Quantification of factor H mediated self and non-self discrimination by mathematical modeling

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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

- quantification of the opsonization process
- determination of driving processes of the opsonization mechanism
- prediction of opsonization based on concentration of surface-bound factor H

Mathematical model

- simplified dynamic system: "as simple as possible, but not simpler"
- evaluating a single cell
- combining dynamics of the fluid phase (PDE) with dynamics of the cell surface (ODE

$$C3b^f(r)^* = \frac{\left(r_{amp}(fH^s)\cdot C3b^s - r_{ops}\cdot B_{C3b,free}\cdot C3b^f(R)\right)\cdot R^2}{D_{C3b}+R\sqrt{D_{C3b}\left(r^f_{inhib}+r^f_{stab}\right)}}\, e^{\left(-\frac{r-R}{\sqrt{D_{C3b}/\left(r^f_{inhib}+r^f_{stab}\right)}}\right)}\frac{1}{r} + \frac{A}{r^f_{inhib}+r^f_{stab}}$$

$$\frac{d}{dt}C3b^s = r_{ops}\cdot B_{C3b,free}(C3b^s, iC3b^s)\cdot C3b^f(R)^* - r^s_{inhib}(fH^s)\cdot C3b^s$$

$$\frac{d}{dt}iC3b^s = r^s_{inhib}(fH^s)\cdot C3b^s - r_{dec}\cdot iC3b^s$$

r ... distance to cell center
R ... cell radius
$r \geq R$

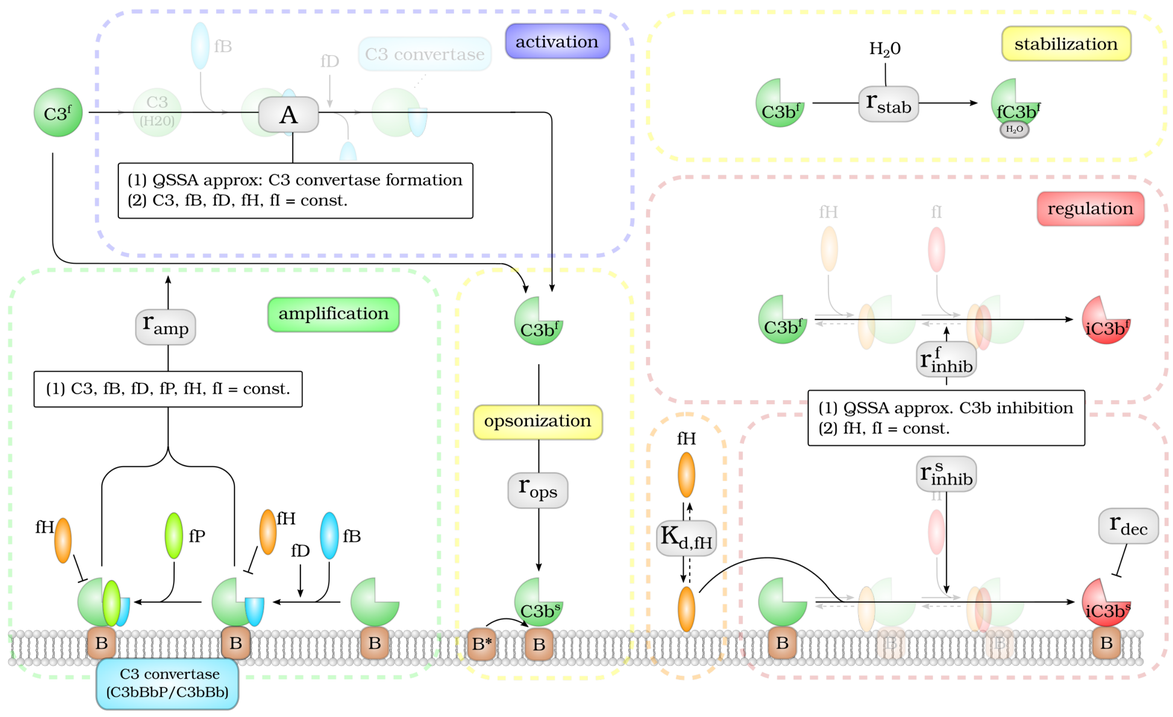
see reaction scheme for definition of parameters

