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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Examiner: Dr. Jaap Kaandorp, University of Amsterdam

OUTLINE

ASPERGILLI AS MODEL SPECIES

Figure: *Aspergillus niger* growing on an onion (Wikipedia).

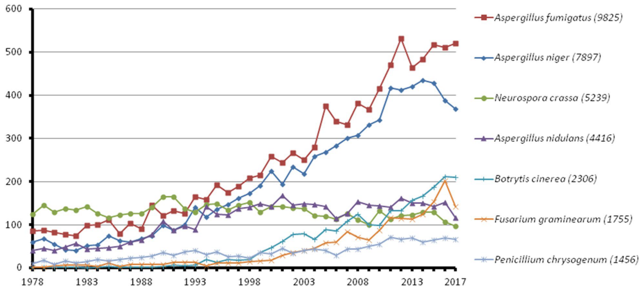


Figure: Number of published papers on PubMed about filamentous fungi[2].

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

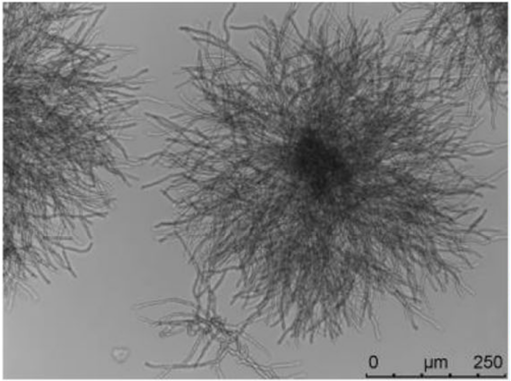


Figure: Pellet (top) vs. free filament (bottom)[13].

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).

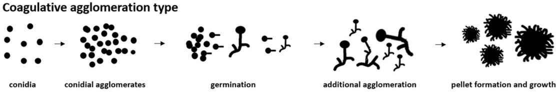


Figure: Stages in coagulative pellet growth[19].

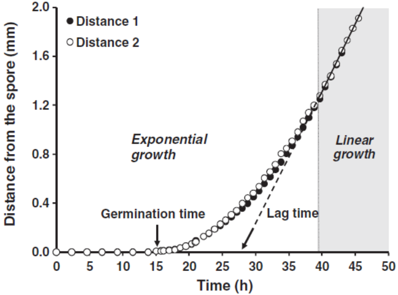


Figure: Relationship between germination time and outgrowth lag[6].

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

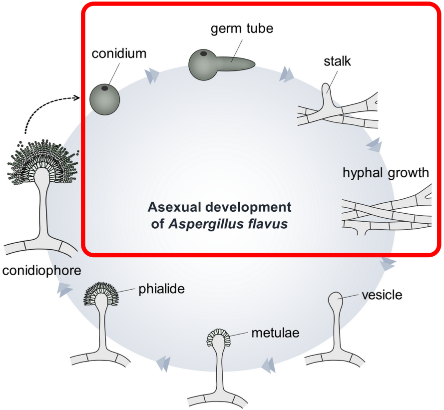
Tentative Schedule

Next steps

THE *ASPERGILLUS* LIFE CYCLE

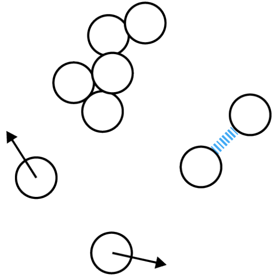
» Phases of interest - inoculation to hyphal outgrowth (excluding reproduction).

» 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

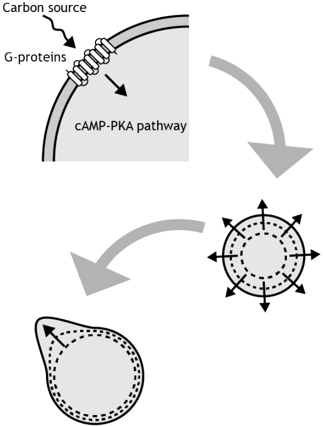


GERMINATION

» **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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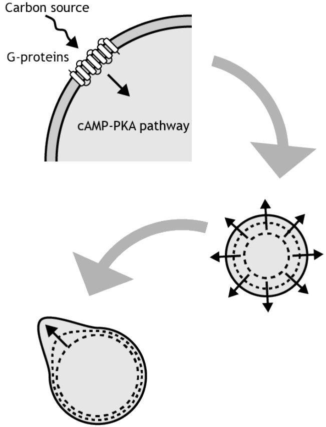

