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Feedback loops between mathematics and microbiology

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ABSTRACT

The combination of mathematical modelling and quantitative video-microscopy provides exciting opportunities for elucidating the mechanisms behind key processes in microbial ecology, ranging from cell navigation and nutrient cycling to biofilm establishment and symbioses. Central to this approach is the iterative process, whereby experiments and modelling inform one another in a virtuous cycle: vast quantities of experimental data help to test and refine mathematical models, the predictions from which feed back to the experimental design itself. This paper discusses recent technologies, emerging applications, and examples where calibrated mathematical models enable calculation of quantities that are otherwise extremely difficult to measure.

Keywords: applied mathematics, chemotaxis, fluid dynamics, microbial ecology, microfluidics, motility, navigation, video-microscopy.

Microorganism behaviour and interactions unfold at the microscale and are inherently dynamic. Ecological processes depend on spatial structure of the environment, as well as the arrangement and behaviour of microbes. For example, the capacity for microbes to actively navigate heterogeneous environments using chemotaxis can dramatically influence their nutrient acquisition and establishment of symbioses;[1] ubiquitous fluid flows in the environment (e.g. ocean, groundwater, gut, mucus) influence the motility of microbes and reshape the environment;[2] and Brownian motion can affect encounter rates between microorganisms.[3] While functional complexity of microbes is well documented, it can be very difficult to examine spatiotemporal processes using traditional tools in microbiology. The combination of visualisation in controlled environments and mathematical modelling is uniquely positioned to resolve dynamic features of microbial lifestyles, and the ways in which these scale up to ecosystem-level processes.

The growing use of microfluidics and video-microscopy has facilitated the direct imaging of microbial behaviour in a range of realistic controlled microenvironments. Typically fabricated from flexible, optically transparent elastomers such as polydimethylsiloxane (PDMS), microfluidic devices can be used to create precisely controlled physicochemical conditions.[4] Steady gradients or transient pulses of oxygen, amino acids, and sugars can be used to interrogate the chemotactic ability of microorganisms.[5,6] Microscale fluid flows can be generated with exquisite precision using ultraslow syringe pumps, with flow fields exactly solvable using known dimensions. Various other additional stimuli – including light illumination patterns, electric and magnetic fields[7] – can readily be overlayed. Taken together, this enables the user to accurately recreate physical and chemical features of realistic microenvironments – for example from the ocean or soil – in a device small enough to fit on a microscope slide (Fig. 1).

Mathematical modelling has been applied extensively over many decades to model phenomena in microbial ecology. These approaches can involve directly simulating the motion of individual cells (agent-based models); abstracting organisms or chemicals as continuous fields which vary in space and time (continuum models); modelling sensory pathways or physical processes using reduced-order dynamical systems; and using statistical models to process and interpret sequencing data. For example, understanding of pattern formation in growing domains,[8] limits to chemoreception,[9] and motility patterns of swimming microorganisms[10] stemmed from mathematical models. More broadly across microbiology, mathematical modelling has been used to investigate metabolism in microbial communities and the transmission of infection in disease epidemiology. The success of mathematical models hinges on accurately identifying the essential features of the biological system that shape the ecological processes, and detailed parameterisation of the model.

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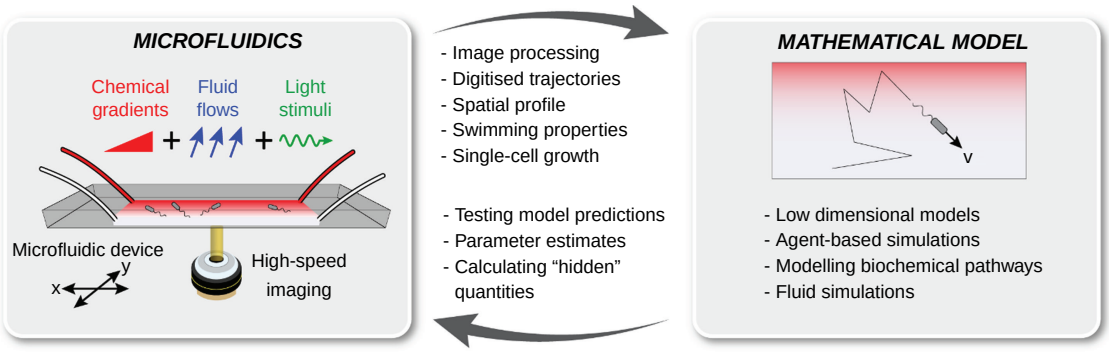

