Spatial distancing: Modeling of a defense mechanism for pathogen immune evasion

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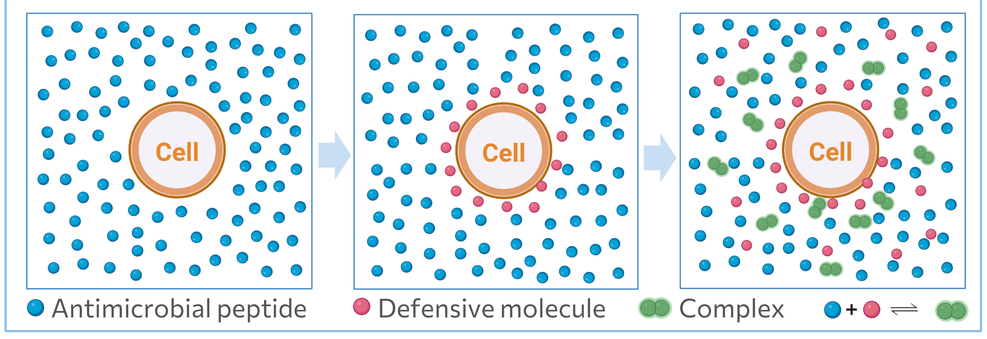
Abstract

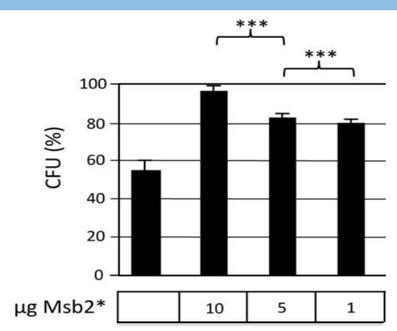
- Some **pathogens**, such as *Candida albicans*, can **evade** the **immune system** and **survive** in the host during **infections**. However, such mechanisms are not yet unraveled.
- In this study, we **investigate** and **simulate** a possible **immune evasive mechanism** referred to as **spatial distancing**: microbial pathogens secrete **defensive molecules** that **bind** to **antimicrobial peptides** and **diffuse away** from the cell due to molecular gradient.
- Two different modeling approaches were used, **Partial Differential Equations** and **Agent-Based Modeling,** both suggesting **spatial distancing** as an **effective way** for microbes to **escape** the **immune system.**

Mechanism



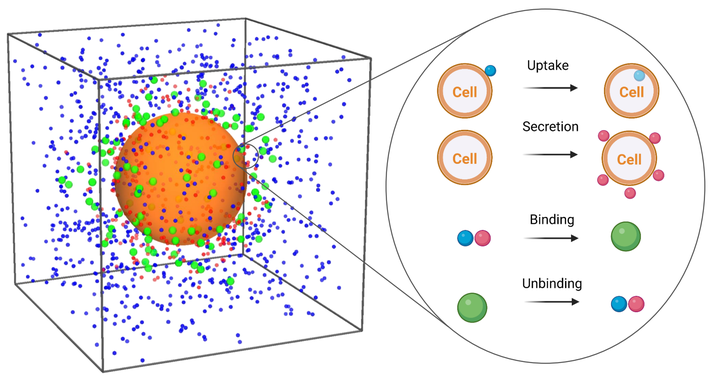
Biological evidence

- *C. albicans* can escape the immune system by protecting itself from AMPs via secretion of Msb2*.
- Figure shows colony forming units (CFU) of *C. albicans* after incubation with human AMP LL37 and in the presence/absence of Msb2*. [1]



