

MSc Computational Science
joint programme UvA/VU



A DIFFUSION-BASED MODEL OF SPATIAL INTERACTIONS IN ASPERGILLUS SPECIES FROM GERMINATION TO OUTGROWTH

THESIS TOPIC PROPOSAL

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October 17, 2024

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Examiner: Dr. Jaap Kaandorp, University of Amsterdam

OUTLINE



1 Introduction

Aspergilli as model species

Relevance of mycelial morphology

Linking germination to hyphal outgrowth

2 Scope of Proposal

The *Aspergillus* life cycle

Unifying principles

3 Model

Ideas and challenges

Data

Possible extensions

4 Outlook

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Next steps

ASPERGILLI AS MODEL SPECIES

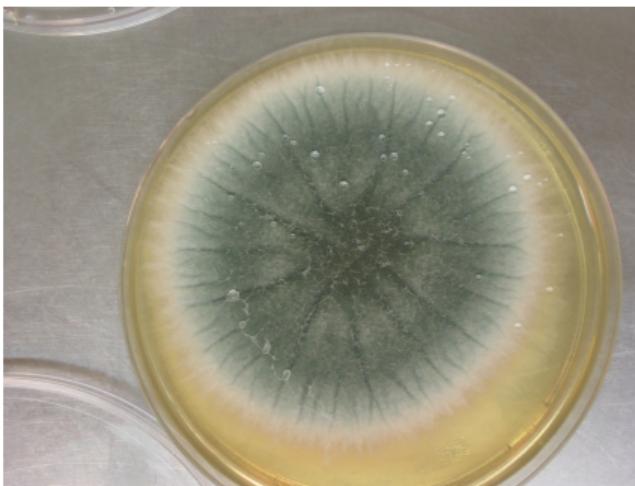


Figure: Colony of *Aspergillus niger* (Wikipedia).

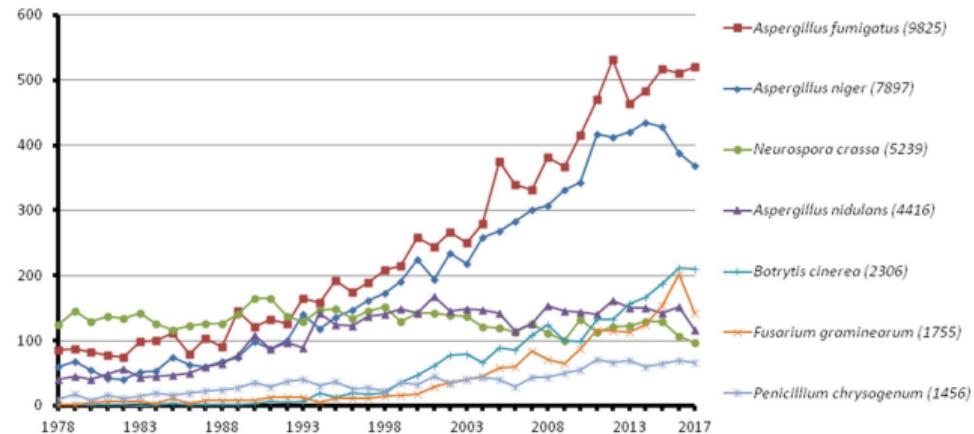


Figure: Number of published papers on PubMed about filamentous fungi[2].

RELEVANCE OF MYCELIAL MORPHOLOGY



» Dispersed mycelia

- higher enzyme productivity
- high viscosity and non-Newtonian behavior, more energy required for mixing

» Pellets

- easier to handle in industrial processes
- density-dependent diffusion limitations, productivity affected by size and compactness

