DynaCoSys: Dynamic model of the complement system to understand pathogen immune evasion

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Biological Background:

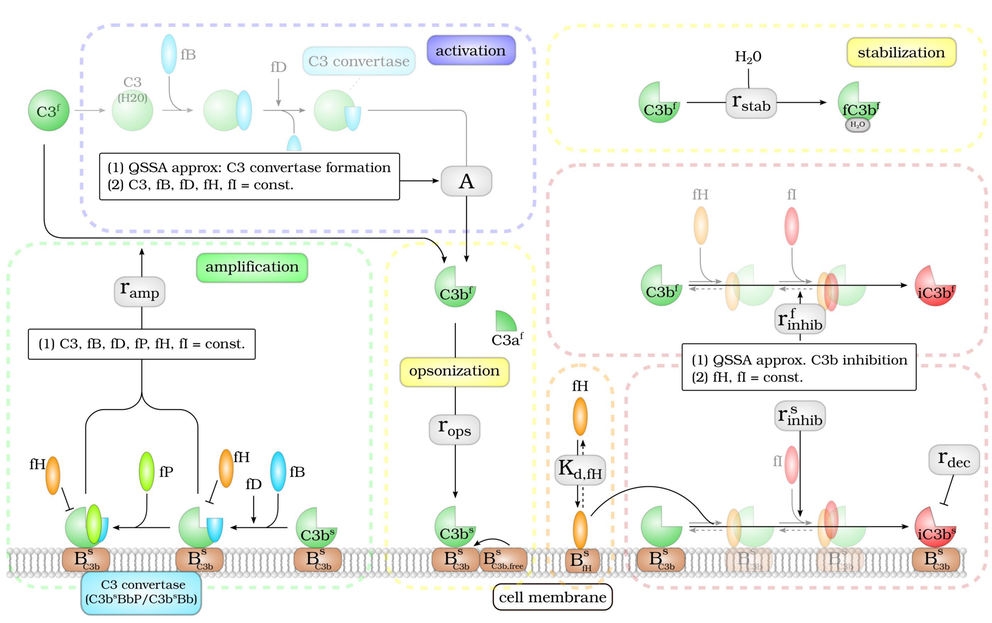
The human **complement system** is part of the innate immune response and plays a key role in defending the host against invading pathogens. Its main task is the **recognition and subsequent opsonization** and lysis of foreign invaders. The central opsonin of the complement system is C3b, which is a product of the proteolytic cleavage of C3. Since there exist a continuous default basal level of active complement molecules, a **tight regulation is required to protect the body's own cells** from opsonization and from complement damage.

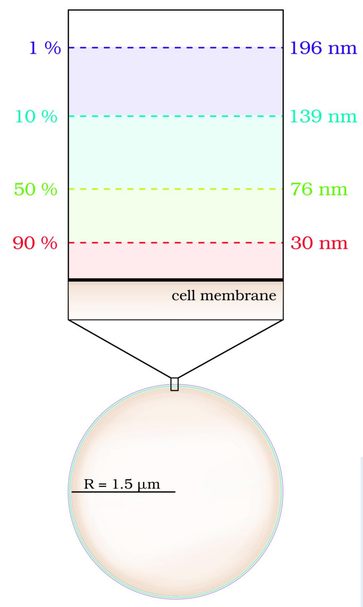
One major complement regulator is Factor H, which attaches to cell surfaces and subsequently controls complement activation. However, some pathogens are also able to bind Factor H to its surface. Furthermore, the invading pathogen *Candida albicans* has established evasion mechanisms to escape the host complement attack utilizing the molecule pH-regulated antigen 1 (Pra1).

