Spatial distancing: Modeling immune evasion by the human-pathogenic fungus *Candida albicans*

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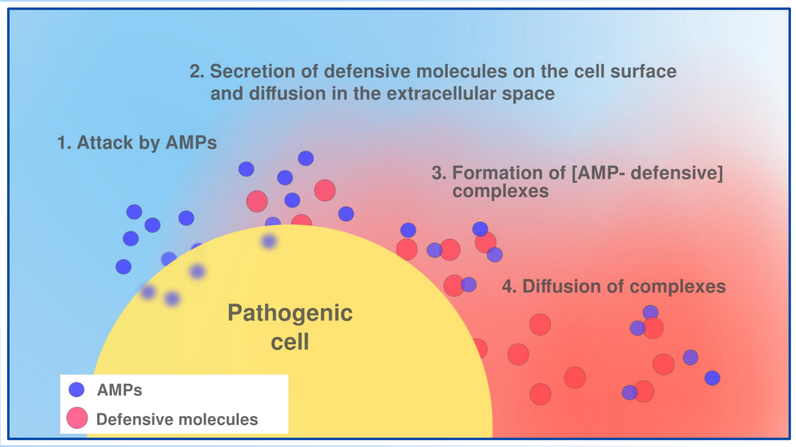
Abstract

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** an **immune evasive mechanism** referred to as **spatial distancing**: microbial **pathogens secrete** defensive **molecules** that **bind** to **antimicrobial peptides** (AMPs) and **diffuse away** from the cell due to a molecular gradient.

First, we present a **theoretical study** on spatial distancing by introducing a **mathematical model** and **exploring** its **parameter space**. Then, we apply spatial distancing to the human-pathogenic fungus ***C. albicans***. By **combining mathematical modeling** and **experimental data**, we could gain insights into the conditions required for *C. albicans* to evade AMPs.

Mechanism



Partial Differential Equation model

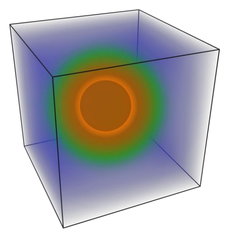
Model system: 3-dimensional, continuous, molecules as concentrations diffusing on a discrete grid according to the gradient.

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

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

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

$$\left.\frac{\partial[A]}{\partial x}\right|_{memb} = -U_A[A]_{memb}\,, \quad \left.\frac{\partial[D]}{\partial x}\right|_{memb} = \frac{-S_D * [A]_{uptaken}^{t-t^*}}{D}, \quad \left.\frac{\partial[C]}{\partial x}\right|_{memb} = 0$$