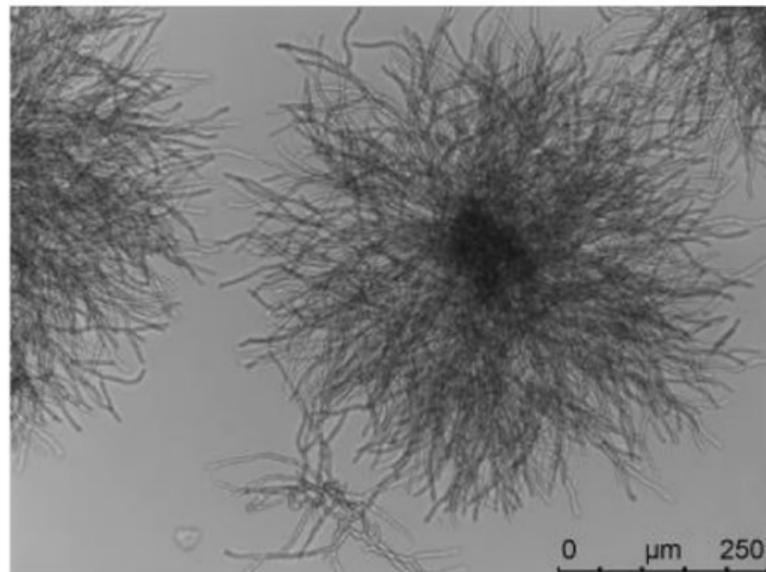


Figure: Pellet (top) vs. free filament (bottom)[13].

LINKING GERMINATION TO HYPHAL OUTGROWTH



- » Outgrowth lag is correlated with germination time[6].
- » Spore density affects both germination[9] and hyphal morphology[16].
- » Medium provides **activation** in spore germination (signaling) and **nutrition** in mycelial growth (consumption).

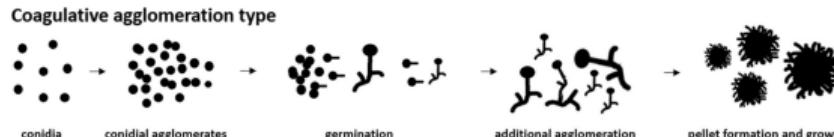


Figure: Stages in coagulative pellet growth[19].

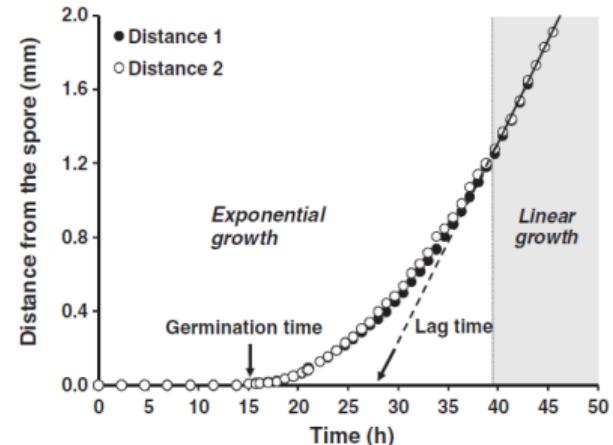


Figure: Relationship between germination time and outgrowth lag[6].

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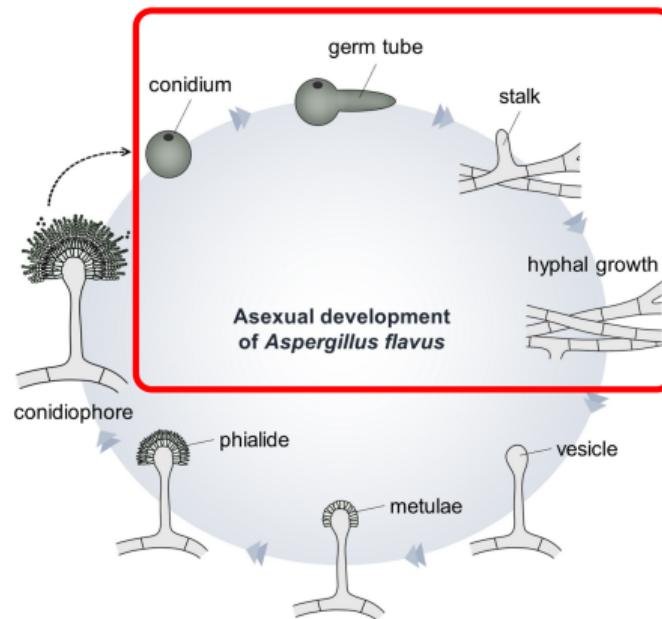
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THE ASPERGILLUS LIFE CYCLE



