Table 1 Parameters' description and value

Parameter	Description	Value
D_{A_O}	diffusion coefficient of AβO	4.32×10^{-2} cm^2 day^{-1} estimated
D_H	diffusion coefficient of HMGB-1	8.11×10^{-2} cm^2 day^{-1} estimated
D_{T_α}	diffusion coefficient for TNF-α	6.55×10^{-2} cm^2 day^{-1} estimated
D_{T_β}	diffusion coefficient of TGF-β	6.55×10^{-2} cm^2 day^{-1} estimated
$D_{I_{10}}$	diffusion coefficient of IL-10	6.04×10^{-2} cm^2 day^{-1} estimated
D_P	diffusion coefficient of MCP-1	1.2×10^{-1} cm^2 day^{-1} estimated
λ_β^i	production rate of A_β^i	9.51×10^{-6} g/ml/day estimated
λ_N	production rate of A_β^o by neuron	8×10^{-11} g/ml/day estimated
λ_A	production rate of A_β^o by astrocytes	8×10^{-12} g/ml/day estimated
$\lambda_{\tau 0}$	production rate of tau proteins in health	8.1×10^{-11} g/ml/day estimated
λ_τ	production rate of tau proteins by ROS	1.35×10^{-11} g/ml estimated
λ_F	production rate of NFT by tau	1.662×10^{-3}/day estimated
λ_{AT_α}	production/activation rate of astrocytes by TNF-α	1.54/day estimated
$\lambda_{AA_\beta^o}$	production/activation rate of astrocytes by A_β^o	1.793/day estimated
λ_{A_O}	production rate of AβO	0.19/day estimated
λ_H	production rate of HMGB-1	3×10^{-5}/day estimated
λ_{MF}	production/activation rate of microglias by NFT	2×10^{-2}/day estimated
λ_{MA}	production/activation rate of microglias by astrocytes	1×10^{-2}/day estimated
λ_{M1T_β}	rate of $M_1 \to M_2$	6×10^{-3}/day estimated
$\lambda_{\hat{M}_1 T_\beta}$	rate of $\hat{M}_1 \to \hat{M}_2$	1.5×10^{-3}/day estimated
$\lambda_{T_\beta M}$	production rate of TGF-β by M	1.5×10^{-2} day^{-1} [1, 2]
$\lambda_{T_\beta \hat{M}}$	production rate of TGF-β by $\hat{M}$	1.5×10^{-4} day^{-1} [1, 2]
$\lambda_{T_\alpha M1}$	production rate of TNF-α by M_1	3×10^{-2} day^{-1} estimated
$\lambda_{T_\alpha \hat{M}_1}$	production rate of TNF-α by $\hat{M}_1$	3×10^{-2} day^{-1} estimated
$\lambda_{I_{10} M_2}$	production rate of IL-10 by M_2	6.67×10^{-3} day^{-1} [3, 4]
$\lambda_{I_{10} \hat{M}_2}$	production rate of IL-10 by $\hat{M}_2$	6.67×10^{-3} day^{-1} [3, 4]
λ_{PA}	production rate of MCP-1 by astrocytes	6.6×10^{-8} day^{-1} estimated
λ_{PM_2}	production rate of MCP-1 by M_2	1.32×10^{-7} day^{-1} estimated
θ	M_2/M_1 effectivity in clearance of A_β^o	0.9 estimated
α	flux rate of macrophages	5 estimated
β	proinflammatory/anti-inflammatory ratio	10 estimated
γ	I_{10} inhibition ratio	1 estimated

Tables

Author details

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Table 2 Parameters' description and value