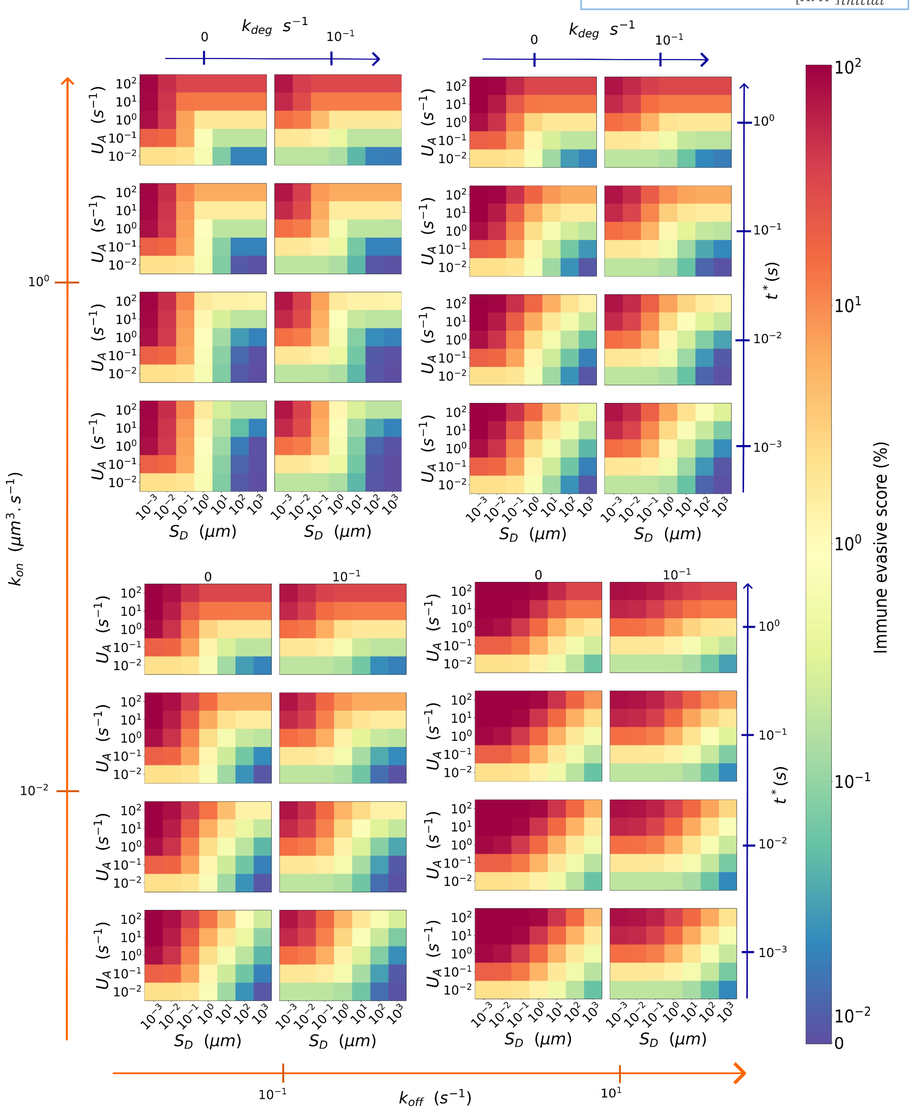


Parameter	Description	Unit
S_D	Secretion rate of defensive molecule	μm
U_A	Uptake rate of AMP	s^{-1}
D	Diffusion coefficients	$\mu m^2 s^{-1}$
k_{on}	Association rate [AMP – Defensive molecule]	$\mu m^3 s^{-1}$
k_{off}	Dissociation rate [AMP – Defensive molecule]	s^{-1}
k_{deg}	Degradation rate	s^{-1}
t^*	Delay in pathogen's response to environment	s
F_A	Inflow of AMPs at the system's boundary	$\mu m^{-2} s^{-1}$

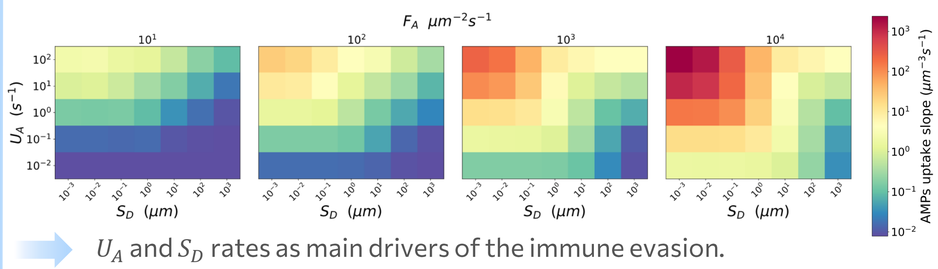
Theoretical approach

AMPs modeled as one-time treatment

Immune-evasive score = $\frac{[AMP]_{uptaken}}{[AMP]_{initial}}$



AMPs modeled as secreted by immune cells



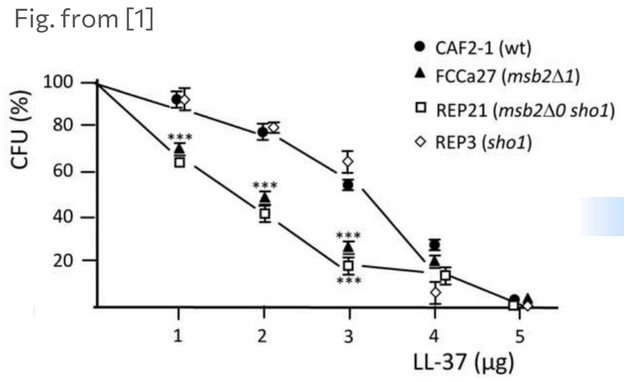
U_A and S_D rates as main drivers of the immune evasion.
High S_D values limit AMP uptake by the pathogen.

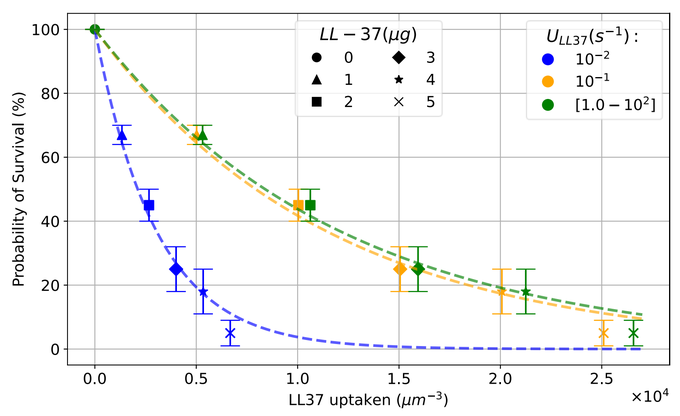
Application to *C. albicans* infection

- AMPs evasion by *C. albicans* via secretion of Msb2* [1].
- High affinity between Msb2* and human AMP LL-37 [1].
- Calibration of the model by using *in vivo* experiments.

