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

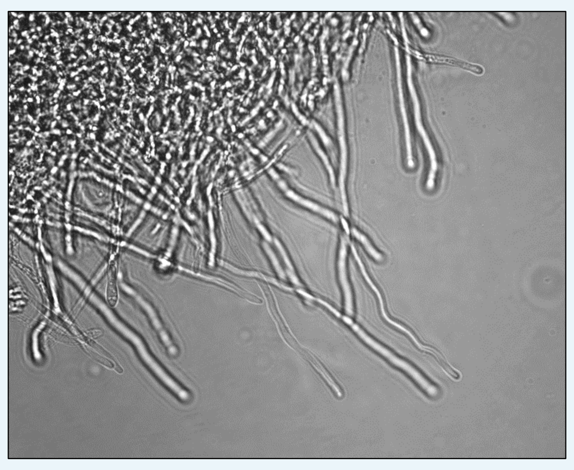


Image provided by Katarina Jojic [2,4]

Candida albicans

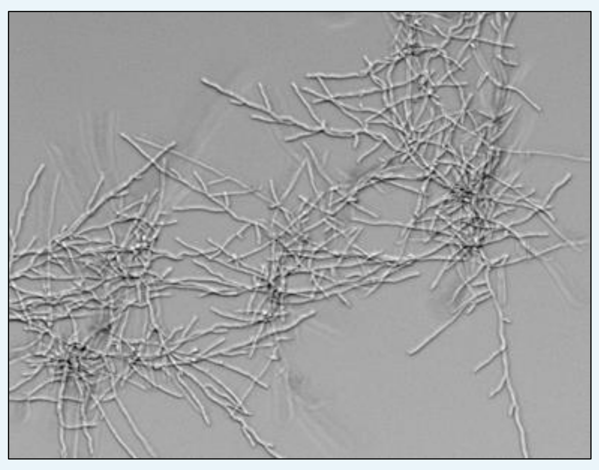


Image provided by Marisa Valentine [2,5]

Candida albicans (Gut-on-Chip)

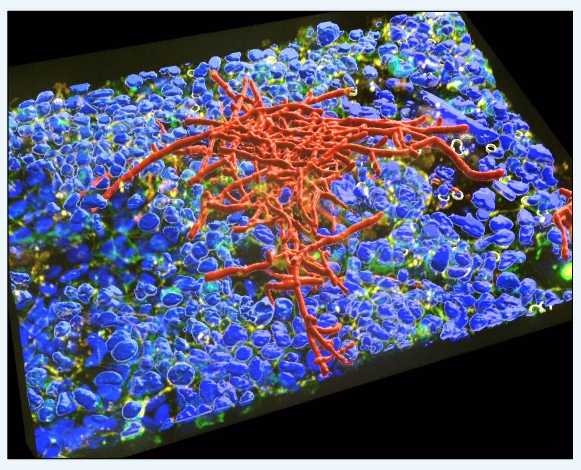


Image provided by Manuel Allwang [2,6]

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].

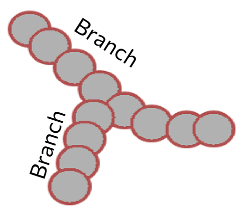
Recursive algorithm

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 (MinOverlap && 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:

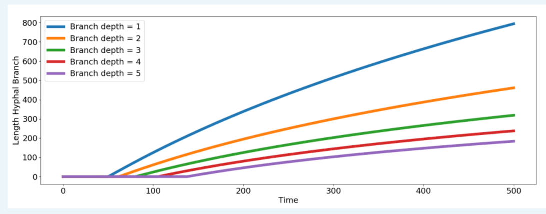
$$\frac{dL}{dt} = \left(k_1 + k_2\left(\frac{L}{satL + L}\right)\right) * decNutr(L)$$