Parameter	Description	Value
$d_{A^i_\beta}$	degradation rate of A^i_β	9.51/day [5]
$d_{A^o_\beta}$	degradation rate of A^o_β	9.51/day [5]
$d_{A^o_\beta M}$	clearance rate of A^o_β by microglia	8×10^{-8}/day estimated
$d_{A^o_\beta \hat{M}}$	clearance rate of A^o_β by macrophages	4×10^{-7}/day estimated
d_τ	degradation rate of tau proteins	0.277/day [6]
d_{F_i}	degradation rate of intracellular NFT	2.77×10^{-3}/day estimated
d_{F_o}	degradation rate of extracellular NFT	2.77×10^{-4}/day estimated
d_N	death rate of neurons	1.9×10^{-4}/day estimated
d_{NF}	death rate of neurons by NFTs	2.27×10^{-4}/day estimated
d_{NT}	death rate of neurons by TNF-α	1.27×10^{-4}/day estimated
$d_{N_d M}$	clearance rate of dead neurons by M	10^{-3}/day estimated
$d_{N_d \hat{M}}$	clearance rate of dead neurons by $\hat{M}$	5×10^{-4}/day estimated
d_A	death rate of astrocytes	1.2×10^{-5} day^{-1} estimated
d_{M_1}	death rate of M_1 microglias	0.015 day^{-1} [3, 7]
d_{M_2}	death rate of M_2 microglias	0.015 day^{-1} [3, 7]
$d_{\hat{M}_1}$	death rate of M_1 macrophages	0.015 day^{-1} [3, 7]
$d_{\hat{M}_2}$	death rate of M_2 macrophages	0.015 day^{-1} [3, 7]
d_{A_O}	degradation rate of AβO	0.951/day estimated
d_H	degradation rate of HMGB-1	58.71/day [8]
d_{T_α}	degradation rate of TNF-α	55.45 day^{-1} [3, 7]
d_{T_β}	degradation rate of TGF-β	3.33×10^2 day^{-1} [1, 2]
$d_{I_{10}}$	degradation rate of IL-10	16.64 day^{-1} [3]
d_P	degradation rate of MCP-1	1.73 day^{-1}[3, 7]
R_0	initial inflammation by ROS	6 estimated
M_0	monocytes concentration in blood	5×10^{-2} estimated
N_0	reference density of neuron	0.14 g/cm^3 estimated
M_G^0	source of microglia	0.047 g/cm^3 estimated
A_0	reference density of astrocytes	0.14 g/cm^3 estimated
$\bar{K}_{A^o_\beta}$	Michaelis-Mention coefficient for A^o_β	7×10^{-3} g/cm^3 estimated
$\bar{K}_{N_d}$	Michaelis-Mention coefficient for N_d	10^{-3} g/ml estimated
$K_{I_{10}}$	half-saturation of IL-10	2.5×10^{-6} g/cm^3 estimated
K_{T_β}	half-saturation of TGF-β	2.5×10^{-7} g/ml [4]
K_M	half-saturation of microglias	0.047 g/ml estimated
$K_{\hat{M}}$	half-saturation of macrophages	0.047 g/ml estimated
K_{M_1}	half-saturation of M_1 microglias	0.03 g/ml estimated
K_{M_2}	half-saturation of M_2 microglias	0.017 g/ml estimated
$K_{\hat{M}_1}$	half-saturation of $\hat{M}_1$ macrophages	0.04 g/ml estimated
$K_{\hat{M}_2}$	half-saturation of $\hat{M}_2$ macrophages	0.007 g/ml estimated
K_{F_i}	half-saturation of intracellular NFTs	3.36×10^{-10} g/ml [9]
K_{F_o}	average of extracellular NFTs	10^{-11} g/ml estimated
K_{A_O}	average of of AβO	2×10^{-5} g/ml estimated
K_P	half-saturation of MCP-1	1.2×10^{-8} g/ml estimated
K_{T_α}	half-saturation of TNF-α	2.5×10^{-5} g/ml estimated

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Supplementary materials

Parameter estimation

In the sequel, in an expression of the form $\frac{X}{X+K_X}$ in the context of activation, the half-saturation parameter K_X is taken to be the steady state of the species X provided X tends to a steady state. Hence in a steady state equation this factor is

equal to $\frac{1}{2}$. If X does not tend to a steady state then the parameter K_X will be taken to be the estimated average of X over a period of 10 years, the average survival time of AD patients [10]. In an expression of the form $\frac{1}{1+\gamma X/K_X}$ (where $\gamma = \gamma(X)$) in the context of inhibition, K_X is again the half-saturation of X, so that in steady state the inhibition is $1/(1+\gamma)$. If cells Y phagocytose species X, then the clearing rate is proportional to $Y\frac{X}{X+\bar{K}_X}$ where the Michaelis-Menten constant $\bar{K}_X$ depends only on the 'eating capacity' of Y, so $\bar{K}_X$ has no relation to the half-saturation of X.

