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Quantitative mathematical modelling of the alternative pathway of the complement system

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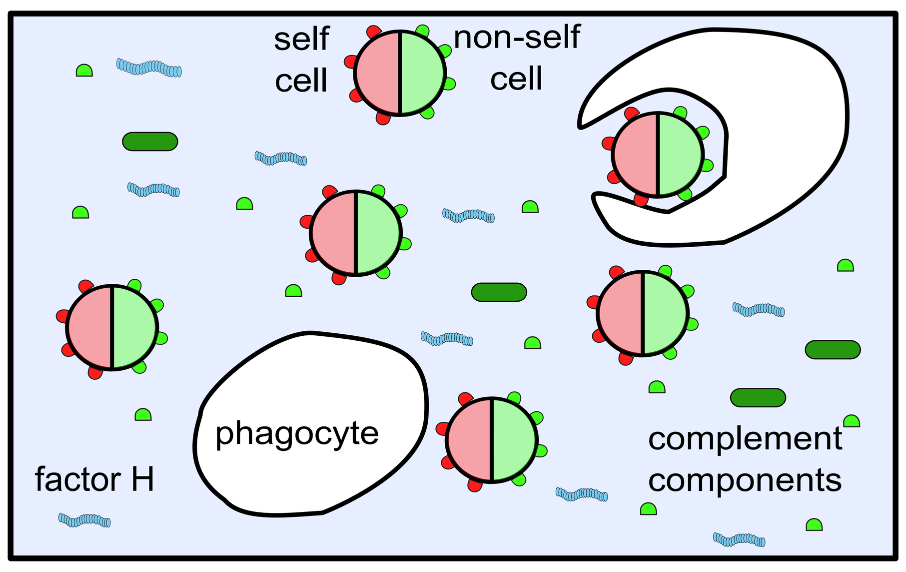
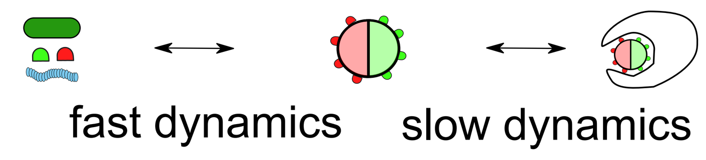
Introduction

The alternative pathway of the human complement system detects and opsonizes pathogens. Opsonized cells are marked for phagocytosis. The destruction of host cells is inhibited through human complement regulators like factor H that are present in plasma and can be bound to cell membranes. The aim is to derive a mathematical model that contains relevant features of the complement system and subsequent phagocytosis events. Furthermore, we suggest how model parameters may be identified in experiment.