QUESTION

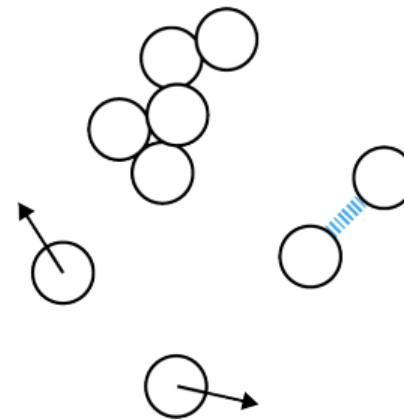
- » Phases of interest - inoculation to hyphal outgrowth (excluding reproduction).
- » How to identify overarching principles among several different and complex phases that can be represented in a much simpler model?



SPORE AGGLOMERATION



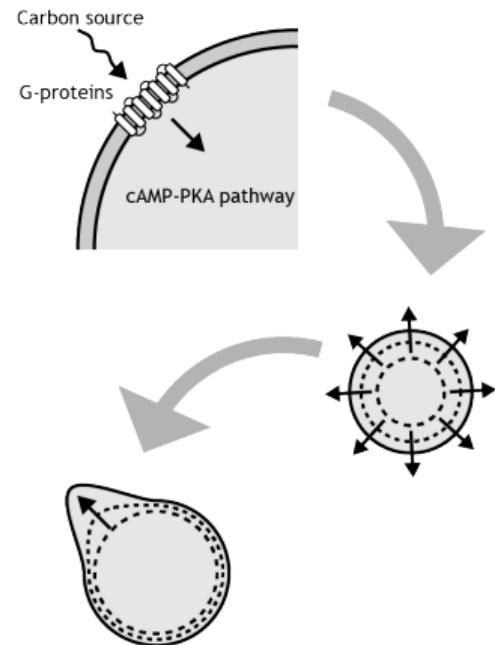
- » Motion of conidia through medium guided by diffusion or currents
- » Electrostatic and salt bridging between cell wall surface polysaccharides
- » Aggregation of multiple conidia into future pellet cores



GERMINATION



- » **Carbon sensing leads to germination:** GanB(α)-SfaD(β)-GpgA(γ) is activated by carbon source and triggers a rapid and transient cAMP signal, which stimulates PKA activity[11]. RasA and RasB also play a role [5, 15, 1].
- » **Isotropic swelling:** breaking of dormancy, restructuring of membrane, switch from fermentative to respiratory metabolism, conidia become larger and more vulnerable.
- » **Polarisation and germ tube formation:** establishment of polarity axis, cortical markers recruit proteins to site of polarisation. A hyphal tip forms.

