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A mathematical approach to studying fungal mycelia

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The study of filamentous fungi can be difficult through experimental means alone due to the complexity of their natural growth habitat (e.g. soils) and the microscopic scale of growth (e.g. tip vesicle translocation and hyphal tip extension). Mathematical modelling provides a complimentary, powerful and efficient method of investigation. In this article, earlier mathematical models are briefly reviewed, before an overview of the construction and resultant predictions of a new model for fungal growth and function is given. Model predictions are compared to experimentally obtained data, giving new insight into the complex interaction between the developing mycelium and its environment.

Keywords: Mathematical model, mycelium, *Rhizoctonia solani*, network, fractal

A mathematical model is "a simplification and an idealisation" (Turing, 1952). The aim of mathematical modelling is *not* to form an extremely complex system of equations in an attempt to mirror reality. Instead, the aim is to reduce a complex (biological) system into a simpler (mathematical) system that can be analysed in far more detail and from which key properties can be identified. Thus, the art of mathematical modelling is not about what to include, but instead, what can be omitted. Fungi are in general very difficult to study in their natural habitats by experimental means alone and mathematical modelling provides a complimentary, powerful and efficient method of investigation.

In most environments, the spatial distribution of nutrient resources is not uniform but patchy; such *heterogeneity* is particularly evident in mineral soils, where an additional level of spatial complexity prevails due to the complex pore network in the solid phases of the soil. Mycelial fungi are well adapted to growth in such spatially complex environments, since the filamentous hyphae can grow with ease across surfaces, and also bridge air gaps between such surfaces. This ability is significantly enhanced by the propensity of many species to translocate materials through hyphae between different regions of the mycelium. Thus, it has been suggested that hyphae growing through nutritionally-impoverished zones of soil, or deleterious regions (e.g. localised deposits of organic pollutants, toxic metals, dry or waterlogged zones), can be supplemented by resources imported from distal regions of the mycelium (Morley *et al*., 1996). This has profound implications for the growth and functioning of mycelia, and attendant effects upon the environment in which they live. Thus, the fungal mycelium represents an extremely efficient system for spatial exploration and exploitation (Ritz & Crawford, 1999).

A brief review of modelling

In general, attempts at the mathematical modelling of fungal growth have either focussed on the mycelium level, using quantities such as biomass yield (e.g. Paustian & Schnürer, 1987; Lamour *et al*., 2000), or have focussed on growth on the hyphal level, such as hyphal tip growth, branching and anastomosis (e.g. Prosser & Trinci, 1979; Heath, 1990; Regalado *et al*., 1997). In the former, spatial properties are in general ignored, while in the latter, temporal effects are often neglected. The detailed review by Prosser (1995) summarises much of the mathematical modelling of fungal growth up to that date. Large-scale,

spatio-temporal properties of fungal mycelia have been less extensively addressed, but progress has been made, in particular by Edelstein (1982), Edelstein & Segel (1983), Edelstein-Keshet & Ermentrout (1989), and Davidson *et al.*, (1996a,b, 1997a,b). In these studies, the approach has been to derive systems of equations (non-linear partial differential equations) that represent the interaction of fungal biomass and a growth limiting substrate (e.g. a carbon source). Recently, more complex models have been formulated that consider the influence of nutritional heterogeneity on growth (Regalado *et al.*, 1996; Davidson, 1998; Davidson & Park, 1998; Davidson & Olsson, 2000). Although a large body of work on the mathematical modelling of fungi is now established, many vital questions still remain unanswered and relevant and important problems unaddressed.

The new model

The questions remaining unaddressed by previous modelling attempts have led to the development of a new mathematical model for fungal growth, which we discuss here. The model connects physiology at the hyphal level (e.g. tip growth and branching) to growth and function at the mycelial level (see Boswell *et al.*, 2002, 2003). This model considers the number and location of hyphae, hyphal tips, and concentration of a growth-limiting substrate and, as shown below, makes useful predictions concerning the roles of nutrient translocation within fungal mycelia. Moreover, it has allowed the study of the functional consequences of fungal growth in a variety of habitat configurations.