Model system

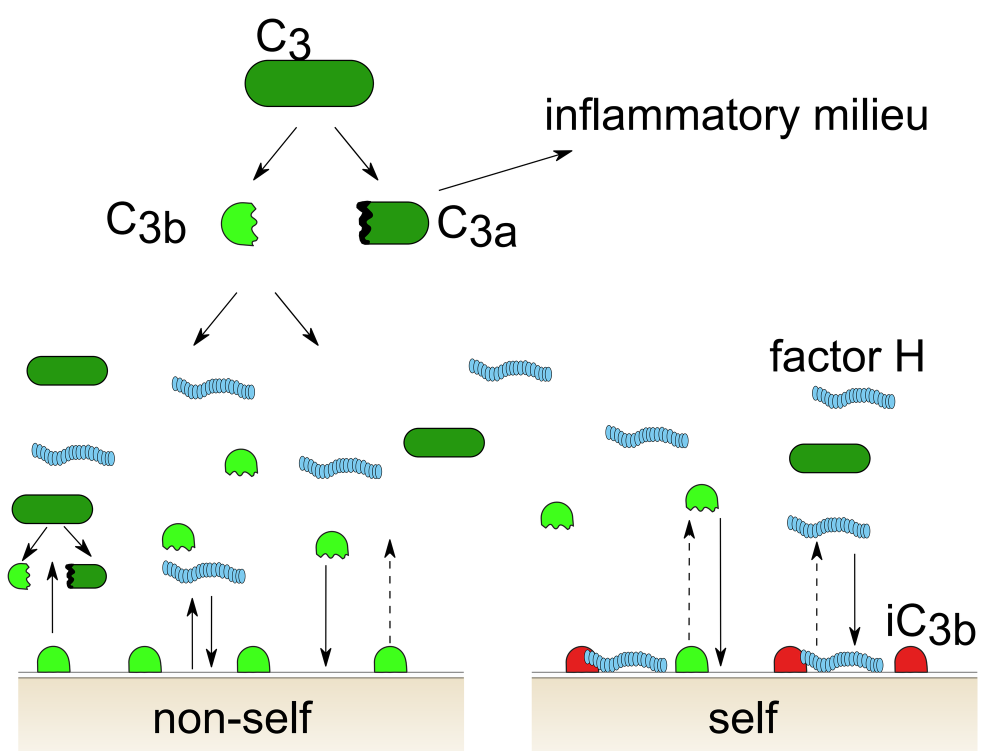


The model describes the interaction of the complement system with self or non-self cells at the molecular level. Additionally phagocytosis of opsoniozed cells is modelled at the cellular level. The processes of the molecular and cellular level take place on different time scales, such that the two levels can be seperated.



Mathematical model at molecular level (fast dynamics)

The complement system is a cascade of reactions which can be transfered to a system of first-order differential equations.



The model is an approximative representation of the alternative pathway. Its aim is to describe the cascade with transitions that can be measured in experiment without neglecting relevant features of the alternative pathway. These features are:

- Spontaneous decay of C3
- Opsonization of cell surface with C3b
- Amplification loop of C3 cleavage mediated by C3b on sell surface
- Inactivation of surface-bound C3b by surface-bound factor H

Biochemical reactions:

$$C_3^f \xrightarrow{r_C} C_{3b}^f \qquad H^f + B \xrightarrow{r_{sH}} H^s + B$$

$$C_{3b}^f + B \xrightarrow{r_{sC}} C_{3b}^s + B \qquad H^s \xrightarrow{r_{fH}} H^f$$

$$C_{3b}^s \xrightarrow{r_{fC}} C_{3b}^f \qquad C_{3b}^s + H^s \xrightarrow{r_{HC}} iC_{3b}^s + H^s$$

$$C_3^f + C_{3b}^s \xrightarrow{r_{fb}} C_{3b}^s + C_{3b}^f \qquad {}^f \mathrel{\widehat{=}} fluid\ ,\ {}^s \mathrel{\widehat{=}} surface$$

Assumptions:

$$(\mathrm{A1}):\quad C_3^f \approx const. \qquad (\mathrm{A3}):\quad H^f \approx const.$$

$$(\mathrm{A2}):\quad B \approx const.$$

Differential equations:

$$\mathrm{I}:\quad \dot{C}_3^f = -r_C C_3^f - r_{fb} C_3^f C_{3b}^s + I$$

$$\mathrm{II}:\quad \dot{C}_{3b}^f = r_C C_3^f - r_{sC} B C_{3b}^f + r_{fC} C_{3b}^s + r_{fb} C_3^f C_{3b}^s$$

$$\mathrm{III}:\quad \dot{C}_{3b}^s = r_{sC} B C_{3b}^f - r_{HC} H^s C_{3b}^s - r_{fC} C_{3b}^s$$

$$\mathrm{IV}:\quad i\dot{C}_{3b}^s = r_{HC} H^s C_{3b}^s$$

$$\mathrm{V}:\quad \dot{H}^f = -r_{sH} B H^f + r_{fH} H^s$$

$$\mathrm{VI}:\quad \dot{H}^s = r_{sH} B H^f - r_{fH} H^s$$

Solution:

$$C_{3b}^f = \frac{r_C C_3^f}{r_{HC}\frac{H^f B}{K_{d,H}} - r_{fb} C_3^f} \frac{r_{fC} + r_{HC}\frac{H^f B}{K_{d,H}}}{r_{sC} B}$$

$$C_{3b}^s = \frac{r_C C_3^f}{r_{HC}\frac{H^f B}{K_{d,H}} - r_{fb} C_3^f}$$

$$iC_{3b}^s = \frac{r_C C_3^f r_{HC}\frac{H^f B}{K_{d,H}}}{r_{HC}\frac{H^f B}{K_{d,H}} - r_{fb} C_3^f} t \qquad H^s = \frac{H^f B}{K_{d,H}}$$

