Mathematical model of the factor H mediated self and non-self discrimination by the complement system

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complement system

- recognization and opsonization of invading microorganisms
- consists of a set of biochemical reactions on distinct pathways
- host cell protection with a tight regulation mechanism

aims of the model

- quantify reaction rates by fitting model to experimental data
- determine driving processes of the opsonization mechanism
- predict opsonization based on concentration of surface-bound factor H

mathematical model

- dynamics of protein concentration with ordinary differential equations
- simplified dynamic system: "as simple as possible, but not simpler"
    - using quasi steady state approximation
    - introducing effective rates: combination of unkown parameters

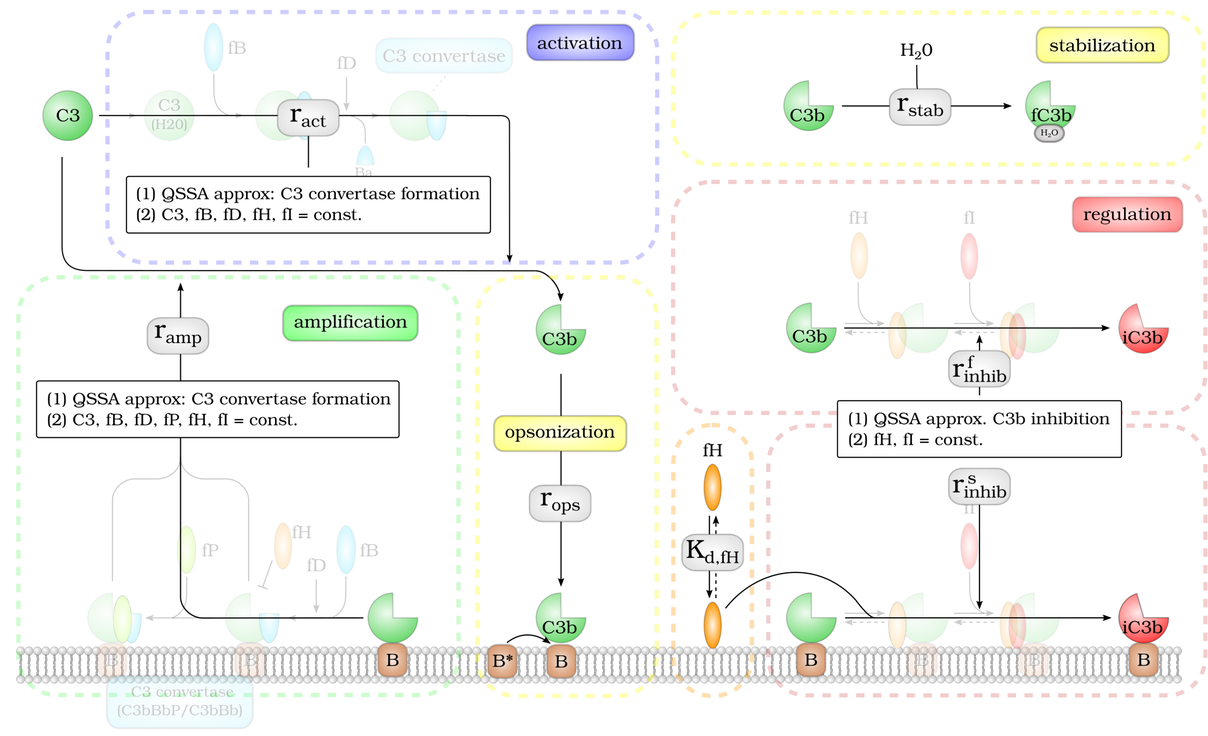
$$\frac{d}{dt}C3b^f = r_{act} + r_{amp}(fH^s, C3b^s) \cdot S_{2D\to 3D} \cdot C3b^s$$
$$- r_{ops} \cdot S_{2D\to 3D} \cdot B^*(fH^s, C3b^s) \cdot C3b^f - r_{stab} \cdot C3b^f - r^f_{inhib} \cdot C3b^f$$
$$\frac{d}{dt}C3b^s = r_{ops} \cdot B^*(fH^s, C3b^s) \cdot C3b^f - r^s_{inhib}(fH^s, C3b^s) \cdot C3b^s$$
$$\frac{d}{dt}iC3b^s = r^s_{inhib}(fH^s, C3b^s) \cdot C3b^s - \mu_{iC3b^s} \cdot iC3b^s$$