The fungal mycelium is modelled as a distribution consisting of three components: *active hyphae* (corresponding to those hyphae involved in the translocation of internal metabolites), *inactive hyphae* (denoting those hyphae not involved in translocation or growth, e.g. moribund hyphae) and *hyphal tips*. An important distinction is made between nutrients located within the fungus (*internal*) and those free in the outside environment (*external*). Internally-located material is used for metabolism and biosynthesis, e.g. in the extension of hyphal tips (creating new hyphae), branching (creating new hyphal tips), maintenance, and the uptake of external nutrient resources. In most environments, a combination of nutrients is necessary for growth (carbon, nitrogen, oxygen, etc.) but, for simplicity, in the model system it is assumed that a single generic element is limiting for growth. This element is assumed to be carbon since nitrogen and oxygen were abundant in the model calibration experiment (Boswell *et al.*, 2002).

This model is based on the physiology and growth characteristics of *Rhizoctonia solani* and it is to the results of growth experiments using this fungus that the model has been initially compared. However, many aspects of the model (and results thereby obtained) are applicable to a large class of fungi growing in a variety of habitats.

In terms of the five variables outlined above (active hyphae, inactive hyphae, hyphal tips, internal substrate and external substrate), the model has the following structure:

change in active hyphae in a given area	=	*new hyphae (laid down by moving tips) + reactivation of inactive hyphae – inactivation of active hyphae*
change in inactive hyphae in a given area	=	*inactivation of active hyphae – reactivation of inactive hyphae – degradation of inactive hyphae*
change in hyphal tips in a given area	=	*tip movement out of / into area + branching from active hyphae – anastomosis of tips into hyphae*
change in internal substrate in a given area	=	*translocation (active and passive mechanisms) + uptake into the fungus from external sources – maintenance costs of hyphae – growth costs of hyphal tips – active translocation costs*
change in external substrate in a given area	=	*diffusion of external substrate out of / into area – uptake by fungus*

It is commonly observed that hyphal tips have a tendency to move in a straight line but with small random fluctuations in the direction of growth (due to the manner new wall material is incorporated at the tip) and that the rate of tip growth depends on the status of internally-located material. The model includes these important growth characteristics. In the model, the 'trails' left behind moving hyphal tips corresponds to the creation of hyphae. It has been widely reported that hyphal branching in mycelial fungi is related to the status of internally-located material: turgor pressure and the build-up of tip vesicles have been implicated (Webster, 1980; Gow & Gadd, 1995). Thus, the branching process is modelled as being proportional to the internal substrate concentration. In mycelial fungi, the uptake of nutrients occurs by active transport across the plasma membrane. Hence, in the model system, the uptake process depends not only on the concentration of

the external substrate, but also on the concentration of the internal substrate (i.e. the energy available for active uptake) and on the amount of hyphae (i.e. membrane surface area). It is known that many species of fungi possess both active (i.e. metabolically-driven) and passive (i.e. diffusive) translocation mechanisms for carbon (Olsson, 1995). Active substrate translocation, unlike diffusion, depletes the energy reserves within the mycelium and is modelled as a process that moves internal substrate towards hyphal tips since they represent the major component of mycelial growth and are therefore likely to be the largest net energy sinks.

Similar to previous models, we assume as a first step that the variables in the model system are *continuous* (i.e. can be viewed as densities) and as such, a partial differential equation system is formed. This treatment results in a system that is best suited to modelling dense mycelial growth of the type often observed in laboratory experiments. However, the true, branched (fractal) nature of the mycelial network (Ritz & Crawford, 1990) is not disregarded in our model; we take account of this by carefully modelling translocation so as to best represent movement inside a branching (fractal) structure (see Boswell *et al.*, 2003 for details).