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

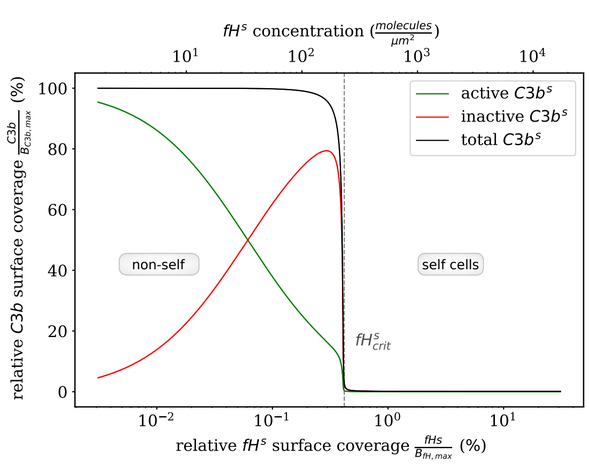
Reaction scheme of simplified mathematical model



Results

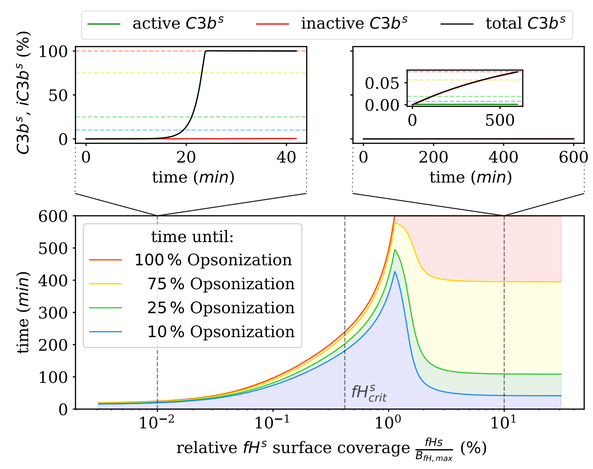
Steady state on cell surface

- analytical solution predicts two distinct regimes:
  - **self regime**
  - **non-self regime**
- regimes are seperated by sharp transition region, marked by fH^s_{crit}



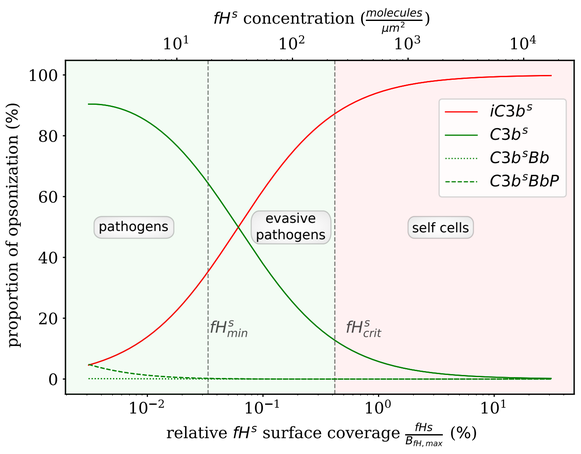
Dynamics on cell surface

- **non-self regime** with sigmoidal shaped opsonization dynamics [1]
- ratio lag : log phase is 3 : 1
- time scale between 10 and 200 min
- **self regime** characterized by very long opsonization processes above 10 hours