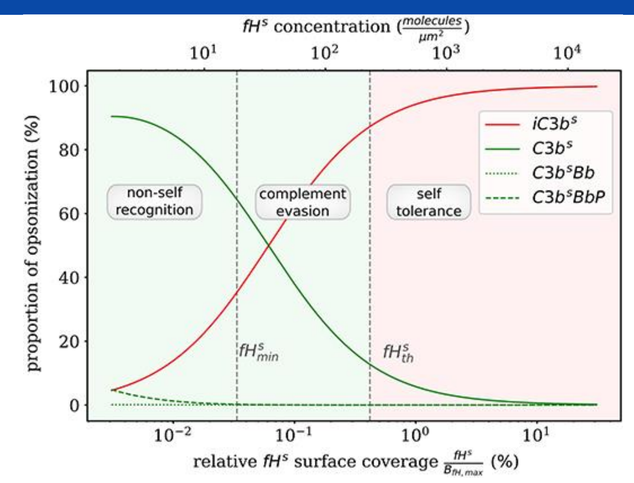
DynaCoSys Model:

- **Model predicts the opsonization level on the cell surface** based on the surface bound Factor H concentration
- **Finite Element-based steady state analysis** describing the dynamics by a set of differential equations
  - **Ordinary differential equations** (ODEs) for cell-surface bound molecules
  - **Partial differential equations** (PDEs) for fluid phase concentration profiles around the cell
  - Investigation of time-resolved dynamics using an implicit Euler approach
- Sensitivity analysis to identify the driving factors and rates of the complement system

Quantification of Factor H mediated self vs. non-self discrimination:

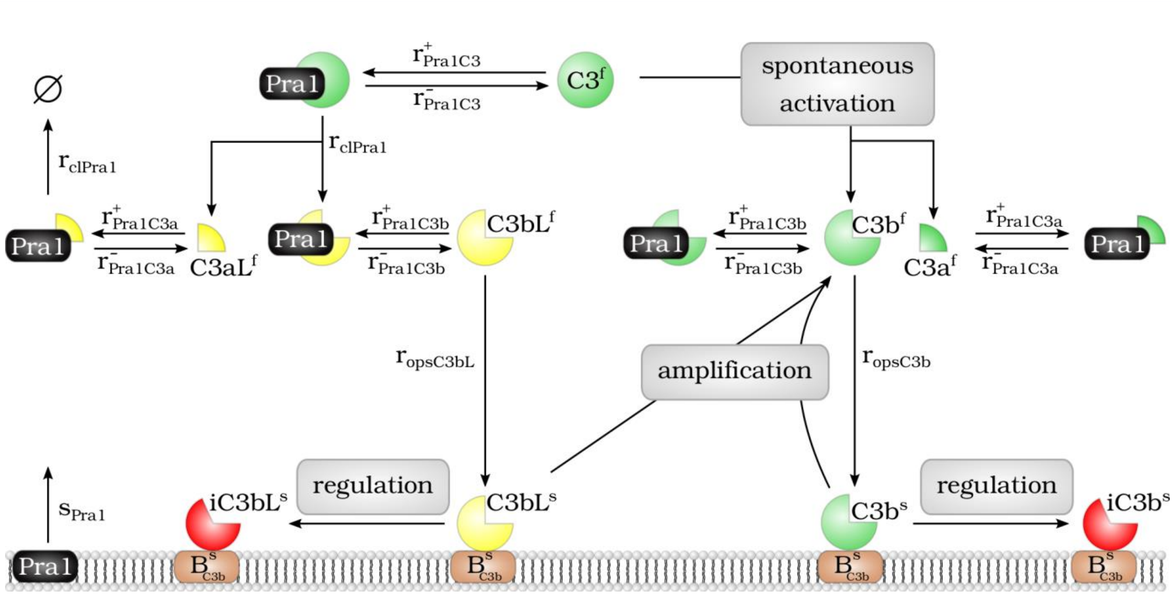


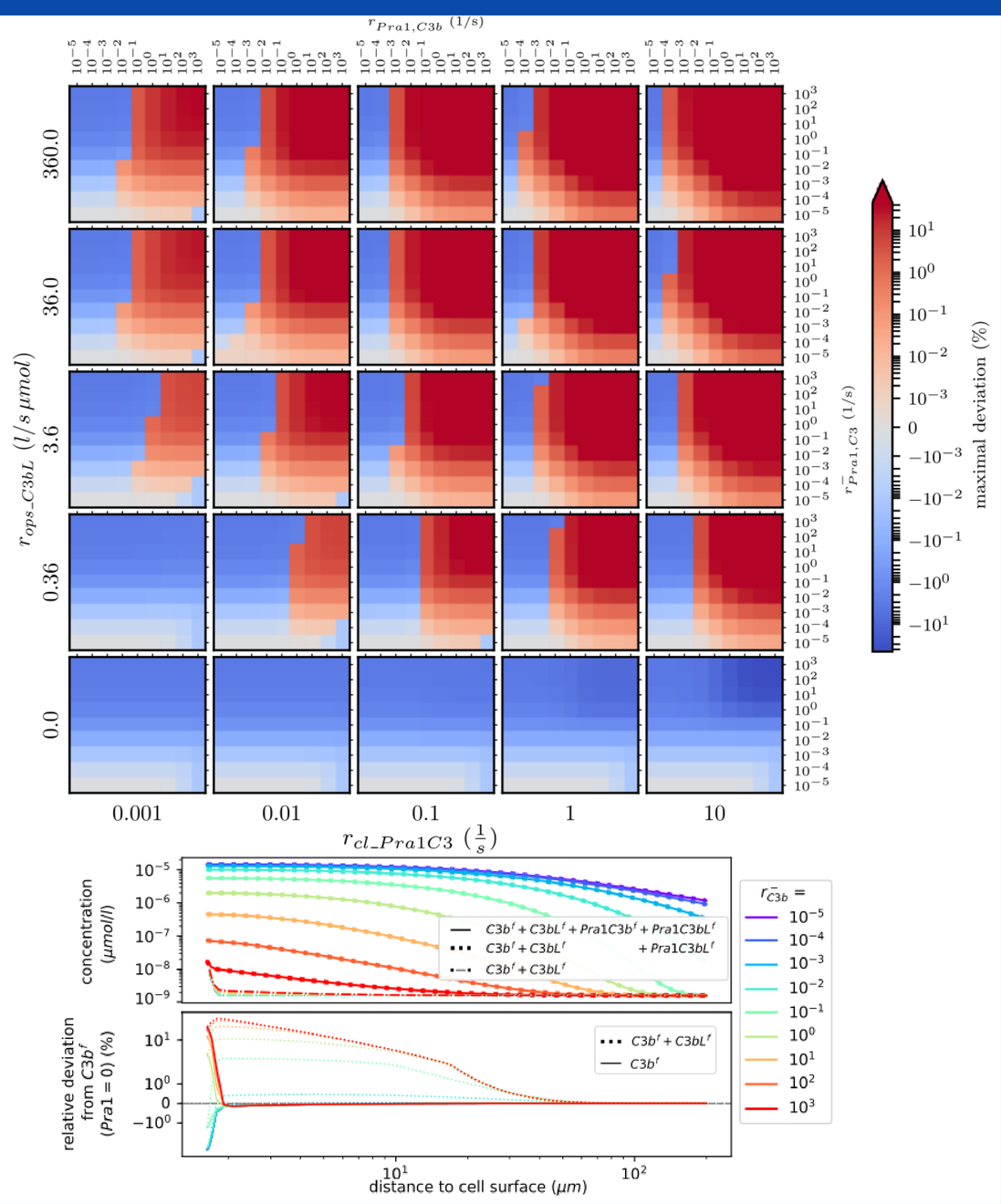




Results:
We can identify **three different regimes** of complement recognition:
- **Non-Self-Regime:** High opsonization level, low model sensitivity
- **Complement-Evasion:** Similar conditions known for evasive pathogens
- **Self-Regime:** Low opsonization level due to immediate deactivation

Extension of DynaCoSys with Pra1-mediated immune evasion:





Interaction between Pra1 and the complement system seems contradictory:
- Binding site of Factor H on the cell surface
- Binding and transport of C3
- Binding and transport of the cleavage products C3a and C3b
- C3-cleaving protease results in products: C3a-like(L) and C3bL
- C3bL may opsonize the fungal cell and interact with complement system

Results:
- Pra1-mediated C3 cleavage decreases opsonization for non-cell surface binding C3bL
- Transportation of C3b and C3bL by Pra1 yields spatial distancing to the cell surface
- Pra1-secretion can inhibit complement activation by reducing the concentration of C3
- Immune evasion occurs via spatial distancing or for C3bL being unable to opsonize

Conclusion & Perspective:
- Identification of regimes of rates for Pra1-mediated immune evasion
- Role of C3bL and binding its affinity needs to be further investigated by experiments
- Further studies about spatial distancing of opsonins with other immune-evasive pathogens

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References
[1] Tille *et al.* 2020. *Front Immunol.* 11:1911