Diffusion coefficients

The diffusion coefficient of proteins (Y) are proportional to $1/M_Y^{1/3}$, where M_Y is the molecular weight [7]. Accordingly, we have the following relation [11]:

$$D_Y = \frac{M_V^{1/3}}{M_Y^{1/3}} D_V,$$

where M_V and D_V are the molecular weight and the diffusion coefficient of VEGF. Since $D_V = 8.64 \times 10^{-2}\ cm^2\ \text{day}^{-1}$[12], $M_V = 24$ kDa [12], $M_P = 8.9$ kDa [13], $M_{T_\beta} = 55$ kDa [14], $M_{T_\alpha} = 55$ kDa [15], $M_{I_{10}} = 70$ kDa [16], and $M_H = 29$ kDa [17], we get $D_P = 1.20 \times 10^{-1}\ cm^2\text{day}^{-1}$, $D_{T_\beta} = 6.55 \times 10^{-2}\ cm^2\text{day}^{-1}$, $D_{T_\alpha} = 6.55 \times 10^{-2}\ cm^2\text{day}^{-1}$, $D_{I_{10}} = 6.04 \times 10^{-2}\ cm^2\text{day}^{-1}$ and $D_H = 8.11 \times 10^{-2}\ cm^2\text{day}^{-1}$.

Molecular weight of $A\beta$ is 24 kDa [18], so in soluble state its diffusion coefficient would be $8.64 \times 10^{-2}\ cm^2\text{day}^{-1}$. We assume that soluble oligomer $A\beta O$ has a smaller diffusion coefficient, namely, $D_{A_O} = 4.32 \times 10^{-2}\ cm^2\text{day}^{-1}$.

Eq. (1)

By [5], the half-life of A_β^i is 1.5-2h in mice. Hence $d_{A_\beta^i} = d_{A_\beta^o} = \frac{ln2}{1.75} \times 24$=9.51 /day. Membrane proteins APP shed amyloid β, some end up inside the cell and some outside the cell. We assume that in healthy steady state $A_\beta^i = A_\beta^o$, however the simulation results do not change appreciably if we take $A_\beta^o > A_\beta^i$. According to [19], the density in brain-gray matter of A_β^o is approximately 1000 ng/g in control and 7000 ng/g in AD. Hence, from the steady state of Eq. (1) in a healthy normal case, $A_\beta^i = 10^{-6}$ g/ml and $\lambda_\beta^i = d_{A_\beta^i} \times 10^{-6}$=$9.51 \times 10^{-6}$ g/ml/day. From the steady state of Eq. (1) in AD and Eq. (21) we then get that $R_0 = 6$.

The brain has 75% water and 60% of its dry matter is fat. We assume that the average density of brain tissue is 1 g/cm^3. The human brain has 100 billion neurons, and its weight is approximately 1400 g, so its volume is approximately 1400 ml. Hence its neurons number density is 7×10^7 neurons/cm^3. The diameter of neurons is 16 μm [20]. Accordingly, we estimate the volume of 1 neuron to be $2 \times 10^{-9}\ cm^3$, and the neurons density is then $7 \times 10^7 \times 2 \times 10^{-9}\ g/cm^3$, that is $N_0 = 0.14\ g/cm^3$.

Eq. (2)

The number of neurons is three times the number of microglia [21], hence $K_{\hat{M}} = \frac{1}{3}N_0 = 0.047$ g/ml.

By [22] an astrocyte produces much less Aβ than a neuron, so we take $\lambda_A = \frac{1}{10}\lambda_N = 8 \times 10^{-11}$ g/ml/day.

Microglias are the first responders to NFTs and AβO. Peripheral macrophages arrive later, and their immune response may perhaps exceed that of microglia, but this is currently not known [23, 24]. We assume that in steady state the microglias density M and the peripheral macrophages density $\hat{M}$ are equal, so that $\hat{M} = K_{\hat{M}} = M = K_M = 0.047$ g/ml. Motivated by the inflammatory immune attack in AD [25], we assume that, in steady state, the proinflammatory macrophages exceed the anti-inflammatory macrophages, and that proinflammatory peripheral macrophages exceed the proinflammatory microglias. Thus, in steady state, $\hat{M}_1 > \hat{M}_2$, $M_1 > M_2$ and $\hat{M}_1 > M_1$, and we take $K_{\hat{M}_1} = 0.04$, $K_{\hat{M}_2} = 0.007$, $K_{M_1} = 0.03$, $K_{M_2} = 0.017$.

Activated microglias are poorly phagocytic for Aβ compared to peripheral macrophages [26]. Accordingly we take

$$d_{A^o_\beta M} = \frac{1}{5} d_{A^o_\beta \hat{M}}.$$

Taking $d_{A^o_\beta \hat{M}} = 4 \times 10^{-7}$/day, we then have

$$d_{A^o_\beta M} = 8 \times 10^{-8}/day.$$

We assume that $\hat{M}_1$ and M_1 are more effective than $\hat{M}_2$ and M_2 in clearing Aβ, and take $\theta = 0.9$.

