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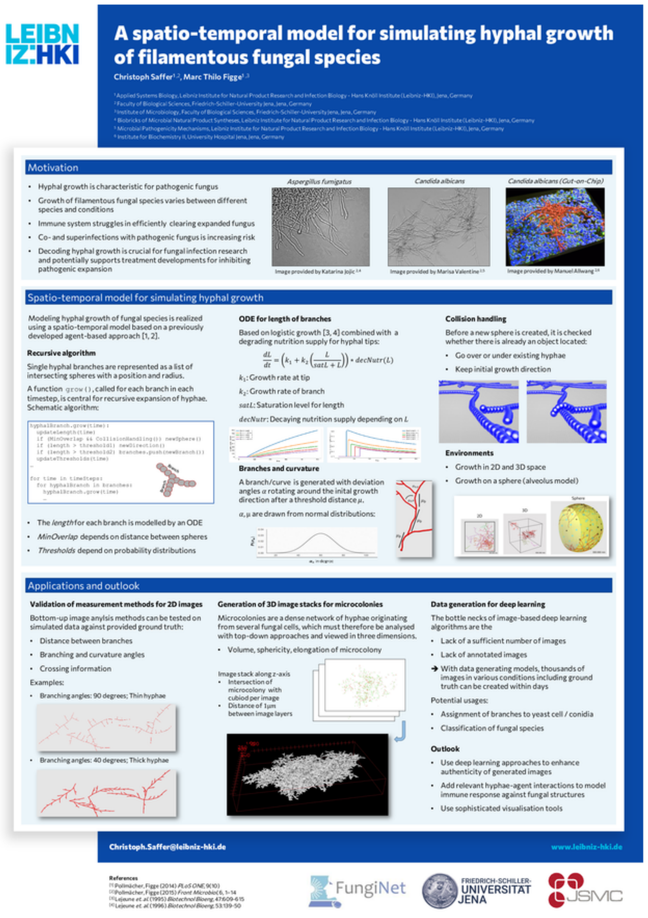

A spatio-temporal model for simulating hyphal growth of filamentous fungal species

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Motivation

- Hyphal growth is characteristic for pathogenic fungus
- Growth of filamentous fungal species varies between different species and conditions
- Immune system struggles in efficiently clearing expanded fungus
- Co- and superinfections with pathogenic fungus is increasing risk
- Decoding hyphal growth is crucial for fungal infection research and potentially supports treatment developments for inhibiting pathogenic expansion

Aspergillus fumigatus

Image provided by Katarina Jojic [4]

Candida albicans

Image provided by Marisa Valentine [5]

Candida albicans (Gut-on-Chip)

Image provided by Manuel Alhwaig [6]

Spatio-temporal model for simulating hyphal growth

Modeling hyphal growth of fungal species is realized using a spatio-temporal model based on a previously developed agent-based approach [1, 2].

Recursive algorithm

Single hyphal branches are represented as a list of intersecting spheres with a position and radius.

A function `grow()`, called for each branch in each timestep, is central for recursive expansion of hyphae. Schematic algorithm:

```
hyphalBranch.grow(time):
  updateLength(time)
  if (NinOverlap && CollisionHandling()) newSphere()
  if (length > threshold1) newDirection()
  if (length > threshold2) branches.push(newBranch())
  updateThresholds(time)
  ...
for time in timeSteps:
  for hyphalBranch in branches:
    hyphalBranch.grow(time)
    ...
```


- The *length* for each branch is modelled by an ODE
- *MinOverlap* depends on distance between spheres
- *Thresholds* depend on probability distributions

ODE for length of branches

Based on logistic growth [3, 4] combined with a degrading nutrition supply for hyphal tips:

$$\frac{dL}{dt} = \left(k_1 + k_2\left(\frac{L}{satL + L}\right)\right) * decNutr(L)$$

k_1: Growth rate at tip

k_2: Growth rate of branch

$satL$: Saturation level for length

$decNutr$: Decaying nutrition supply depending on L

Branches and curvature

A branch/curve is generated with deviation angles α rotating around the initial growth direction after a threshold distance μ.

α, μ are drawn from normal distributions:

Collision handling

Before a new sphere is created, it is checked whether there is already an object located:

- Go over or under existing hyphae
- Keep initial growth direction

Environments

- Growth in 2D and 3D space
- Growth on a sphere (alveolus model)

Applications and outlook

Validation of measurement methods for 2D images

Bottom-up image anylsis methods can be tested on simulated data against provided ground truth:

- Distance between branches
- Branching and curvature angles
- Crossing information

Examples:

- Branching angles: 90 degrees; Thin hyphae

- Branching angles: 40 degrees; Thick hyphae

Generation of 3D image stacks for microcolonies

Microcolonies are a dense network of hyphae originating from several fugal cells, which must therefore be analysed with top-down approaches and viewed in three dimensions.

- Volume, sphericity, elongation of microcolony

Image stack along z-axis
- Intersection of microcolony with cubiod per image
- Distance of 1µm between image layers

Data generation for deep learning

The bottle necks of image-based deep learning algorithms are the

- Lack of a sufficient number of images
- Lack of annotated images

➔ With data generating models, thousands of images in various conditions including ground truth can be created within days

Potential usages:

- Assignment of branches to yeast cell / conidia
- Classification of fungal species

Outlook

- Use deep learning approaches to enhance authenticity of generated images
- Add relevant hyphae-agent interactions to model immune response against fungal structures
- Use sophisticated visualisation tools

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References
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[2] Pollmächer, Figge (2015) *Front. Microbiol.* 6, 1-14
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