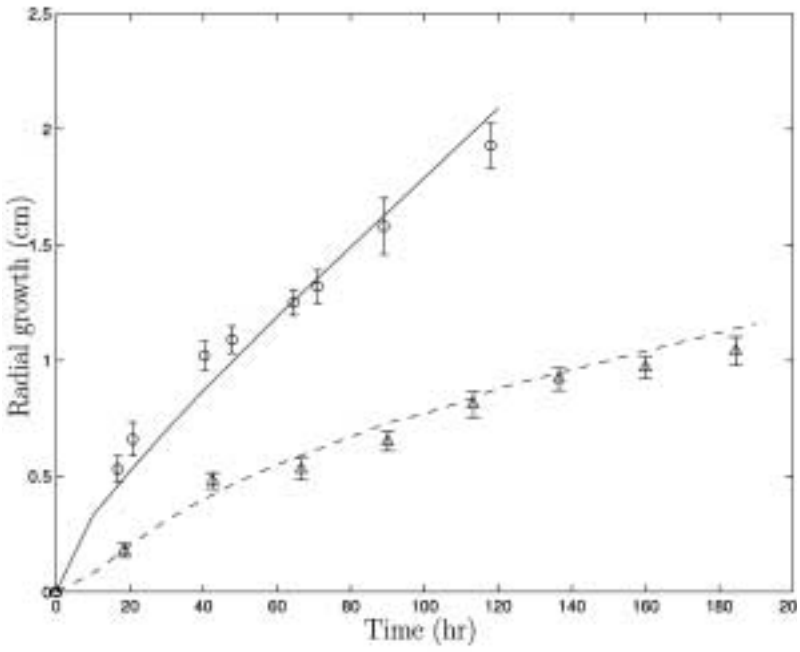

Fig 1 Experimental and model colony radial growth plotted over time. Experimental data for growth measurements at 30°C are denoted by ○ while experimental data for growth measured at 15°C are denoted by △ and both are augmented with standard error bars. The solid line corresponds to the model biomass radius growth for the 30°C calibration and the dashed line corresponds to the model biomass radius growth at 15°C using the reduction of tip-velocity corresponding to the Q_{10}-rule (redrawn from Boswell *et al.*, 2002).

Although the core of the model is formed from a consideration of the general growth characteristics of mycelial fungi, as mentioned above, for direct comparison with experimental observations, the results presented here were obtained in conjunction with experiments using the fungus *Rhizoctonia solani* Kühn anastomosis group 4 (R3) (IMI 385768) cultured on mineral salts media (MSM) containing 2% glucose (w/v) at 30°C. The model was calibrated using simple growth experiments and approximate tip velocities and branching and anastomosis rates were estimated by visually inspecting enlarged images of a mycelium grown over a 15 h time period. Other parameters were taken from the literature, namely, the diffusion of internal and external substrate and the uptake rate of the substrate (see Boswell *et al.*, 2002, for details).

The model equations were solved on a computer using a 'finite-difference' approximation, which involves dividing time and space into discrete units. A square grid is superimposed on the (continuous) growth domain so that each square (or cell) in the grid contains a quantity of active and inactive biomass, hyphal tips, and internal and external substrate. Thus the densities and concentrations of the model system are stored on the computer in a series of two-dimensional arrays. These quantities change in subsequent time steps by the rules given in the model equations according to the status of each 'cell' and its neighbouring 'cells'. In this way, both local concentrations and gradients of concentrations of the five model variables can be considered. By repeatedly applying the above process using finer grids and smaller time steps, the numerical approximation obtained progressively resembles the true solution of the model equations.

A simple quantitative test of the model's predictive power is given by comparing the colony radial expansion, measured experimentally, to the biomass expansion obtained from the solution of the model equations. The colony radial expansion of *R. solani* was obtained by inoculating MSM with 0.25 cm radius plugs of the fungus previously grown on tap water agar. The plates were incubated at 15°C and 30°C and at regular time intervals the colony radii were measured in perpendicular directions. The radius of growth is defined as the mean of these distances once the radius of the initial inoculation has been subtracted. The mean radial growth from five replicates was determined (Fig 1).