We assume that survival time of patients with AD is 10 years, and that at the end-stage 50% of their neurons have died [10]. Hence, the death rate of N is $d_N = \frac{ln2}{10\ years} = 1.9 \times 10^{-4}$/day.

By [19], $A^o_\beta = 7 \times 10^{-6}$ g/ml. We assume that the clearance of A^o_β by macrophages and microglias is nearly unlimited (i.e., it is almost linear in A^o_β) by taking $\bar{K}_{A^o_\beta} = 10^3 A^o_\beta = 7 \times 10^{-3}$ g/ml. To estimate λ_N, we first consider the steady state of Eq. (2),

$$10^{-6}\Big|\frac{\partial N}{\partial t}\Big|_{\text{average}} + \lambda_N + \frac{1}{10}\lambda_N = \Big(d_{A^o_\beta \hat{M}}(K_{\hat{M}_1} + 0.9K_{\hat{M}_2}) + d_{A^o_\beta M}(K_{M_1} + 0.9K_{M_2})\Big)\frac{A^o_\beta}{A^o_\beta + \bar{K}_{A^o_\beta}}.$$

To estimate the average of $\left|\frac{\partial N}{\partial t}\right|$, we use the equation

$$N(t) = N_0 e^{-d_N t},\ N(0) = 0.14\ g/ml,$$

so that

$$\left|\frac{dN}{dt}\right| = 0.14 \times 1.9 \times 10^{-4} e^{-1.9\times 10^{-4} t}.$$

The values of $\left|\frac{\partial N}{\partial t}\right|$ for $500 < t < 1000$ days vary very little, i.e., from 1.8×10^{-5} g/ml/day to 1.9×10^{-5} g/ml/day. We take $\left|\frac{dN}{dt}\right| = 1.8 \times 10^{-5}$ g/ml/day as the

average of $\left|\frac{dN}{dt}\right|$ over 10 years, but other choices do not affect significantly our simulation results. We then get that $\lambda_N = 4 \times 10^{-11}$ g/ml/day.

The estimate of λ_N was based on the steady-state assumption in Eq. (2). However, in AD the Aβ peptides are continuously aggregating, so that the steady state assumption needs to be revised. We do this by increasing the value of λ_N: we take $\lambda_N = 2 \times 4 \times 10^{-11}$=$8 \times 10^{-12}$ g/ml/day, and then $\lambda_A = 8 \times 10^{-12}$ g/ml/day.

The number of astrocytes is approximately equal to the number of neurons [27, 28], hence $A_0 = N_0 = 0.14$ g/ml.

Eq. (3)

Half-life of tau proteins is 60 hours [6]. Hence $d_\tau = \frac{ln2}{60/24} = 24ln2$=0.277/day. Concentration of tau proteins is in healthy normal individuals is 137 pg/ml and, in AD, 490 pg/ml [9]. From the steady state of Eq. (3) in the healthy case, we have $\lambda_{\tau 0} = d_\tau \tau$, where $\tau = 137$ pg/ml. Hence $\lambda_{\tau 0}$=3.78×10^{-11} g/ml/day. Similarly, $\lambda_{\tau 0} + \lambda_\tau R = d_\tau \tau$ in AD, where $\tau = 490$ pg/ml. Hence we have $\lambda_\tau R = 8.1 \times 10^{-11}$ g/ml, or $\lambda_\tau = 1.35 \times 10^{-11}$/day.

Eqs. (4) and (5)

We assume that neurofibrillary tangles inside neurons are much more stable than tau proteins, taking $d_{F_i} = \frac{1}{10^2} d_\tau = 2.77 \times 10^{-3}$/day. We also assume that extracellular NFTs do not degrade as fast as internalized NFTs, taking $d_{F_o} = \frac{1}{10} d_{F_i} = 2.77 \times 10^{-4}$/day.

We also assume that 60% of the hyperphosphorglated tau proteins become neurofibrillary tangles. From the steady state of Eq. (4) we then have that $\lambda_F = 0.6 d_{F_o}$. Hence $\lambda_F = 1.662 \times 10^{-3}$/day.