Fig. 1. Feedback loop between microfluidic experiments and mathematical models. High-speed imaging of microbes in precisely controlled microenvironments provides data that can be analysed using image processing algorithms. The digitised trajectories provide vast quantities of single-cell data, for example, spatial distribution of cells, individual swimming properties over time and single-cell growth rates across the population. These data inform mathematical models, enabling robust model testing, parameter estimates, and the calculation of quantities that are extremely difficult to measure experimentally. These model outputs facilitate refinement of experimental design.

The feedback loop between experiments and mathematical modelling is essential for understanding various processes in microbial ecology. Previous works have highlighted the utility of microfluidic devices for visualising dynamic processes.[4] However, these technologies realise their full potential when combined with mathematical modelling, particularly through iteration between experiments and theory. Because experimental environments (e.g. chemical gradients, flow, light, fields) can be independently and continuously varied, the predictions of mathematical models can be thoroughly scrutinised. Where differences occur, models can be updated, and further experiments conducted (Fig. 1).

What are the key elements that facilitate this iterative loop? Video-microscopy of microbes in carefully controlled arenas enables collection of vast quantities of data, for example in the form of high-speed movies, time-lapse photographs, or fluorescence intensity. Image processing algorithms – often conducted in MATLAB, Python, ImageJ – result in digitised trajectories, for example, the position of all motile bacteria at all time-steps[11] or the growth dynamics and lineages of cells throughout a biofilm.[12] From these data, cell concentration profiles, swimming speeds, turning angles, and attachment events[13] can be quantified with great precision. Although visualisation is a key step, this methodology is not merely 'observational'. The extracted information can be either used to parameterise mathematical models or directly compare with the predictions of simulations or modelling efforts.

Many aspects of microorganisms' environment and lifestyle can be modelled explicitly using known governing equations and physical principles. The Navier–Stokes equations can be used to precisely calculate how fluid flows and local shear transport and rotate microbes;[14] the transport and spread of dissolved organic matter can be solved using the advection-diffusion equation; and buoyancy forces, gravitational torques and magnetic fields can be readily included.[15] Explicit calculation of the hydrodynamic flow fields around swimming microorganisms[16] allows one to determine how organisms physically interact with one another[17] as well as in dense suspensions.[18] Mathematical modelling can also shed light on complex biochemical pathways and whole cell dynamics. These range from low-dimensional models, where a full sensory pathway can be abstracted as a dynamical system with few parameters,[19] through to systems biology approaches that involve high-dimensionality modelling of many processes in a cell.[20] Despite their apparent simplicity, minimal models have elucidated how different bacteria navigate chemical profiles using for example logarithmic sensing[21] or fold change detection,[22] and how the discrete molecular nature of chemical attractants places limits on gradient detection.[23] These models, which enable prediction of microbial dynamics in arbitrary settings with great accuracy (~1% fitting error)[24] despite few parameters, were developed and validated with the large quantities of data obtained through microfluidics and microbial tracking.

To close the feedback loop, model predictions must be able to inform refinements of experimental design. In the simplest case, this can be using mathematical models to identify the key regions of parameter space to be studied experimentally, for example, determining the domain size, imaging timescales or nutrient concentrations at which specific phenomena are likely to occur. Pioneering work of Berg and Purcell,[9] later extended by others, calculated the strength of a chemical gradient necessary to elicit a chemotactic response. Experiments can also be designed to test the robustness of the model – for example, would a model for chemotaxis still work if the gradients were increased by a factor of 10 or 100? Challenging models through a suite of different experiments removes the likelihood of coincidental agreement between experiments and modelling.