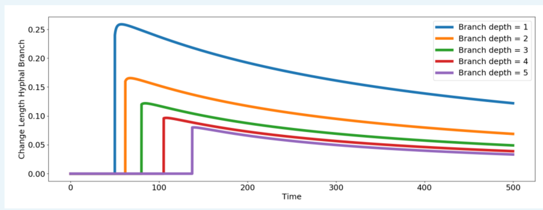
k_1: Growth rate at tip

k_2: Growth rate of branch

$satL$: Saturation level for length

$decNutr$: Decaying nutrition supply depending on L

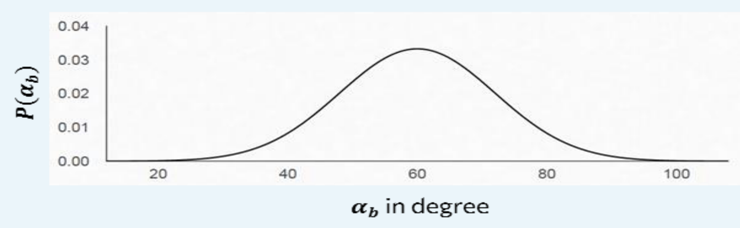


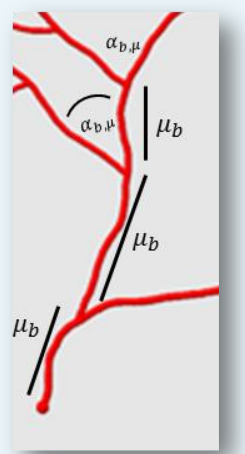


Branches and curvature

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

α, μ are drawn from normal distributions:

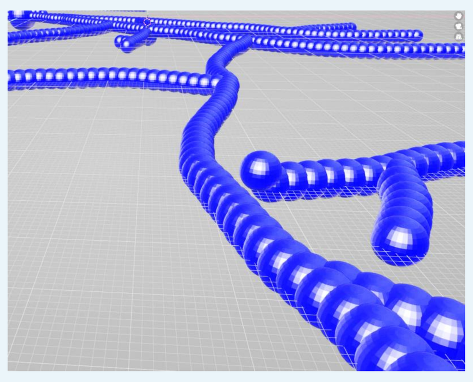


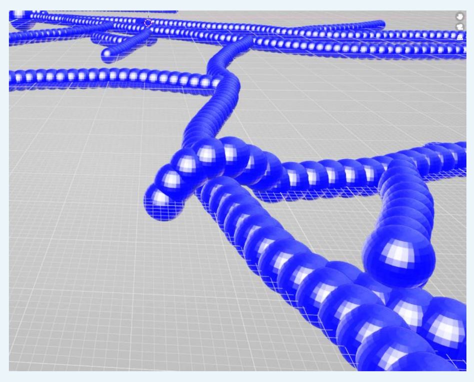


Collision handling

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

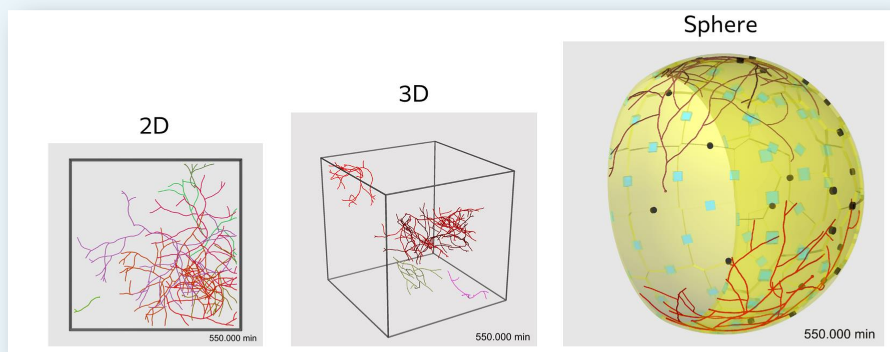
- Go over or under existing hyphae
- Keep initial growth direction