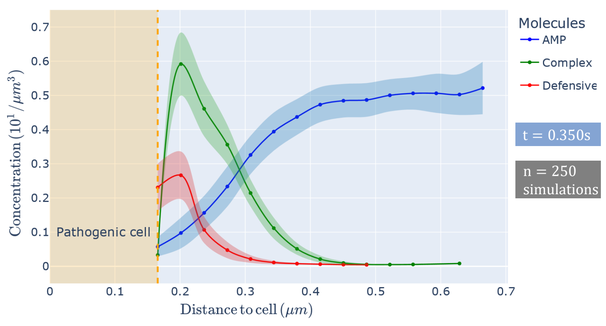
Agent-Based Modeling approach

- **Environment:** 3-dimensional, continuous
- **Molecules**: single agents performing Brownian motion
- **Suited for low concentrations:** formations of complexes are rare events



- Downscaled system with factor 10^{-3}

Spatiotemporal distributions of molecules



- Secretion of defensive molecules at the cell surface
- Formation of complex
- Concentration of AMPs lowered in the vicinity of the pathogenic cell

Partial Differential Equation model

- **Environment:** 3-dimensional, continuous
- **Molecules:** concentrations diffusing on a discrete grid according to the gradient
- **Suited for high concentrations:** formations of complexes are frequent events

AMP

$$\frac{\partial[A]}{\partial t} = D_A\nabla^2[A] + K_{off}[C] - K_{on}[A][D] - K^A_{deg}[A]$$

Defensive molecule

$$\frac{\partial[D]}{\partial t} = D_D\nabla^2[D] + K_{off}[C] - K_{on}[A][D] - K^D_{deg}[D]$$

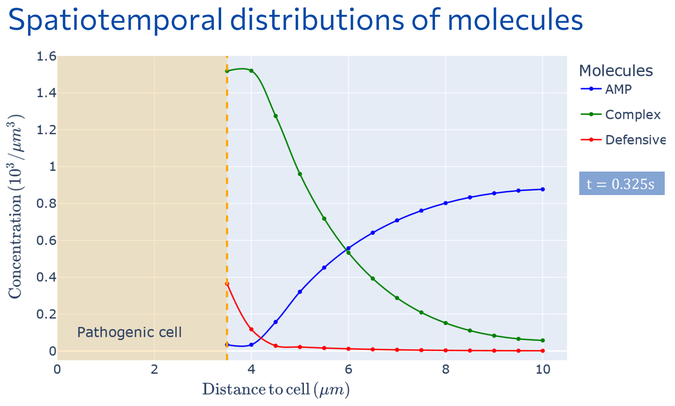
Complex

$$\frac{\partial[C]}{\partial t} = D_C\nabla^2[C] + K_{on}[A][D] - K_{off}[C]$$

Parameter	Description	Unit
S_D	Secretion rate of defensive molecule	$\mu m^{-3}s^{-1}$
U_A	Uptake rate of AMP	s^{-1}
D_A	Diffusion coefficient of AMP	$\mu m^2 s^{-1}$
D_D	Diffusion coefficient of defensive molecule	$\mu m^2 s^{-1}$
D_C	Diffusion coefficient of complex	$\mu m^2 s^{-1}$
K^A_{deg}	Degradation rate of AMP	s^{-1}
K^D_{deg}	Degradation rate of defensive molecule	s^{-1}
K_{on}	Association rate [AMP – Defensive molecule]	$\mu m^3 s^{-1}$
K_{off}	Dissociation rate [AMP – Defensive molecule]	s^{-1}

Initial condition	Description	Unit
$[A]_{t=0}$	Concentration of AMP	μm^{-3}

Spatiotemporal distributions of molecules



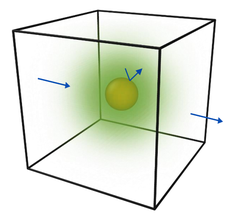
Boundary conditions

- **At the cube limit**: periodic boundaries
- **At the cell surface**: reflective boundaries