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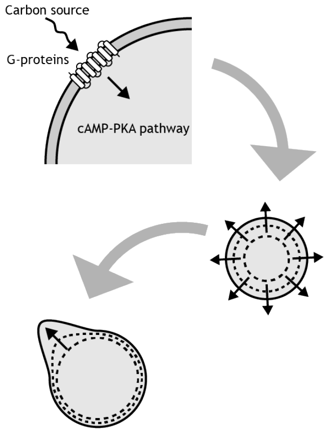
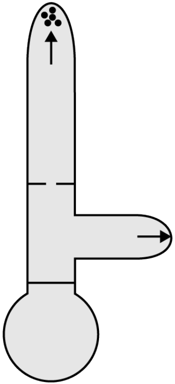


HYPHAL GROWTH

- 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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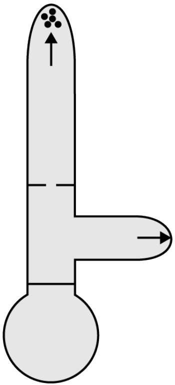

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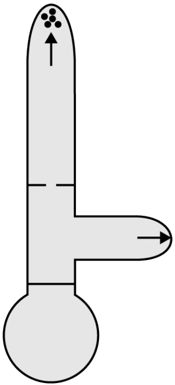

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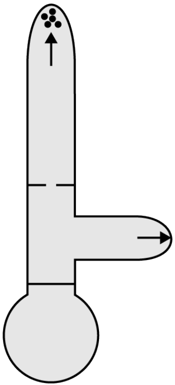
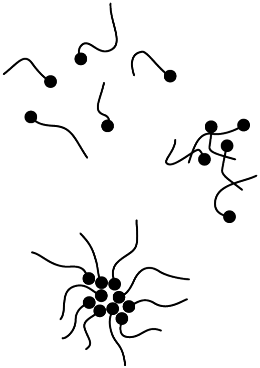


PELLETS, CLUMPS AND FREE FILAMENTS

- Spore density, agglomeration and glucosamine production influence the hyphal **macromorphologies**[16].
- **External transport**: different densities, e.g. in pellets, cause spatially differentiated nutrient supply, which reflects back on growth[13].
- **Internal transport**: cytoplasmic streaming along hyphal network, glucose can be transported even if septal pores are closed. Hyphal fusion improves long-range transport of nutrients[18].



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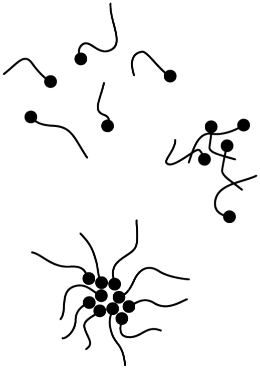

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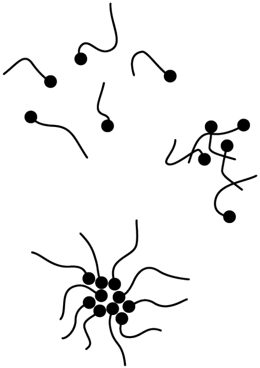

UNIFYING PRINCIPLES

- **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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OUTLINE

MINIMAL MODEL

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

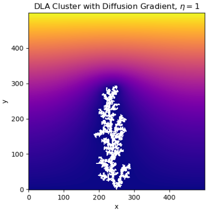


Figure: PDE-based DLA.

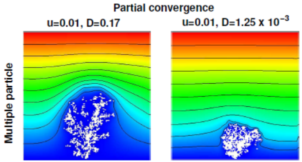


Figure: DLA-generated coral morphology section under laminar flow[12].

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].

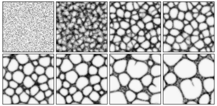


Figure: Simulated *Physarum* transport network patterns[10].