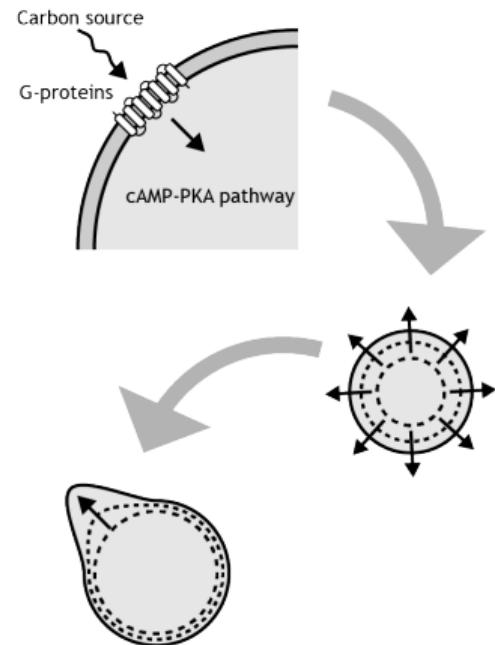


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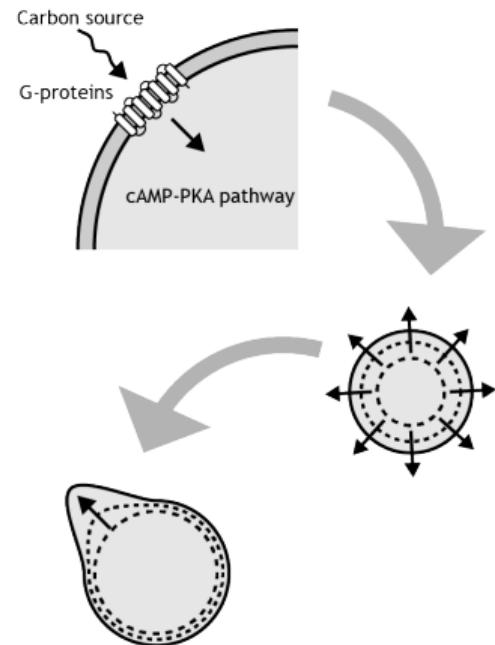


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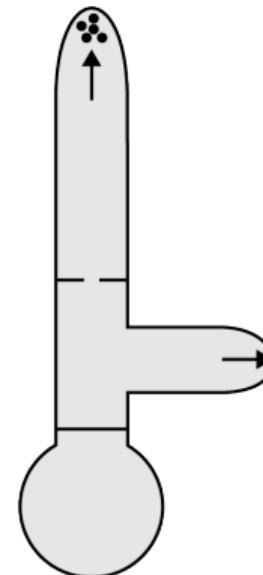
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HYPHAL GROWTH



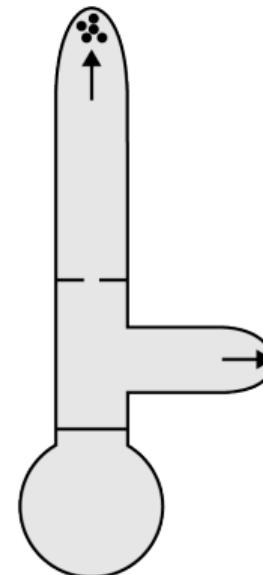
- » Traffic of **vesicles** (EEs) along microtubuli delivers proteins to hyphal tip.
- » Spitzenkörper (SPK) as central hub for distribution of vesicles to the cell membrane via actin filaments.
- » Compartmentalisation of hyphae via **septa**. Opening and closure of **septal pore** can control diffusion between different regions.
- » Secondary polarity axes cause formation of **lateral** branches.



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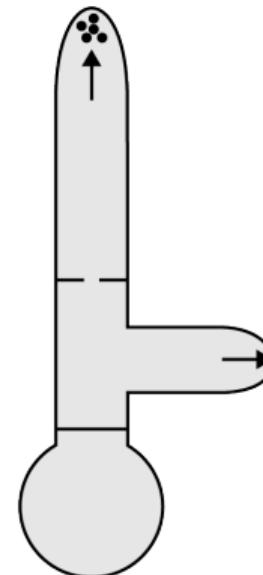
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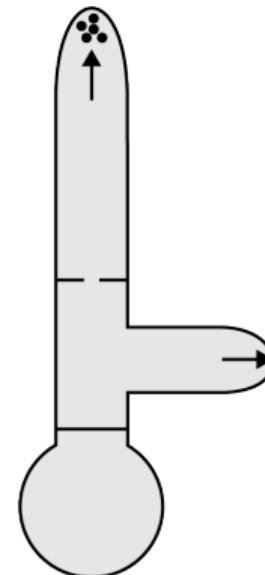