The calibrated model equations were solved with initial data representing the experimental protocol described above for growth at 30°C. The radius of growth in the model system was determined in a consistent manner to that in the experimental system (Fig 1). The total hyphal density, (i.e. active and inactive hyphae) is shown in Fig 2 (a)-(d) and there is good quantitative agreement between the experimental and model biomass values obtained (Boswell *et al.*, 2002). By assuming that tip velocity captures the cumulative effects of temperature on a cascade of metabolic processes within the mycelium, a simple reduction of tip velocity by an amount consistent with the Q_{10}-rule generates a predictive radial growth rate at the lower temperature of 15°C that is surprisingly consistent with experimental data (Fig 1). (The Q_{10}-rule is a rule of thumb that states a metabolic reaction approximately halves with a 10°C decrease in temperature). Thus it appears that the apparently complex effects of temperature on the growth of *R. solani* may be easily accounted for in the mathematical model by varying a *single* parameter.

A remarkable result arises when the active translocation term in the model is turned off (i.e. the parameter associated with active translocation is set to zero); the radial growth rate and biomass distributions are largely unaffected. We conclude from this observation that modelling translocation by diffusion of internal substrate is sufficient to accurately replicate the experimental growth behaviour of *R. solani* in uniform, substrate-rich conditions. Therefore, the model predicts that *R. solani* does not use active translocation in nutrient-rich, uniform habitats and instead relies on the 'energy-free' process of diffusion for the redistribution of internal metabolites.

In addition to modelling fungal growth and the subsequent nutrient depletion, the production of acidity can be modelled, generating further qualitative and quantitative data. It has been shown that acidity (which can arise from, for example, proton efflux and organic acid excretion) is produced by *R. solani* only in the presence of a utilizable carbon source (Jacobs *et al.*, 2002a, 2002b). Since the internal substrate in the model system represents such a carbon source, the production of acidity can be modelled as being proportional to the concentration of internal substrate (Boswell *et al.*, 2003). This assumption provides the model pH profiles shown in Fig 2 (e)-(h), which accurately replicate (and extend) results obtained when pH gradients are measured experimentally (e.g. Sayer & Gadd, 1997).

The cases considered above are all concerned with mycelial growth in initially uniform conditions. However, the model can easily be adapted to consider nutritionally heterogeneous environments, for example, the tessellated agar droplet system discussed by Jacobs *et al.* (2002b). In that system, molten agar (MSM) was pipetted onto the bases of 9 cm diameter Petri dishes forming a hexagonal array comprising 19 circular droplets each of radius 10 mm and separated at their closest point of contact by a nutrient-free gap of 2 mm. In total, 16 combinations of tessellations were considered by using MSM, MSM amended with glucose, MSM amended with insoluble calcium phosphate, and MSM amended with both glucose and calcium phosphate, to form the (seven) interior and (twelve) exterior droplets. The central droplet was inoculated and the system was sealed to prevent dehydration and contamination and inspected daily.

Recall that in the model system described above, fungal growth depends on a single generic element that is assumed to be a carbon source. Thus, the model can be applied without alteration to a subset of the tessellations considered in Jacobs *et al.* (2002b) corresponding to those four configurations constructed using standard MSM and glucose-amended MSM (Fig 3). The model predicts general growth characteristics that are similar to those observed experimentally (Figs 3 & 4). In fact, the model extends the experimental results by, for example, explicitly mapping internal substrate concentrations.

In the tessellated agar droplet system, the production of acidity was observed by augmenting the growth media with the pH indicator bromocresol purple (Fig 5 (a)-(c)). The explicit mapping of the internal substrate by the model allows for the extension of these experimental results (Fig 5 (d)-(f)).