key molecules

opsonin C3b: - forms a molecular complex, that activates new C3b molecules

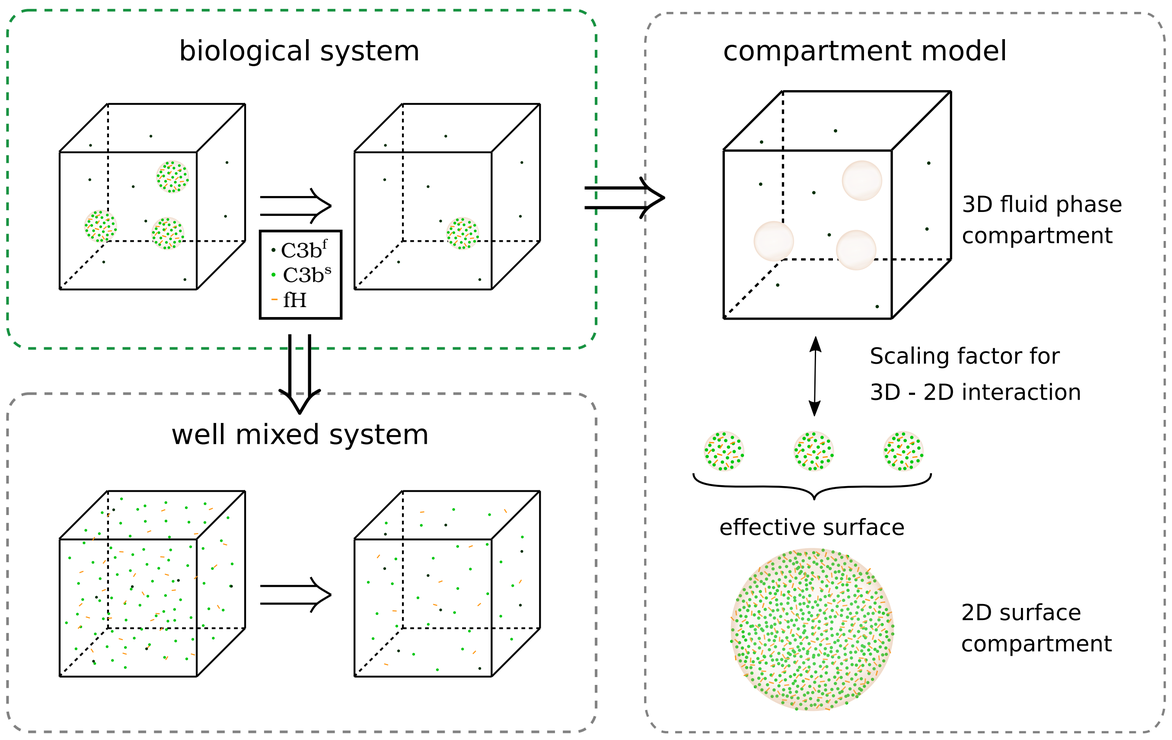
regulator factor H (fH): - plasma protein that can be bound to surfaces
- accelerates decay of C3b amplification complex
- mediates C3b degradation

reaction scheme of simplified mathematical model



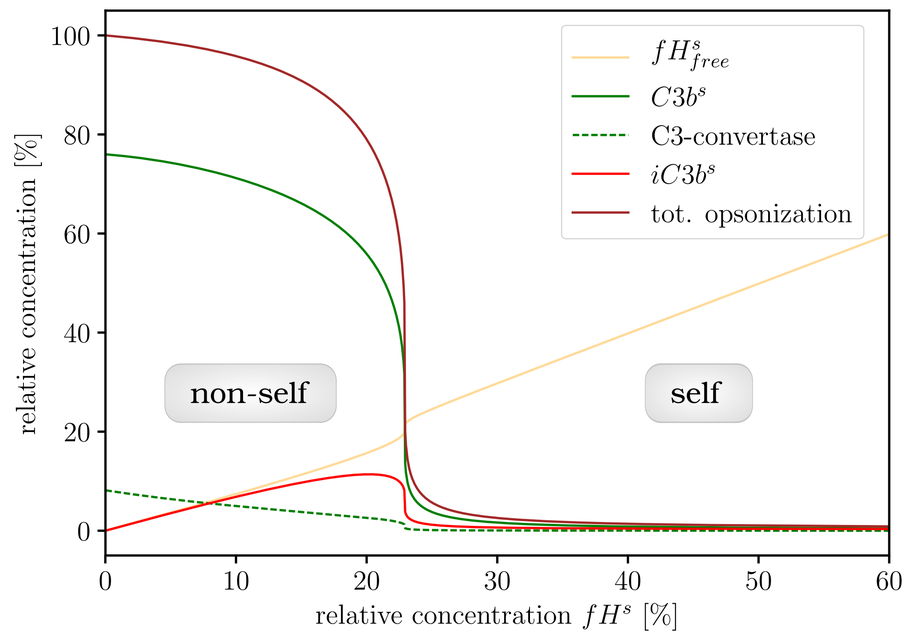
capturing spatial information of the model

- a compartment model describes the molecule concentrations correctly



results

- steady state analysis for varying parameters
- change of surface bound fH^s reveals sharp transition between two regimes
    - self regime: neglectable opsonization
    - non-self regime: massive opsonization, caused by an weakened regulation



experimental validation

in cooperation with Infection Biology Group, N.Reiher and P. Zipfel

idea:

- tuning surface-bound fH concentration of a model particle and measure C3b concentration on the surface

current experiments:

- coat latex beads with different concentrations of fH binding molecules

future experiments:

- investigate different mutants of *Candida albicans*, that express different amounts of fH binding molecules

summary

- model predicts opsonization level of a cell-based on the concentration of surface-bound fH
- simplified model is able to reproduce biological system qualitatively
- dominating processes of self and non-self regimes can be identified

perspective

- quantification of effective rates by model calibration with experimental data
- add a phagocytosis model/experiments
- investigate pathogens that are able to hide from complement (*C. albicans*)
- extend the model by more proteins to create a more realistic cell

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