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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 opsonized 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 separated.

Mathematical model at molecular level (fast dynamics)

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

Biochemical reactions:

$$C_3 \xrightarrow{r_{C_3}} C_3 + B \xrightarrow{r_{C_3B}} H^* + B$$

$$C_3 + B \xrightarrow{r_{C_3B}} C_3 + B$$

$$C_3 + H^* \xrightarrow{r_{C_3H^*}} iC_3 + H^*$$

$$C_3 + C_3 \xrightarrow{r_{C_3C_3}} C_3 + C_3$$

Assumptions:

(A1): $C_3 \approx \text{const.}$ (A3): $H^* \approx \text{const.}$
(A2): $B \approx \text{const.}$

Differential equations:

I: $\dot{C}_3 = -r_{C_3}C_3 - r_{PH}C_3C_3 + I$
II: $\dot{C}_3^b = r_{C_3}C_3 - r_{C_3B}C_3^b + r_{C_3B}C_3^b + r_{PH}C_3^bC_3$
III: $\dot{C}_3^b = r_{C_3}C_3 - r_{C_3B}C_3^b - r_{PH}C_3^bC_3$
IV: $\dot{iC}_3 = r_{C_3H^*}C_3$
V: $\dot{H}^* = -r_{C_3H^*}H^* + r_{PH}H^*$
VI: $\dot{H}^* = r_{C_3H^*}H^* - r_{PH}H^*$

Solution:

$$C_3^b = \frac{r_{C_3}C_3}{r_{C_3B}K_{d,C_3} + r_{PH}C_3} + \frac{r_{PH}C_3^b}{r_{C_3B}}$$

$$iC_3 = \frac{r_{C_3}C_3}{r_{C_3B}K_{d,C_3} + r_{PH}C_3} + \frac{r_{PH}C_3^b}{r_{C_3B}}$$

$$H^* = \frac{H^*B}{K_{d,H^*}}$$

Species:

C_3	C_3 in fluid	mol
C_3^b	C_3 in fluid / on surface	mol
iC_3	inactive C_3 on surface	mol
H^*	factor H in fluid / on surface	mol
Z	number of self / non-self cells	-
P	number of phagocytes	-
B	number of free binding sites	$\sim 10^6 \cdot Z$

Reaction rates:

r_{C_3}	decay of C_3	$\frac{1}{s}$
r_{C_3B}	attachment of C_3^b to cell surface	$\frac{1}{s}$
r_{C_3B}	detachment of C_3^b from cell surface	$\frac{1}{s}$
r_{PH}	feedback for C_3 cleavage	$\frac{1}{s}$
$r_{C_3H^*}$	association of H^* to C_3^b	$\frac{1}{s}$
r_{PH}	attachment of H^* to cell surface	$\frac{1}{s}$
r_{PH}	detachment of H^* from cell surface	$\frac{1}{s}$
K_{d,C_3}	$\frac{r_{C_3}}{r_{C_3B}}$	$\frac{1}{s}$
K_{d,H^*}	$\frac{r_{PH}}{r_{C_3H^*}}$	$\frac{1}{s}$

Mathematical model at cellular level (slow dynamics)

The phagocytosis event is described as biochemical reaction.

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

$$r_P = \frac{C_3^b}{(K_{d,P})^n + (C_3^b)^n}$$

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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