Eq. (6)

It is not known whether the rate of death of neurons caused by NFT is larger or smaller than the death rate caused by T_α. We take $d_{NF} = 2d_{NT}$, but the simulation of the model in the case where $d_{NT} = 2d_{NF}$ are very similar (not shown here). Assuming that at steady state of Eq. (6) the concentrations of F_i, T_α and I_{10} are at half-saturation, we get $d_{NF}\left(\frac{1}{2} + \frac{1}{4}\frac{1}{1+\gamma}\right) = d_N$, so that $d_{NF} = \frac{4+4\gamma}{3+2\gamma} \times 1.9 \times 10^{-4}$/day and $d_{NT} = \frac{2+2\gamma}{3+2\gamma} \times 1.9 \times 10^{-4}$/day. In particular, if $\gamma = 1$ then $d_{NF} = 2.27 \times 10^{-4}$/day and $d_{NT} = 1.27 \times 10^{-4}$/day. We take $K_{I_{10}} = 2.5 \times 10^{-6}$ g/cm^3 (which is somewhat larger than the estimated half-saturation of I_{10} in lung inflammation [3, 4]). We assume that in AD, 70% of hyperphosphorylated tau proteins (whose concentration in disease is 490 pg/ml [9]) are in NFT form, so that $K_{F_i} = 0.7 \times 490$ pg/ml=3.36×10^{-10} g/ml. In [9] the concentration of tau protein was taken uniformly in the tissue of patients. We assume, however, that the concentration of NFT is higher inside neurons than outside neurons, and take $K_{F_i} = 3.36 \times 10^{-10}$ g/ml, $K_{F_o} = 10^{-11}$ g/ml. From the steady state of Eq. (17) and the estimates of $\lambda_{T_\alpha M_1}$ and $\lambda_{T_\alpha \hat{M}_1}$ (see under Eq. (17) below) we get $T_\alpha = 2.5 \times 10^{-5}$ g/ml, so that $K_{T_\alpha} = 2.5 \times 10^{-5}$ g/ml.

Eq. (7)

We take the half-life of astrocytes to be the same as the half-life of ganglionic glial cells, that is, 600 days [29]. Hence we take a 10 times smaller value in our model

and $d_A = 1.2 \times 10^{-4}$/day. We assume that the activation of astrocytes is due more to TNF-α than to Aβ, and take $\lambda_{AT_\alpha} T_\alpha = 2\lambda_{AA^o_\beta} A^o_\beta$. By the steady state of Eq. (7) we then get $\lambda_{AT_\alpha} = 1.4$/day, and $\lambda_{AA^o_\beta} = 1.63$/day. Actually, in a mouse model of AD, the number of activated astrocytes is increasing [30]. So we compensate for this by increasing both λ_{AT_α} and $\lambda_{AA^o_\beta}$ by a factor 1.1, taking $\lambda_{AT_\alpha} = 1.54$/day and $\lambda_{AA^o_\beta} = 1.793$/day.

Eq. (8)
In mice experiments [31], macrophages phagocytosed apoptotic cells at rates that varied in the range 0.1-1.27/h. We assume that necrotic cells (and their debris) in human brain are phagocytosed by peripheral macrophages at rate $d_{N_d \hat{M}} = 5 \times 10^{-4}$/day. We also assume that microglia play a greater role in clearing necrotic neurons, and take $d_{N_d M} = 2 \times 0.2 = 10^{-3}$/day. We also take $\bar{K}_{N_d} = 10^{-3}$ g/ml.

Eq. (9)
We assume the degradation rate of A_O is much slower than that of A^o_β, taking $d_{A_O} = \frac{1}{10} d_{A^o_\beta} = 0.951$/day. The ratio of soluble A_O to total A^o_β is approximately $\frac{1}{25}$ [32].

From the steady state of Eq. (9) we then get $\lambda_{A_O} = \frac{1}{25} d_{A_O} = 3.8 \times 10^{-2}$/day.

The estimate of λ_{A_O} was based on the steady-state assumption in Eq. (9). However, in AD the soluble Aβ oligomer is continuously increasing, following the increase in A^o_β, so the steady-state assumption needs to be revised. We do this by increasing the above value of λ_{AO} by five times, taking the new value to be $\lambda_{AO} = 0.19$/day.

Eq. (10)
Concentration of HMGB-1 in neurons is 1.3 *ng/ml* [33], hence $H = 0.14 \times 1.3$ ng/ml$=1.8 \times 10^{-10}$ g/ml. Half-life of HMGB-1 is 17 minutes [8], so that $d_H = 58.71$/day. We assume that N_d stabilizes somewhere below 2.5×10^{-4} g/ml. From the steady state of Eq. (10), we then get $\lambda_H = 3 \times 10^{-5}$/day.