As before, the roles and functions of active translocation can be easily and quickly investigated by altering the strength of the terms in the model relating to that process. Upon decreasing the rate of active translocation in the model system, it was observed that the rate of substrate uptake on a newly-colonised droplet decreased since less internal substrate was carried at the hyphal tips and thus less 'energy' was available to drive the (active) uptake. This result therefore offers a new insight into the roles of active and passive translocation. Active translocation has in the main been thought to be associated with exploration (outgrowth), while passive translocation (diffusion) has been traditionally associated with exploitation (substrate utilization). The modelling results suggest the reverse; that active translocation is crucially involved in the initial exploitative phase, whereas diffusive translocation is in the main used as a short-range explorative mechanism.

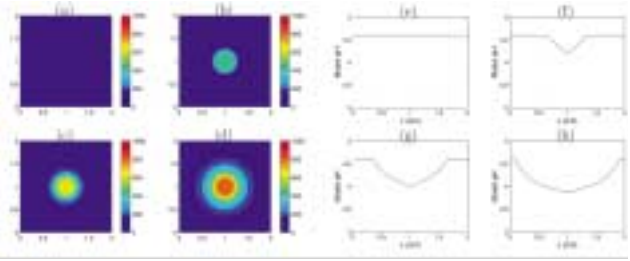

Fig 2 The images (a)-(d) show the biomass densities (cm hyphae cm^{-2}) at the time of "inoculation" up to a time representing 2 days. The images (e)-(h) show a cross-section of the corresponding model acidification of the growth medium.

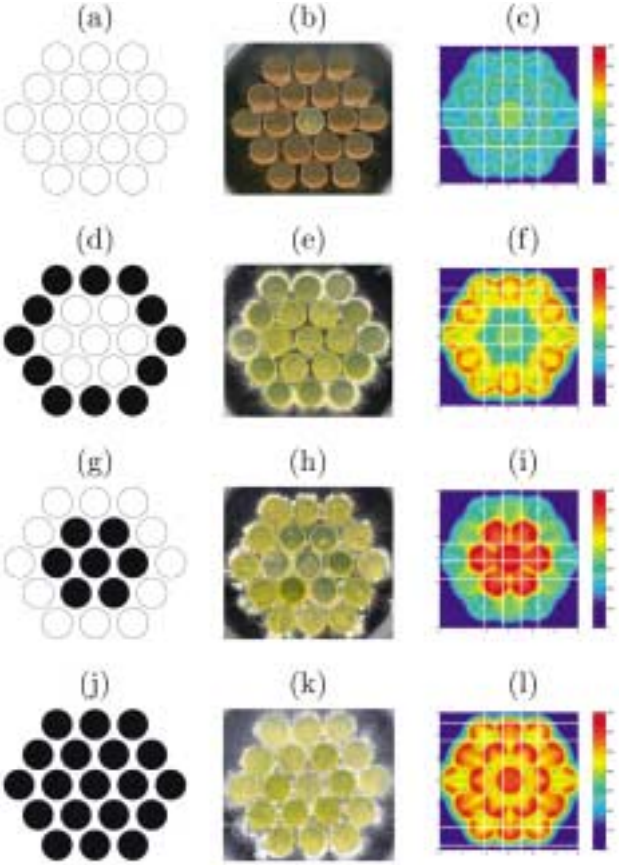

Fig 3 The experimental and model biomasses are shown for four of the agar droplet tessellations described by Jacobs *et al.* (2002b). The images (a), (d), (g), (j) show the tessellations where solid circles denote agar droplets formed using glucose-amended MSM while the open circles denote agar droplets formed using unamended MSM. The images (b), (e), (h), (k) show the fungus 7 days after inoculation of the central droplet (and correspond respectively to tessellations (a), (d), (g), (j)) and are obtained by scanning the underside of a 9 cm diameter Petri dish. The images (c), (f), (i), (l) show the corresponding model biomass densities after a time representing 7 days (cm hyphae cm^{-2}).