Species:

C_3^f	C_3 in fluid	$\frac{mol}{l}$
$C_{3b}^{f,s}$	C_{3b} in fluid / on surface	$\frac{mol}{l}$
iC_{3b}^s	inactive C_{3b} on surface	$\frac{mol}{l}$
$H^{f,s}$	factor H in fluid / on surface	$\frac{mol}{l}$
Z	number of self / non-self cells	-
P	number of phagocytes	-
B	number of free binding sites [1]	$\sim 10^6 \cdot Z$

[1] estimated: Pangburn *et al.*, J Immunol., 1983

Reaction rates:

r_C	decay of C_3	$\frac{1}{s}$
r_{sC}	attachment of C_{3b}^f to cell surface	$\frac{1}{s}$
r_{fC}	detachment of C_{3b}^s from cell surface	$\frac{1}{s}$
r_{fb}	feedback for C_3 cleavage	$\frac{1}{mol \cdot s}$
r_{HC}	association of H^s to C_{3b}^s	$\frac{1}{mol \cdot s}$
r_{sH}	attachment of H^f to cell surface	$\frac{1}{s}$
r_{fH}	detachment of H^s from cell surface	$\frac{1}{s}$

$$K_{d,C} = \frac{r_{fC}}{r_{sC}} \qquad K_{d,H} = \frac{r_{fH}}{r_{sH}}$$

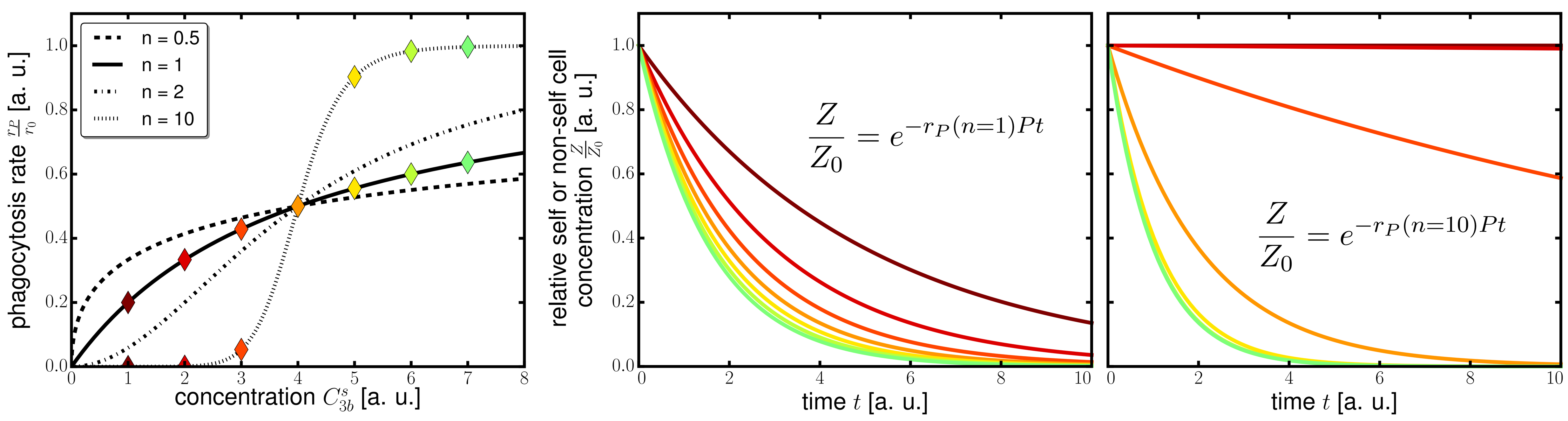
Mathematical model at cellular level (slow dynamics)

The phagocytosis event is described as biochemical reaction.

$$\mathrm{Z} + \mathrm{P} \xrightarrow{r_P} \mathrm{P}$$

$$\frac{r_P}{r_0} = \frac{(C_{3b}^s)^n}{(K_{d,P})^n + (C_{3b}^s)^n}$$

Due to the fast dynamics of the molecular level, the concentrations of the complement components are constant during the cellular interaction.



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Acknowledgement