Environments

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



Applications and outlook

Validation of measurement methods for 2D images

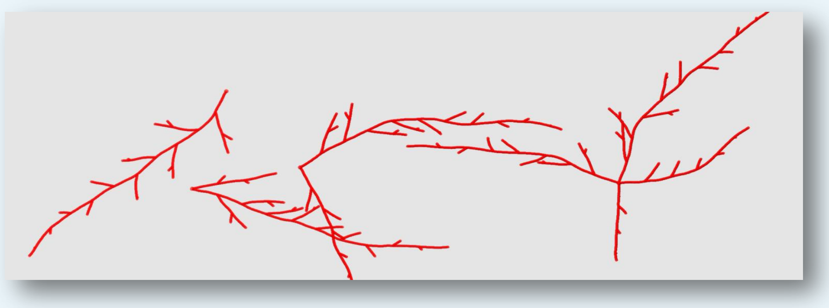
Bottom-up image anylsis methods can be tested on simulated data against provided ground truth:

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

Examples:

- Branching angles: 90 degrees; Thin hyphae

- Branching angles: 40 degrees; Thick hyphae

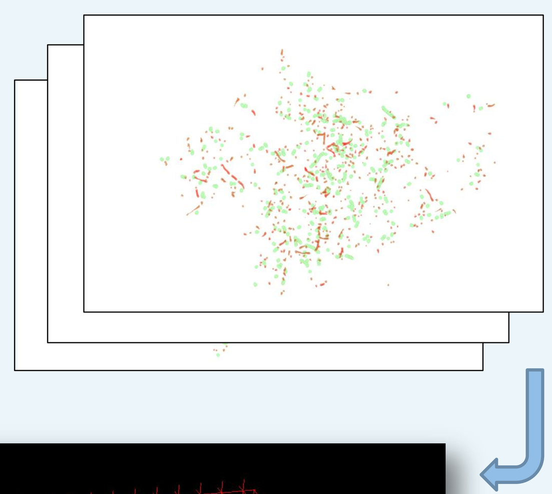


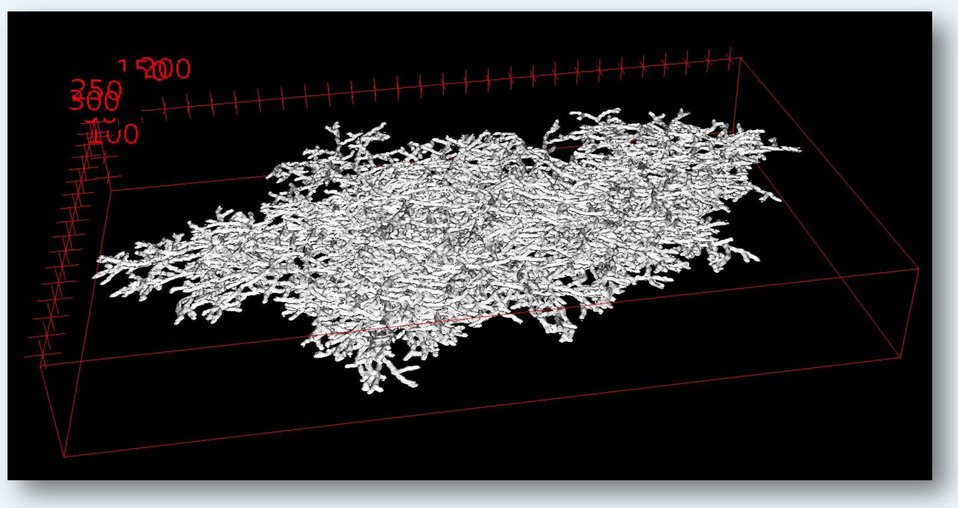
Generation of 3D image stacks for microcolonies

Microcolonies are a dense network of hyphae originating from several fungal 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 $1\mu m$ 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 visualization tools

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References
[1] Pollmächer, Figge (2014) *PLoS ONE*, 9(10)
[2] Pollmächer, Figge (2015) *Front Microbiol*, 6, 1–14
[3] Lejeune *et. al.* (1995) *Biotechnol Bioeng*, 47:609-615
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