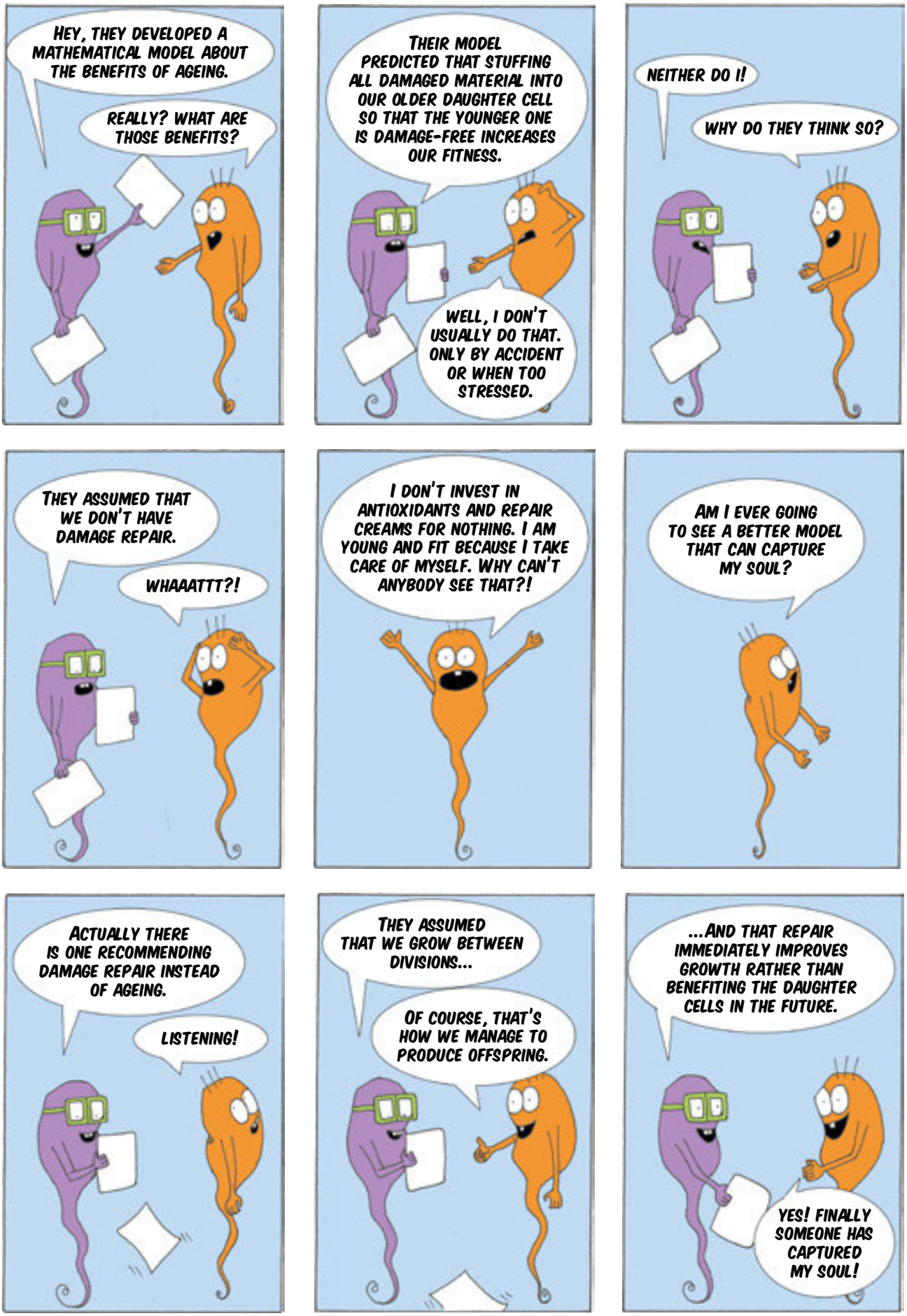


***Figure 2*** *Assumptions simplify or distort reality*

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## FURTHER READING


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## Feedback, trade-offs and biofilms

An example of spatial pattern formation driven by positive feedback is the fingering instability in biofilms that explains how finger-like structures can emerge from initially flat biofilms. Similar positive feedback can arise in biofilms if individual cells cooperate by refraining from competition for limiting resources. Cells with a higher growth yield, producing more biomass per substrate consumed, use these resources more economically. Due to a trade-off, they have a lower growth rate (maximum specific growth rate) as a disadvantage. Surprisingly, a cluster of such economical cells with a lower growth rate grows faster in a biofilm than a cluster of cells with a higher growth rate. This is because a cluster of economical cells, consuming less substrate, benefit from the locally higher substrate concentration boosting their growth. As the cluster grows larger, the benefit increases, leading to positive feedback. Recognising the benefits of a higher yield when living in biofilms where growth is limited by the diffusion of substrate into the biofilm led us, in 2006, to predict that complete ammonia oxidation (comammox) should have fitness benefits in biofilms. By oxidising ammonia completely to nitrate rather than nitrite, the growth yield was predicted to be higher but the growth rate was lower according to the kinetic theory of optimal pathway length (Figure 3). Comammox was discovered in 2015.