Eqs. (11) and (12)
We take $d_{M_1} = d_{M_2} = 0.015$/day [3, 4]. Then, our assumption (under Eq. (2)) that $K_{M_1} > K_{M_2}$ suggests that $\beta > 1$. We take $\beta = 10$.

We take $M^0_G = K_M = 0.047$ g/ml and $\alpha = 5$. In the absence of data, we take the production rate λ_{MF} of macrophages by NFT to be the same as the production rate under stimulation by *M. Tuberculosis* in [4], namely, $\lambda_{MF} = 2 \times 10^{-2}$/day. We assume that production rate of macrophages by NFT is larger than the production rate by A_O, and take $\lambda_{MA} = 10^{-2}$/day.

By [19] the concentration of Aβ in AD is 7×10^{-6} g/ml and, by [21], the ratio of A_O to A^o_β is $\frac{1}{25}$, so that $K_{A_O} = 2 \times 10^{-5}$ g/ml.

We assume that more NFT reside within neurons than outside them, so that K_{F_o} is smaller than K_{F_i}. Recalling that $K_{F_i} = 3.36 \times 10^{-10}$ g/ml, we take $K_{F_O} = 10^{-11}$ g/ml.

The coefficient $\lambda_{M_1 T_\beta}$ is the rate by which TGF-β affects the change of phenotype from M_1 to M_2. In the case of infection in the lung by *M. tuberculosis*, under inflammatory conditions caused by the pathogen, $\lambda_{M_1 T_\beta} = 6 \times 10^{-3}$/day [4]; we take it to be the same in the present case. We take $K_{T_\beta} = 2.5 \times 10^{-7}$ g/ml, and $K_{I_{10}} = 2.5 \times 10^{-6}$ g/ml.

Eqs. (13) and (14)

Peripheral macrophages immigrate into the brain of AD [34, 35]. We assume that, because of the BBB, the concentration of monocytes in the brain capillaries must be significantly higher than the concentration of peripheral macrophages already in the tissue. Recalling that in steady state $\hat{M} = 0.047$ g/ml, we take $M_0 = 0.05$ g/ml. The parameter α was estimated by 5, in order to make the asymptotic behavior of $\hat{M}$ in the simulations agree with its assumed steady state of 0.047 g/ml (under Eq. (2)). When microglia cells are activated, they become either of M_1 or M_2 phenotype. But peripheral macrophages are initially biased toward $\hat{M}_1$ phenotype rather than $\hat{M}_2$ phenotype, since $K_{T_\alpha} > K_{I_{10}}$. We assume, in line with this bias toward $\hat{M}_1$, that the transition rate from $\hat{M}_1$ into $\hat{M}_2$ phenotype by TGF-β is at a smaller rate than the corresponding transition rate for microglias, that is, $\lambda_{\hat{M}_1 T_\beta} < \lambda_{M_1 T_\beta}$. We take $\lambda_{\hat{M}_1 T_\beta} = 1.5 \times 10^{-3}$/day.

Eq. (17)

Activated alveolar macrophages produce TNF-α at rate 4.86×10^{-3}/day [3]. We assume that proinflammatory macrophages produce TNF-α at a larger rate (five fold), taking $\lambda_{T_\alpha M_1} = \lambda_{T_\alpha \hat{M}_1} = 3 \times 10^{-2}$ g/ml.

Eq. (18)

Astrocytes secrete MCP-1 [36, 37, 38] but activated anti-inflammatory microglias also secrete MCP-1. We assume that the production rate by astrocytes in larger than that by M_2, and take $\lambda_{PA} = \frac{1}{2}\lambda_{PM_2}$. MCP-1 concentration in initial stages of AD is 750 pg/ml [39]. Using the steady state equation

$$\lambda_{PM_2}\frac{1}{2}A_0 + \lambda_{PM_2}M_2 = d_P P,$$

with $P = 6 \times 10^{-9}$ g/ml and $d_P = 1.73$/day [7], we get $\lambda_{PM_2} = 1.2 \times 10^{-7}$/day and $\lambda_{PA} = 6 \times 10^{-8}$/day[3].

Since A is increasing in time, also P is increasing in time. Hence the steady state assumption needs to be revised. We do it by increasing λ_{PA} and λ_{PM_2} by a factor 1.1, taking $\lambda_{PM_2} = 1.32 \times 10^{-7}$/day, and $\lambda_{PA} = 6.6 \times 10^{-8}$/day.