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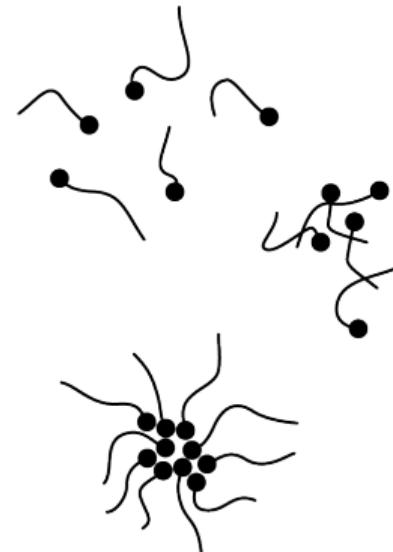
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PELLETS, CLUMPS AND FREE FILAMENTS



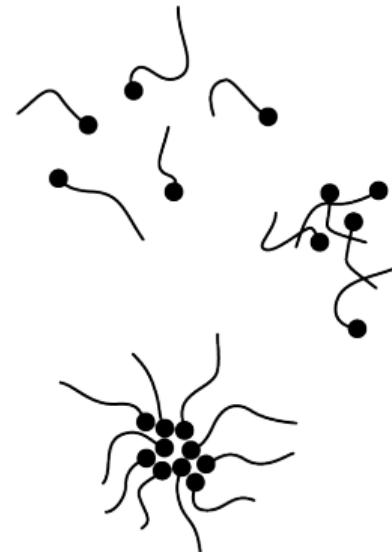
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- » External transport: different densities, e.g. in pellets, cause spatially differentiated nutrient supply, which reflects back on growth[13].
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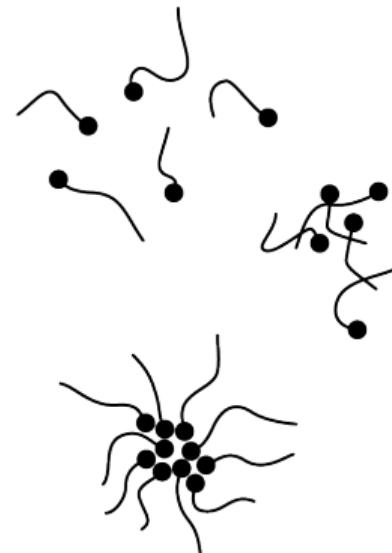


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UNIFYING PRINCIPLES



- » Diffuse and directed transport through space plays an important role in all phases:
 - Motion of conidia leading to agglomeration;
 - Transmission of carbon signals to conidial membrane proteins (possible self-inhibition of conidia due to crowding);
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Minimum viable product of Thesis:

- » A **spatio-temporal model** of growing hyphal morphologies, starting from ungerminated spores.
- » Starting from a **minimal set of assumptions** and gradually incorporating more mechanisms where necessary.
- » The model should be able to **explain and represent** characteristic phenomena from phases like agglomeration, germination and mycelial outgrowth.

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EXISTING MODELS

Diffusion-limited aggregation

- » Model by Witten and Sander (1981)[20]
- » Based on the aggregation of randomly moving particles, can also be expressed in terms of concentration-based probabilities
- » The interplay between aggregate and diffusion can be represented well

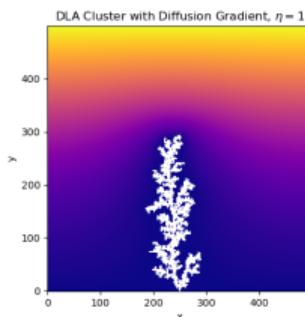


Figure: PDE-based DLA.

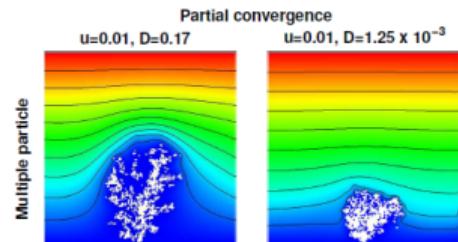


Figure: DLA-generated coral morphology section under laminar flow[12].

EXISTING MODELS



Vector-based growth

- » Many existing models generate the hypha through addition of discrete segments by vector operations.
- » Such formations can be superimposed over concentration gradients or be discretised on a lattice.



Figure: Simulated 3D fungal pellet[3].

