Comparative simulations of fungal infection dynamics in the human and murine lung

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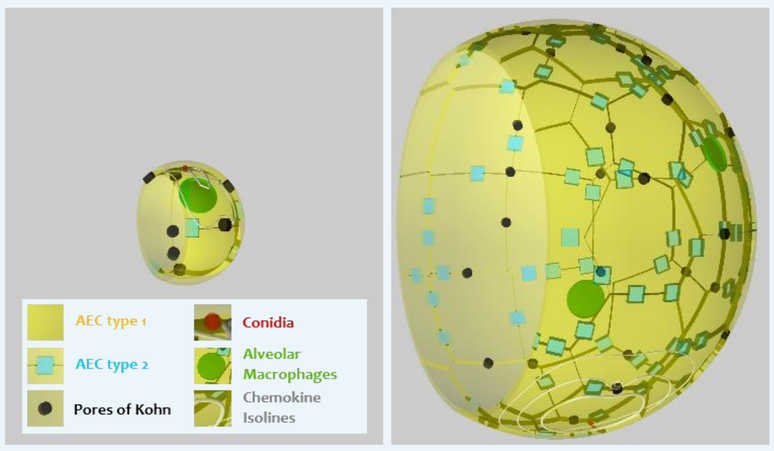
Virtual infection model of *Aspergillus fumigatus* in the human and murine alveolus

- Hybrid modeling approach [1, 2]
- Cells as interacting agents
- Chemokines as molecule concentrations
- Parameters obtained from literature search [4]:

	Human	Mouse
Radius alveolus	$116.5\ \mu m$	$26.2\ \mu m$
Area alveolus	$1.3 \cdot 10^5\ \mu m^2$	$6.5 \cdot 10^3\ \mu m^2$
Radius Alveolar Macrophages (AM)	$10.6\ \mu m$	$9.5\ \mu m$
Number of AM n_{AM}	$2.1 \cdot 10^9$	$2.4 \cdot 10^6$
Alveoli in lung	$4.8 \cdot 10^8$	$3.3 \cdot 10^6$
AEC I (II)	45 (84)	4 (4)
Pores of Kohn (PoK)	24	7



Realistic to-scale model of the murine (left) and the human alveolus (right) represented as a ¾ - Sphere

Virtual Experiments

- Large-scale experiments: High (up to 5000) number of runs per set of parameters

Measurement:

- **Infection Score (IS)** – empirical probability of an infection
- Onset of hyphal growth 6 hours post infection under certain conditions:

$$IS = \frac{\#runs\ with\ \textbf{undetected}\ conidium\ at\ \textbf{6 hours}}{Total\ \#runs}$$

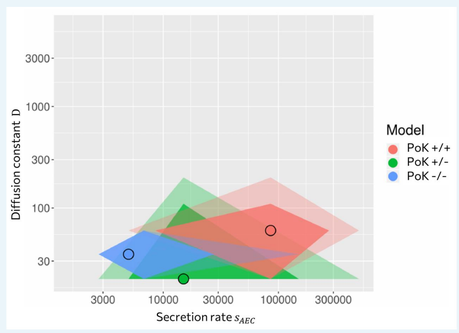
Study about role of Pores of Kohn [3]

Aim: Investigate the role of PoK in human alveolus. Three models were designed to measure significant differences in infection clearance:

- PoK +/+ , Chemokines flow out at PoK, AM enter and exit there (standard)
- PoK +/- , Chemokines flow out at PoK , AM cannot enter or exit there
- PoK -/-, PoK serve neither as chemokine outflow nor as AM migration path

➢ Determined: $n_{AM} = 4.375$, $n_{Con} = 1$, s_{AEC} and D were scanned

Results: Infection scores of parameter optima for $s_{AEC_{opt}}$ and D_{opt}



- Different parameter optima
- In PoK +/- and PoK -/-, AM aggregate at entrance ring
- Spatial advantage in PoK +/+
- $\mathrm{IS}_{POK+/+} < \mathrm{IS}_{POK+/-} = \mathrm{IS}_{POK-/-}$

→ PoK beneficial for clearance

Infection dynamics for varying numbers of AM

- More than 10 million simulations were performed to observe parameters

Parameter ranges to scan	Human	Mouse
Number of AM n_{AM} per alveolus	$2, 4, 6, \dots, 50$	$0.1, 0.2, 0.3, \dots, 2.5$
Number of conidia n_{Con}	$1, 2$	$1, 2, 3$
Secretion rate s_{AEC} in $\frac{molecules}{min}$	$1500, 5000, 15000, 50000, 150000, 500000$	
Diffusion constant D in $\frac{\mu m^2}{min}$	$20, 60, 200, 600, 2000, 6000$	

Simulation results (human):