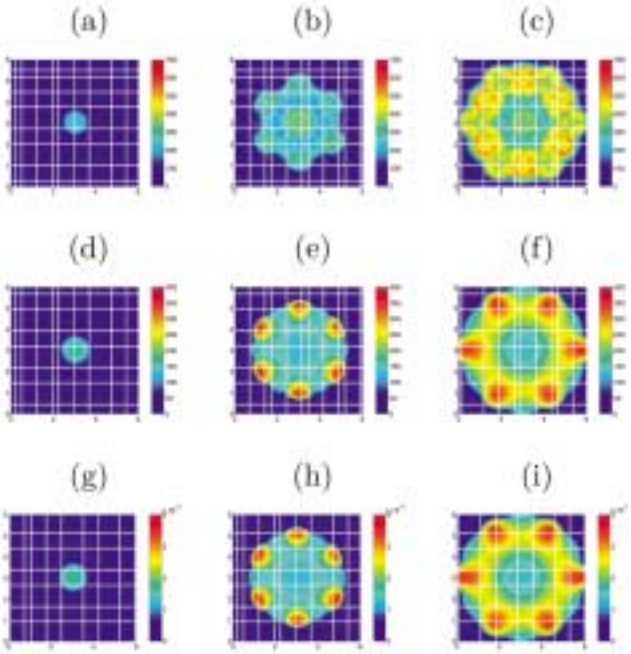

Fig 4 The temporal development of total hyphal density (a)-(c) (cm hyphae cm^{-2}), hyphal tip density (d)-(f) (tips cm^{-2}), and internal substrate concentration (g)-(i) (mol cm^{-2}) for the tessellation in Fig 3(d). Images (a), (d), (g) denote the values at a time corresponding to 1 day after inoculation; (b), (e), (h) denote the values at a time corresponding to 3 days after inoculation; (c), (f), (i) denote the values at a time corresponding to 5 days after inoculation.

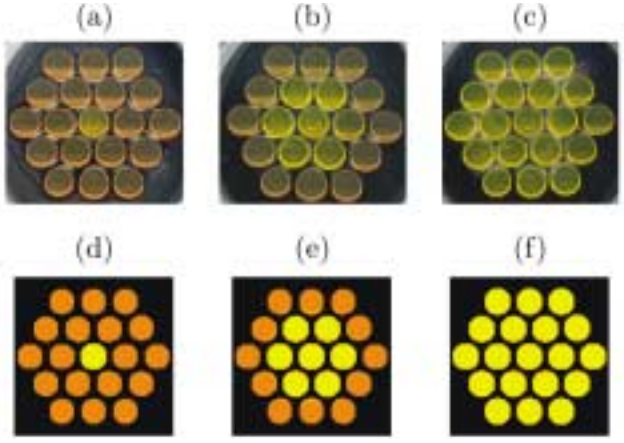

Fig 5 Experimental and model acidity as a result of fungal growth in the agar droplet tessellation formed entirely using glucose-amended MSM (Fig 3(j)). Images (a)-(c) show the acidification of the droplets on successive days from day 1 to day 3 where the central droplet was inoculated on day 0. The images (d)-(f) show the corresponding model acidification. The pH colour indicator (bromocresol purple) has an operational range between pH 6.8 (orange) and pH 5.2 (yellow) (redrawn from Boswell *et al.*, 2003).