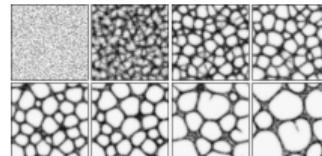


Figure: Simulated *Physarum* transport network patterns[10].

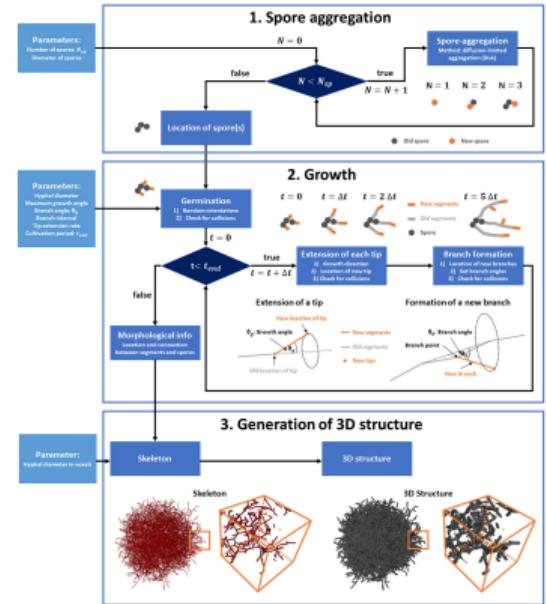
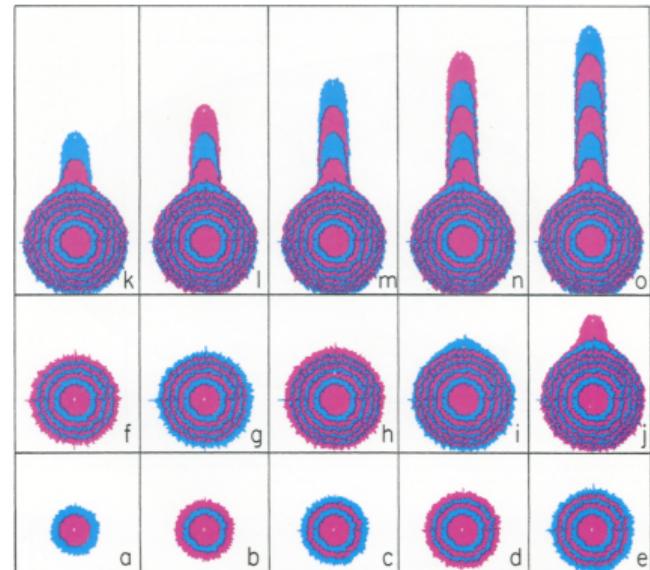


Figure: Growth simulation of a fungal pellet, including DLA in spore agglomeration[17].

EXISTING MODELS

The VSC model

- » Vesicle Supply Centre (VSC) model proposed by Bartnicki-Garcia (1989)
- » Moving VSC uniformly radiates vesicles in random angles, which accumulate more material in the cell membrane



CHALLENGES



- » Finding the right resolution to incorporate phenomena of very **different scales**
- » From 2D to 3D representation - 3D simulations are computationally expensive, but assumptions can be more accurate
- » Validation data - access and comparison can be non-trivial, should start early with this

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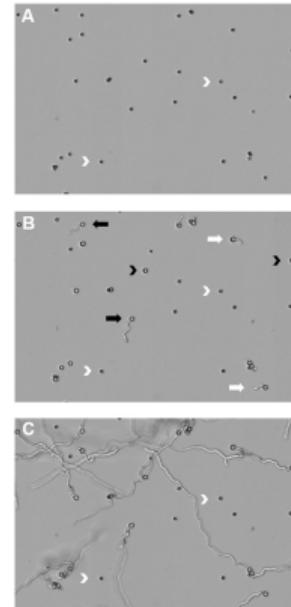


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INPUT DATA

Experiments by Ijadpanahsaravi et al.