Calibration of the model

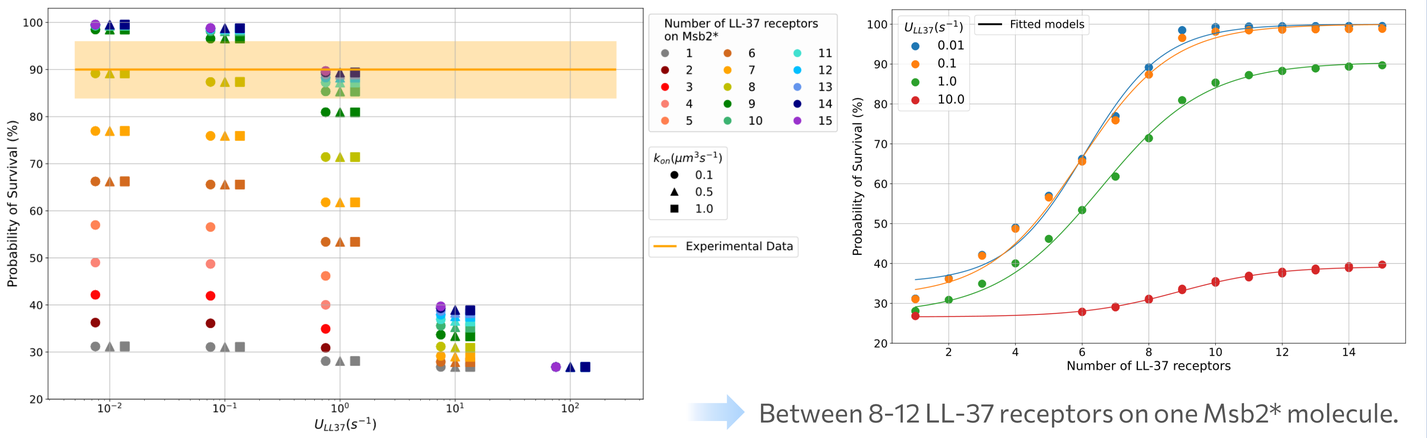
Fig. from [1]





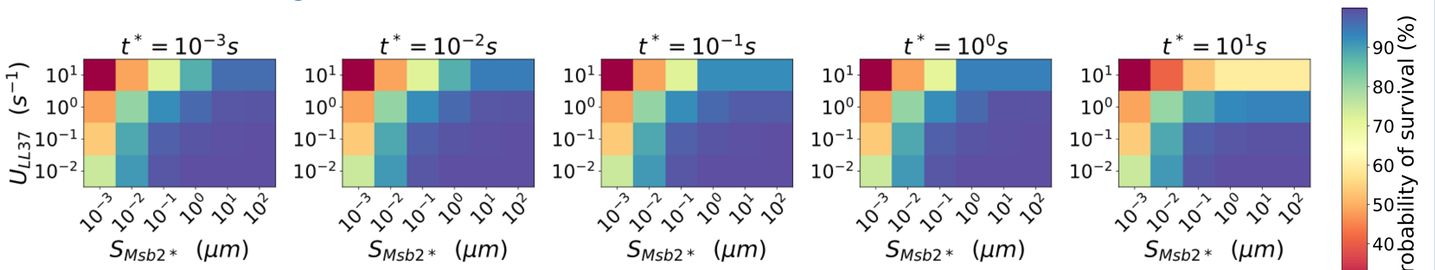
Relation between the probability of survival (experiments) and quantity of LL-37 uptaken (modeling).

Estimation of the number of LL-37 receptors on Msb2* protein



Between 8-12 LL-37 receptors on one Msb2* molecule.

Immune-evasion regimes of *C. albicans*



Efficient protection against LL-37 by secretion of Msb2*.

Conclusion

Spatial distancing is an **effective** and robust strategy for pathogens to **protect** themselves from **AMPs** and enhance their chances of survival. The **theoretical model** provides a general **understanding** of the **mechanism** and the impact of the parameters. **Modeling** also allows in-depth analysis by **simulating different scenarios** and **switching on** and **off properties**. **Combining experimental data** with **modeling** gives us further insights into the complex host-pathogen molecular interactions in ***Candida* infections**.

The **inhibition** of **Msb2*** in *Candida* infections 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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