Mathematical models can reveal specific phenomena that might not otherwise be seen in experimental systems. Knowledge of how fluid gradients reorient cells suggested that swimming microbes exhibit different behaviours as fluid shear is varied; advection–diffusion modelling suggests that external flow can dramatically influence quorum sensing of microbial communities;[25] and theoretical work on confined active suspensions[26] hinted that confining boundaries could stabilise bacterial suspensions into vortical flow patterns.

Mathematical modelling enables one to calculate important parameters and quantities that cannot currently be measured directly. Marine nutrient cycling and

biogeochemistry is underpinned by the concerted action of microbial populations, and determining precisely how microbial behaviour (e.g. motility, navigation) influences nutrient uptake, represents a key challenge. Resource acquisition is readily measured using bulk techniques, for example by examining cell growth rates and dry mass measurements. At the single-cell level, Nanoscale secondary ion mass spectrometry (NanoSIMS) and other quantitative imaging tools[27] provide highly quantitative measurements for nutrient uptake, but can be prohibitively expensive and time-consuming. However, in microfluidic arenas where the nutrient landscape can be spatially controlled and the bacterial positions readily measured,[24] it is straightforward to calculate single-cell nutrient exposure across the entire bacterial population. Quantities such as the energetic cost of swimming, which can be extremely challenging to measure biochemically, can be readily calculated using fluid dynamical models which consider the shape, swimming speed, and hydrodynamic drag on a cell body.[28] This enables quantitative predictions about optimal strategies for microorganisms in various realistic environments. For example, the competition between non-motile and chemotactic bacteria is shown to depend sensitively on the local ocean productivity.[29]

Perhaps the most powerful aspect of mathematical modelling is the capacity to investigate the implications of varying key physical parameters and examining how sensitive results are to changes in microbial behaviour. For example, how does the nutrient uptake change as chemotactic sensitivity is modified, and is there an optimal value? How does IgA-mediated agglutination of pathogens vary as antibody stickiness and cell growth rates change? Mechanistic models can either examine key metrics for given parameters, or allow these parameters to vary over time, known as *in silico* evolutionary experiments.

Future directions. We have discussed the iteration between experiments and modelling, communicated through data and model outputs. The greatest advances thus far have been in relation to single microbial species or simple communities. Community analysis is typically performed at a very high level, e.g. through metagenomics, but is not well suited to exploring spatial and temporal effects, and physical processes involved in the microbial lifestyles. An important area for future exploration will be examining interaction between multiple species and assessing the role of spatial heterogeneity and resource diversity in natural communities.

Another clear future area of research is the application of machine learning (ML) and artificial intelligence (AI). In the shorter time, this is likely to assist with the extraction of data from experimental results (e.g. image segmentation, cell identification), which can be fed to mathematical models as outlined earlier. However, in the longer term, AI will likely assist in the modelling phase itself, proposing and testing reduced order models, or guiding human intuition.[30] Through exposure to large datasets, AI may be able to 'learn' how microorganisms behave, either as individuals (e.g. chemotaxis, motility patterns, growth rates), or communities (e.g. symbiosis partnerships, community dynamics). This offers the tantalising possibility of extrapolating behaviour from small numbers of different species – for example, chemotaxis towards specific compounds, symbiosis between pairs of organisms – to complex communities with multiple metabolic interactions. Despite these possibilities, ML and AI find it difficult to provide reasoning for their predictions. So, there will be a trade-off between accurate prediction of dynamics and revealing underlying mechanisms or physical principles (at least in the short term). Taken together, the combination of quantitative video-microscopy, mathematical modelling, and machine learning, is promising for providing quantitative understanding of how complex microbial communities behave.

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Data availability. Data sharing is not applicable as no new data were generated or analysed during this study.

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Biography

Dr Douglas Brumley, BSc (Hons), PhD (Cantab) is a Senior Lecturer at The University of Melbourne. He leads an interdisciplinary research group that utilises mathematics, microfluidics and microscopy to study a range of dynamic processes in biology including bacterial motility, symbioses, nutrient cycling and flows around coral reefs.