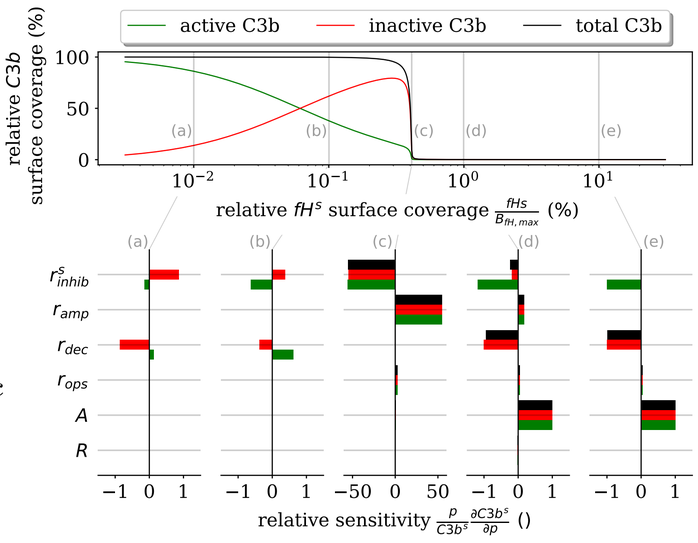
Biological interpretation

- **non-self regime** can be divided into two sub-regimes: *pathogens* and *evasive pathogens*
- evasive pathogens show an $iC3b^s$ to $C3b^s$ ratio of 30% up to 70% [2]
- **self regime** with $iC3b^s$ to $C3b^s$ ratio of more than 80%
- dynamics in the range of $fH^s = (230 \dots 10^3)\,\frac{molecules}{\mu m^2}$ can be explained with the opsonization of apoptotic cells [3,4]



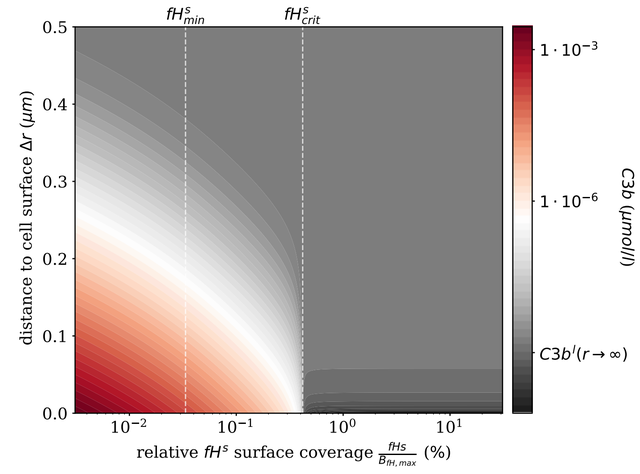
Driving processes and sensitivity analysis

- r^s_{inhib} and r_{amp} determine fH^s_{crit}
- **non-self regime** is sensitive to r^s_{inhib} and r_{dec}, only molecule proportion is changed
- **transition region** sensitive to r^s_{inhib} and r_{amp}, highest sensitvities
- **self regime** is sensitive to r^s_{inhib}, r_{dec} and A
- fluid phase activation influences only the steady state of the self regime



Fluid phase concentration profile

- **non-self regime** with increased $C3b^f(R)^*$ concentration of up to six orders of magnitude compared to equilibrium
- **self regime** with decreased $C3b^f(R)^*$ concentration compared to equilibrium
- equilibrium concentration reached within less than $0.5\,\mu m$ from the cell surface
- encorporating PDE is essential in order to calculate the molecular dynamics on the surface correctly



Summary

- model quantifies opsonization level of a cell - based on the concentration of surface-bound fH
- fast opsonization dynamics in the non-self regime and slow dynamics in the self regime
- model is able to reproduce biological system qualitatively
- dominating processes of self and non-self regimes can be identified
- encorporation of spatial inhomogeneities using PDEs is important for a correct representation of the opsonization process

[1] Pangburn M. *et al.*, J. of Immunology (1983)
[2] Newman S. and Mikus L., J. Exp. Med. 161(1985)
[3] Trouw L. *et al.*, Molecular Immunology (2008)
[4] Takizawa F., FEBS Letters (1996)

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