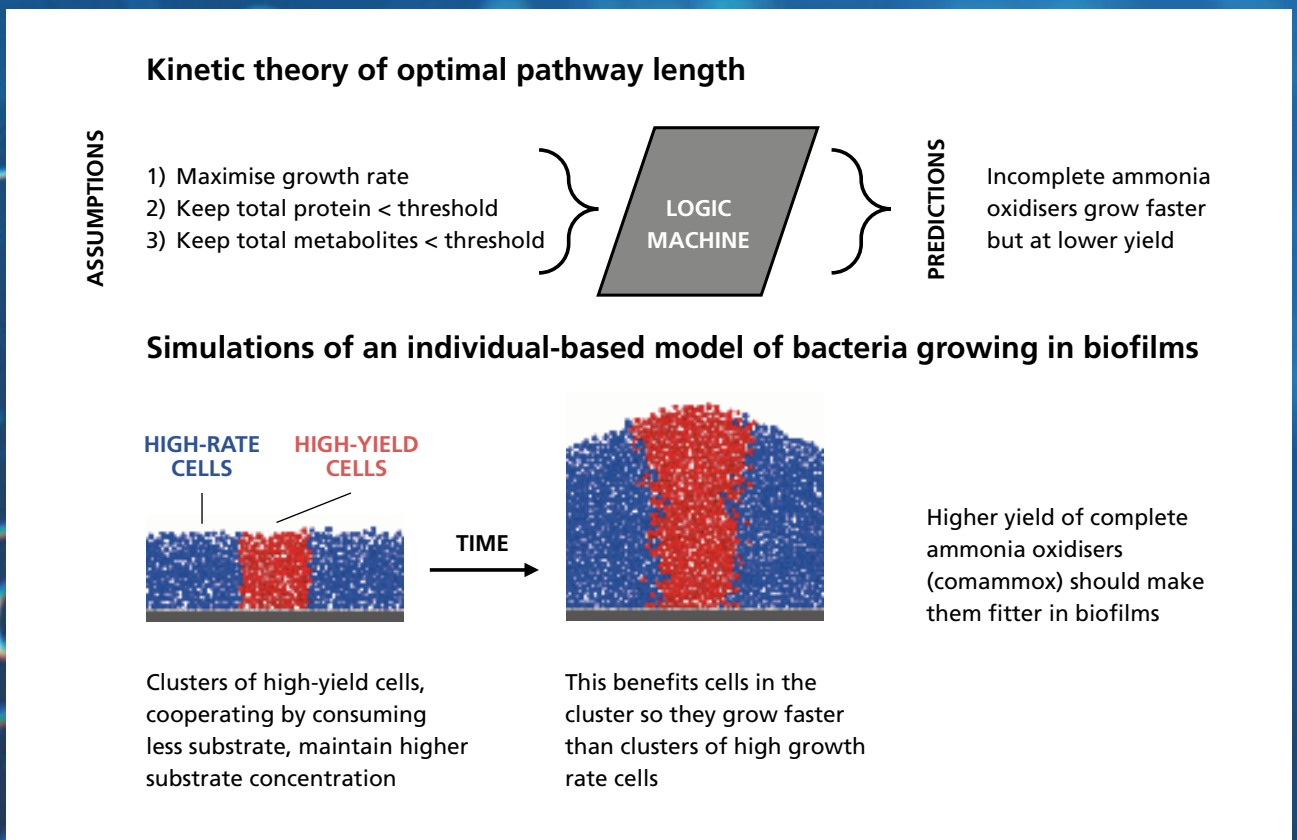
## What we learned from mathematical modelling

From a personal perspective, using mathematical models helped us to gain a deeper understanding of the role of stochastic processes, positive and negative feedback and the emergence of complex macroscopic behaviour from simple microscopic rules or vice versa. We have learned to consider different time and spatial scales and recognised that models are our only chance to cope with the complexity that makes biology unique and fascinating.

## True or false?

Returning to our logical machine perspective for our conclusions, mathematical models are not true or false by virtue of being models but they are 'truer' if their assumptions and predictions have stronger empirical support and if alternative models have been tested and found to be less adequate. To recast George EP Box's famous yet misleading quip 'all models are wrong but some are useful', where he had statistical models in mind, mathematical models are not useful because they are wrong, but they are useful due to the extent to which they are not wrong. The truer the model, the more useful it is.

***Figure 3*** *below: From studies of growth rate versus yield trade-off in biofilms and kinetic theory to the prediction of complete ammonia oxidation (comammox)*

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