- » Germination data from *A. niger* based on fitted asymmetrical model (P_{max} , τ , d)[8, 9, 7]
- » Can be used to model the distributions from which germination times of individual spores are randomly drawn



VALIDATION DATA

»

- » Available data on 3D pellet morphologies of a hyper-branching *A. niger* strain
- » Can serve as an extreme case validation
- » Alternative sources might also be available

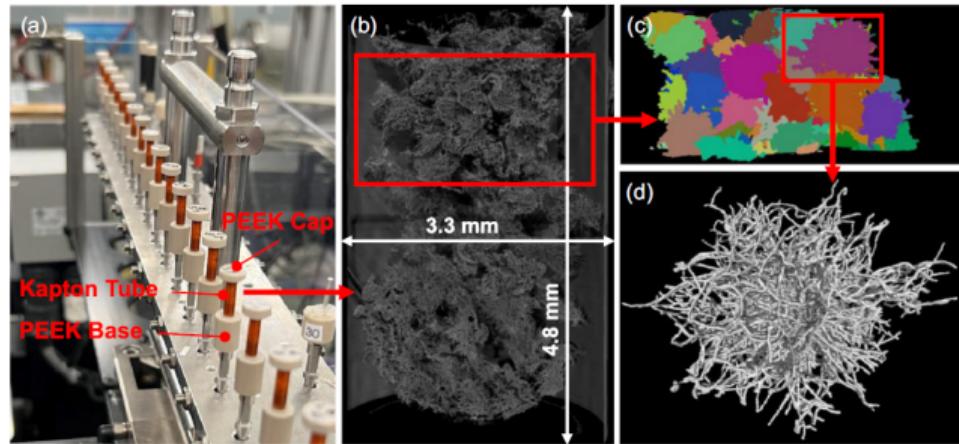


Figure: Process of identifying *A. niger* pellets in 3D microtomography imaging[14].

POSSIBLE EXTENSIONS



- » The asymmetric model for germination by Dantigny[4] yields a good fit with experimental data, but is not necessarily based on **first principles**.
- » Could the framework for our model be used to model explain the statistical results through **spatial interactions** between conidia?
- » Then the input data could become validation data.

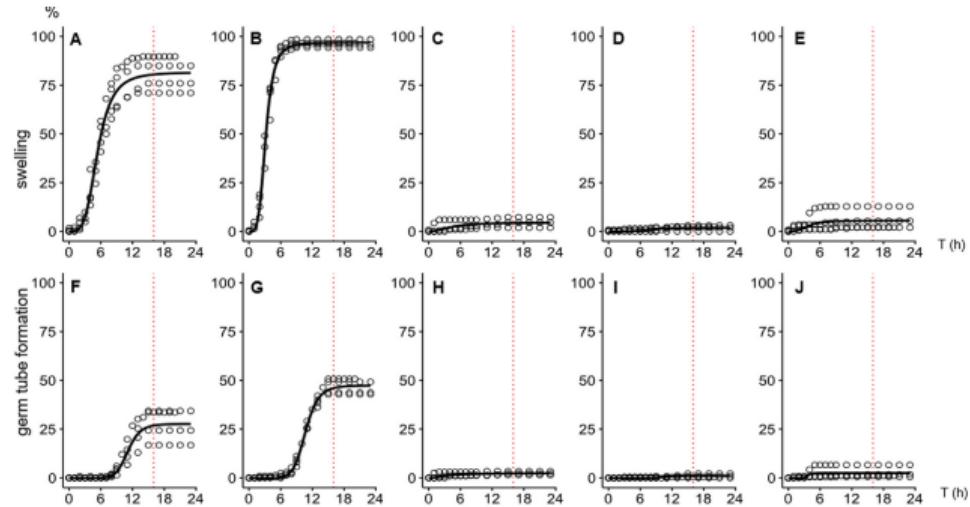


Figure: Fitted asymmetrical model[4] on *A. niger* data measured in different media: alanine (A, F), proline (B, G), glutamate (C, H), histidine (D, I), phenylalanine (E, J)[8].