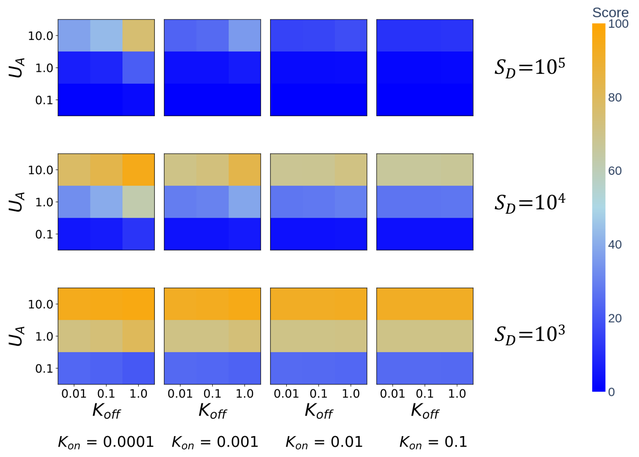
$$\left.\frac{\partial[A]}{\partial x}\right|_{surf} = 0, \quad \left.\frac{\partial[D]}{\partial x}\right|_{surf} = 0, \quad \left.\frac{\partial[C]}{\partial x}\right|_{surf} = 0$$

$$\left.\frac{\partial[A]}{\partial t}\right|_{x=surf} = -U_A[A]_{surf}$$

$$\left.\frac{\partial[D]}{\partial t}\right|_{x=surf} = S_D$$



Parameter screening

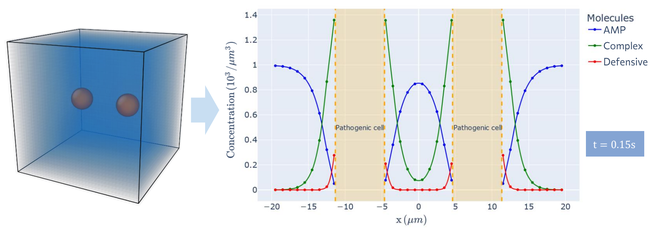


$$\text{Score} = \frac{\text{A}_{\text{uptaken}}}{\text{A}_{\text{total}}} \cdot 100$$

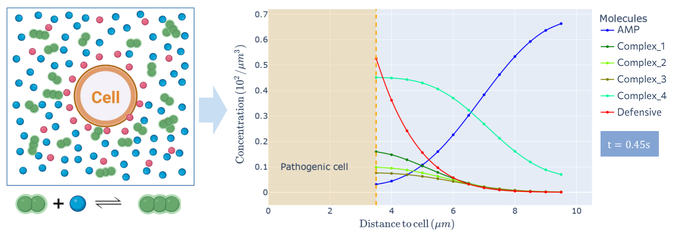
- High S_D and K_{on} rates lead to a reduction in the uptake of AMPs by the pathogenic cell
- Beneficial regime for the pathogenic cell with a wide range of parameter combinations

Model extension

Two pathogenic cells

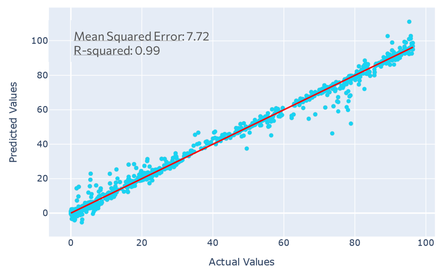


Multi-binding sites on defensive molecules



Surrogate model

- Training of an ML model (Light Gradient Boosting Machine) on simulations from screening
- Prediction of score based on simulations' input parameters



Conclusion

- **Secretion** of **molecules** by the pathogenic cell **reduces** the **concentration** of **AMPs** in the **vicinity** of the **microbial cell.**
- Extended models including **two pathogens** and the **binding** of **multiple AMPs** by one defensive molecule induce **stronger survival chances** for the microbe.
- **Both PDE** and **ABM** approaches show **qualitatively similar dynamics**, suggesting **spatial distancing** as an **effective immune evasion mechanism**.
- **Inhibition** of **molecules secreted by pathogens** in defense against AMPs could be a **target** for **therapeutic interventions**.

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References
[1] Szafranski-Schneider, E. *et al.* 2012. *PLoS Pathogens*.8(2):e1002501

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