Low infection scores for

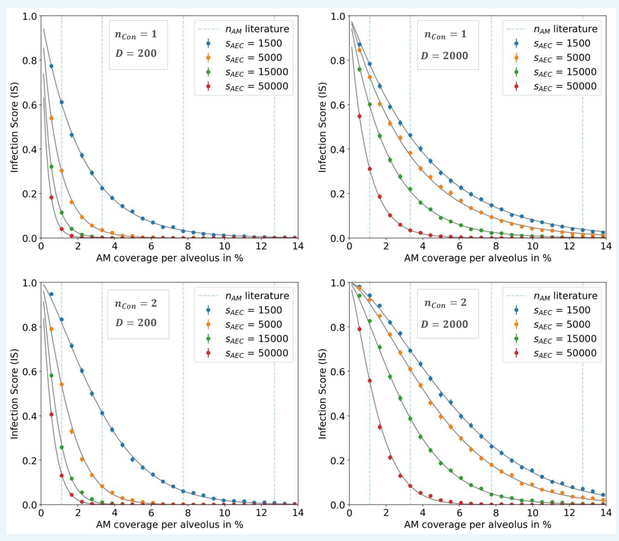
- High n_{AM}
- Low n_{Con}
- High s_{AEC}
- Low D

Curve properties along n_{AM}:

- Exponential decay $e^{-b\ n_{AM}}$
- Different shape for $n_{Con} > 1$

→ $\mathrm{IS}(n_{AM}) = e^{-b\ n_{AM}{}^{c}}$

Fit: Distributions b and c are obtained



Snapshot of simulation data

Surrogate Model

Fit analytical functions f, g to distributions b and c:

- $b \approx f\left(n_{Con}, \frac{s_{AEC}}{D}\ ; \theta_1\right)$
- $c \approx g\left(n_{Con}, \frac{s_{AEC}}{D}\ ; \theta_2\right)$

Generalized surrogate model for infection score IS:

$$\mathrm{IS}\left(n_{AM}, n_{Con}, \frac{s_{AEC}}{D}; \theta_1, \theta_2\right) = e^{-f\left(n_{Con}, \frac{s_{AEC}}{D}; \theta_1\right) n_{AM}{}^{g\left(n_{Con}, \frac{s_{AEC}}{D}; \theta_2\right)}}$$

for functions f and g and parameter vectors θ_1, θ_2

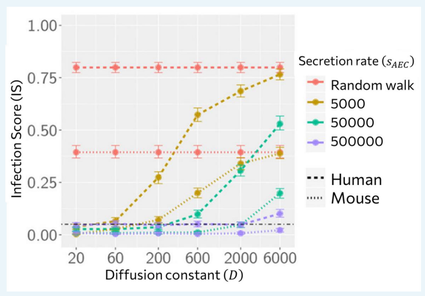
Study about infection clearance in human and mouse [4]

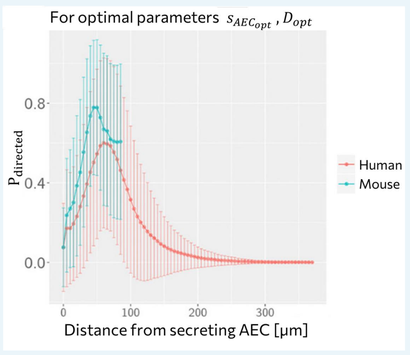
Aim: Investigate the differences in infection clearance in human and mouse

➢ Determined: Human $n_{AM} = 4.375$, Mouse $n_{AM} = 0.727$, s_{AEC} and D were scanned

Results:

- Infection score lower in murine alveolus
- Infections still more efficiently cleared for higher n_{Con} in murine alveolus
- Directed migration of AM more likely in human





Predictions for various infection scenarios in human and mouse

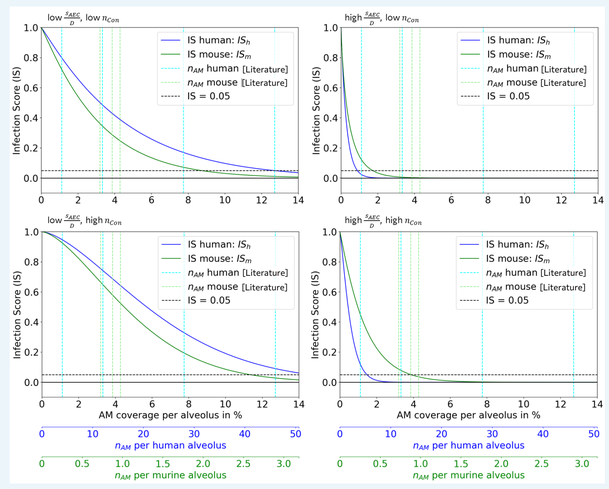
Conclusions for **equal** n_{AM}:

- IS human lower under optimal conditions (high $\frac{s_{AEC}}{D}$)
- IS mouse lower for random walk (low $\frac{s_{AEC}}{D}$)

Outlook:

- Narrow down ranges of parameters (*i. e.* identify min/max n_{AM})
- Hypothesis about importance of parameters for infection clearance

Surrogate model predicts IS in human and mouse:



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References

[1] Pollmächer and Figge. 2014. *PLoS ONE*. 9:10
[2] Pollmächer and Figge. 2015. *Front Microbiol*. 6:1-14
[3] Blickensdorf *et. al.* 2020. *Front Microbiol*. 11:1-13.
[4] Blickensdorf *et. al.* 2019. *Front Immunol*. 10