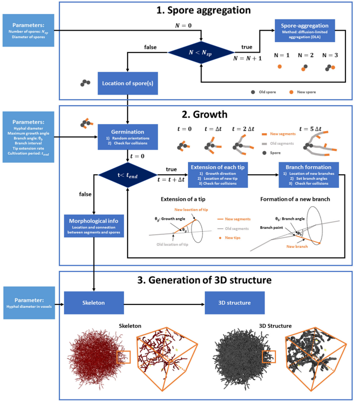


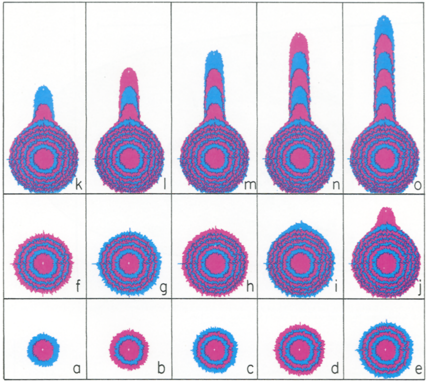
Figure: Growth simulation of a fungal pellet, including DLA in spore agglomeration[17].

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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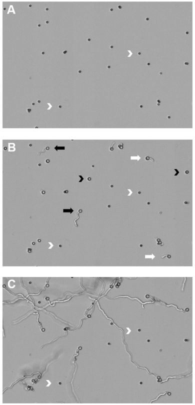
INPUT DATA

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

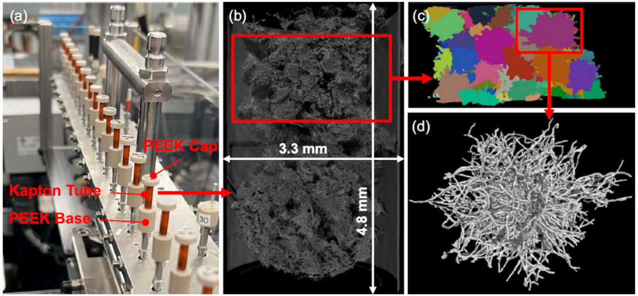


Figure: Process of identifying *A. niger* pellets in 3D microtomography imaging[14].

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**.

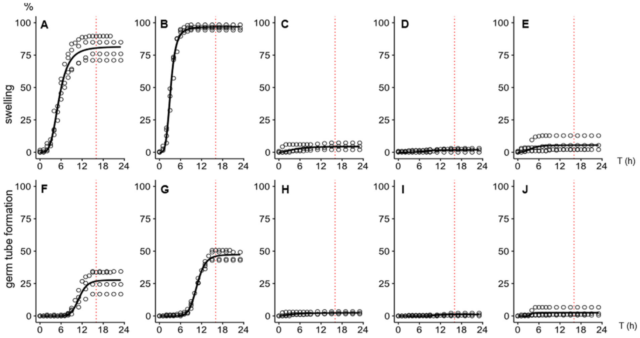


Figure: Fitted asymmetrical model[4] on *A. niger* data measured in different media: alanine (A, F), proline (B, G), glutamate (C, H), histidine (D, I), phenylalanine (E, J)[8].

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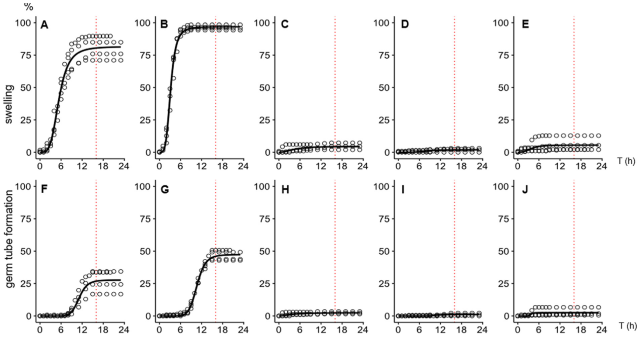

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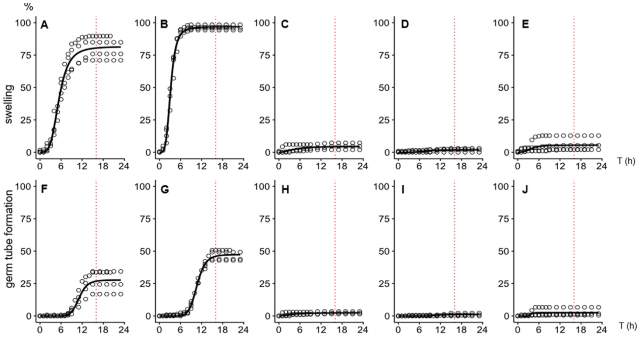

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OUTLINE

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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