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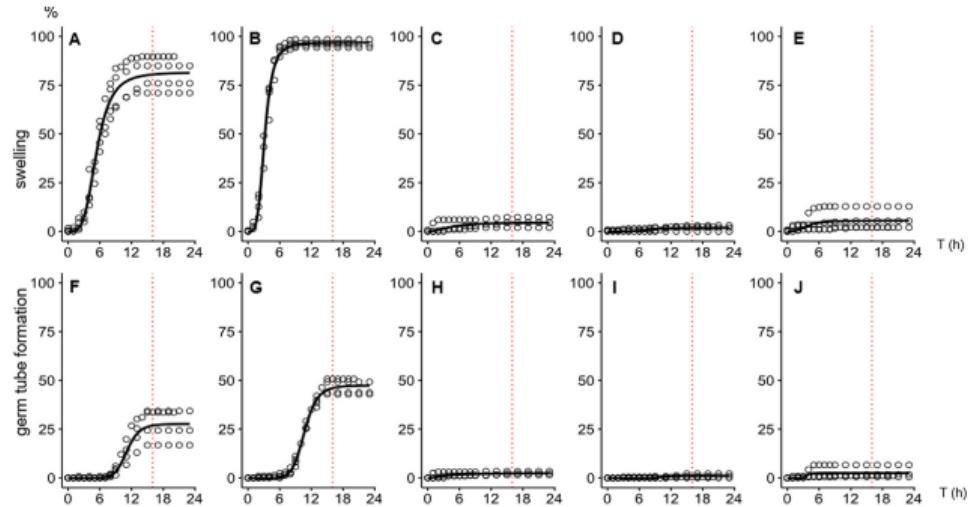


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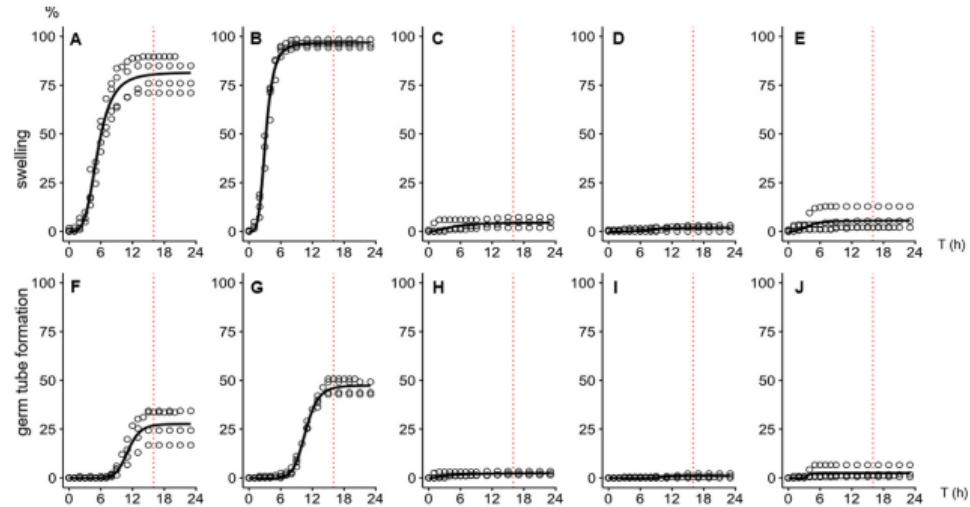


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TENTATIVE SCHEDULE



1. Week 43, 2024 - Submission of Thesis Proposal;
2. Week 49, 2024 - Completed literature review (biological principles and existing models);
3. Week 3, 2025 - Minimal model completion and data access setup;
4. Week 9, 2025 - Validation, verification and potential correction of the model;
5. Week 13, 2025 - Analysis of model results;
6. Week 17, 2025 - Model extensions;
7. Week 22, 2025 - Documentation (writing of Thesis).

NEXT STEPS



- » In-depth literature review on relevant phenomena - agglomeration, apical extension, lateral branching.
- » In-depth literature review on related models.
- » Extraction, connection and reduction of relevant principles and their model representations.

THANK YOU!



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