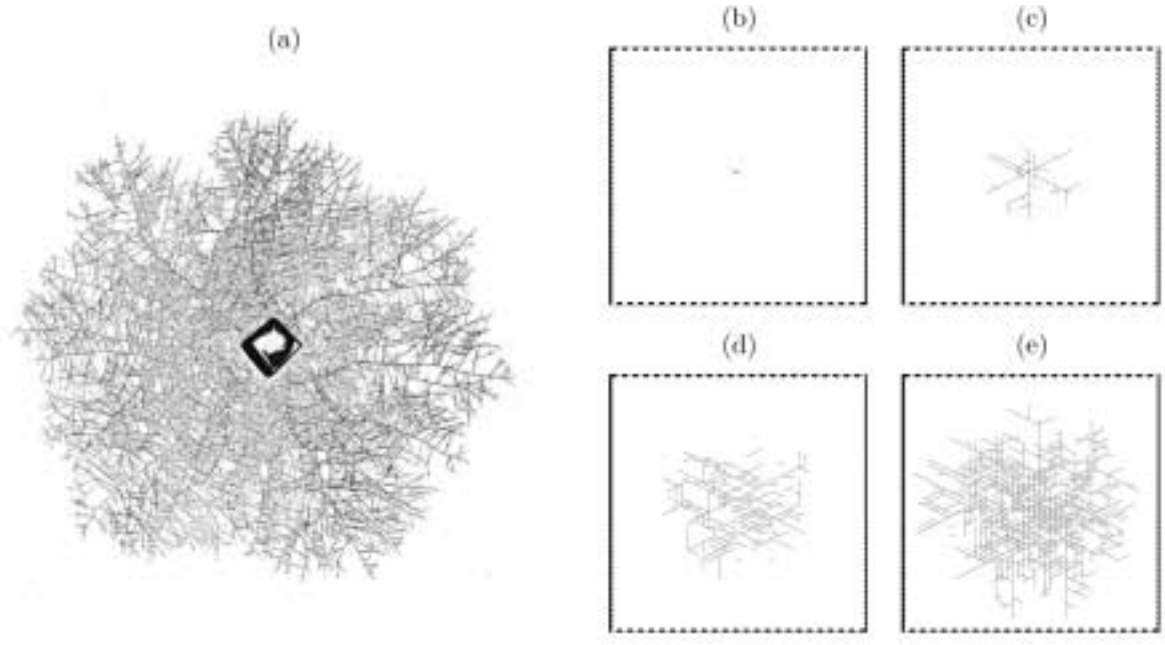

Fig 6 (a) A typical mycelium of *Rhizoctonia solani*. (b)-(e) A model "inoculum" develops into a complex network reminiscent of mycelial fungi.

An alternative modelling formulation

An alternative approach to modelling fungal growth has been recently undertaken by us to model the true filamentous nature of the mycelium. Previously, such *discrete* models (i.e. models that consider individual hyphae and hyphal tips as opposed to densities) have taken the form of computer simulations derived through the statistical properties of the experimental system under investigation (e.g. Cohen, 1967; Lindenmayer, 1968a, 1968b; Hutchinson *et al.*, 1980; Soddell *et al.*, 1995). These models typically use non-mechanistic rules to generate hyphal tip growth and branching. Although these models can often produce realistic looking branched structures, the fact that the rules are not directly connected to the underlying physiological processes of growth means that the models require reformulation to consider the growth of the same species in a different environment or to consider the growth of a different species. Furthermore, previous models typically neglect anastomosis and, because of the overwhelming computational difficulties, have always neglected substrate uptake and translocation. Consequently, previously developed discrete models have only (and indeed *can* only) be applied to uniform environments.

We have developed a discrete model that is derived from the continuum model described above. It is based on the underlying processes of growth and the interaction of the fungus with its environment and explicitly includes anastomosis and translocation, thus allowing growth to be simulated in both uniform and heterogeneous environments. In our approach, space is modelled as an array of hexagonal 'cells' and the model mycelium is defined on the embedded triangular lattice (i.e. the lattice formed by connecting the centres of adjacent hexagonal cells). Time is also modelled as discrete steps and the probabilities of certain events occurring during each time interval are derived from the assumptions used in the previously described (continuum) approach. This discrete model replicates many of the important qualitative features associated with mycelial growth in uniform environments (Fig 6). Work is currently underway applying this discrete model to nutritionally-heterogeneous environments (the agar droplet tessellations). This discrete approach is essential for the accurate modelling of growth and function in soils since mycelial growth is often sparse in such environments.

Overview

Mathematical modelling yields considerable insight into the functional consequences of mycelial growth. By combining modelling with experimental data, more detailed qualitative *and* quantitative results can be obtained. We conclude that our modelling approach described above provides a powerful tool to augment experimental studies of growth, function and morphogenesis of mycelial fungi in uniform and heterogeneous environments. Consequently, we predict that mathematical modelling can play a central role in the successful application of fungi to biotechnological areas such as biocontrol and bioremediation.

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