"How the formation of amyloid plaques and neurofibrillary tangles may be related – A mathematical modeling study"

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Supplementary material

Table S1. Dependent variables in the model of tau transport.

Symbol	Definition	Units
n_a^*	Concentration of on-track tau moving along MTs anterogradely, propelled by molecular motors	μm^{-1}
n_r^*	Concentration of on-track tau moving along MTs retrogradely, propelled by molecular motors	μm^{-1}
n_{a0}^*	Concentration of pausing on-track tau that is still associated with molecular motors and can resume its anterograde motion	μm^{-1}
n_{r0}^*	Concentration of pausing on-track tau that is still associated with molecular motors and can resume its retrograde motion	μm^{-1}
n_{free}^*	Concentration of free (off-track) tau in the cytosol	μm^{-1}
n_{st}^*	Concentration of stationary tau bound to MTs, no association with motors	μm^{-1}
n_{dif}^*	Concentration of tau diffusing along MTs, no association with motors	μm^{-1}
n_{mis}^*	Concentration of misfolded tau, no mobility	μm^{-1}

Table S2. Independent variables in the models of tau and APP transport.

Symbol	Definition	Units
x^*	Cartesian coordinate along the axon	μm
t^*	Time	s

Table S3. Parameters characterizing transport of tau protein and their estimated values. Utilizing Least Squares Regression (LSR), in ref. [30] we determined values of 18 of these parameters that give best-fit with published experimental data.

Symbol	Definition	Units	Estimated value	Reference or estimation method
A	Coefficient in Eq. (2.15)		5.079×10^{-2}	LSR
D^*_{free}	Diffusivity of tau protein in the cytosolic state	$\mu m^2/s$	3	[25]
D^*_{mt}	Diffusivity of tau protein along MTs	$\mu m^2/s$	0.153	[28]
$j_{tot,tau,x=0}$ [a]	Dimensionless total flux of tau into the axon		3.753×10^{-3}	LSR
k_1^*	Rate constant for the first pseudoelementary step of F-W model (nucleation) describing $n^*_{free}\rightarrow n^*_{mis}$ transition	s^{-1}	3.011×10^{-8}	See the discussion leading to Eq. (3.5)
$k_2^* n^*_{tot,x=0}$	Rescaled rate constant for the second pseudoelementary step of F-W model (autocatalytic growth) describing $n^*_{free}\rightarrow n^*_{mis}$ transition	s^{-1}	2.727×10^{-8}	See the discussion leading to Eq. (3.5)
L^*	Length of the axon	μm	600	[31]
$n_{free,x=0}$ [b]	Dimensionless concentration of free (cytosolic) tau at the		1.616×10^{-6}	LSR

	axon hillock			
$n_{dif,x=0}$ [c]	Dimensionless concentration of MT-bound tau protein capable of diffusing along MTs at the axon hillock		7.849×10^{-1}	LSR
$T^*_{1/2\,free}$ [d]	Half-life of free monomeric tau protein	s	2.16×10^{5}	[41]
$T^*_{1/2,mis}$ [e]	Half-life of misfolded (aggregated) tau protein	s	2.16×10^{5}	See footnote "e" after Table S3
v^*_a, v^*_r	Velocities of rapid motions of tau on MTs propelled by kinesin and dynein motors, respectively	μm/s	0.5, 0.5	[25]
γ^*_{10}	Kinetic constant describing the rate of transitions $n^*_a \rightarrow n^*_{a0}$ and $n^*_r \rightarrow n^*_{r0}$	s^{-1}	1.710×10^{-1}	LSR
γ^*_{01}	Kinetic constant describing the rate of transitions $n^*_{a0} \rightarrow n^*_a$ and $n^*_{r0} \rightarrow n^*_r$	s^{-1}	5.403×10^{-3}	LSR
γ^*_{ar}	Kinetic constant describing the rate of transition $n^*_{a0} \rightarrow n^*_{r0}$	s^{-1}	7.904×10^{-7}	LSR
γ^*_{ra}	Kinetic constant describing the rate of transition $n^*_{r0} \rightarrow n^*_{a0}$	s^{-1}	5.988×10^{-5}	LSR
$\gamma^*_{on,a}$	Kinetic constant describing the rate of transition $n^*_{free} \rightarrow n^*_{a0}$	s^{-1}	1.072×10^{-2}	LSR
$\gamma^*_{on,r}$	Kinetic constant describing the rate of transition $n^*_{free} \rightarrow n^*_{r0}$	s^{-1}	9.985×10^{-6}	LSR
$\gamma^*_{off,a}$	Kinetic constant describing the rate of transition $n^*_{a0} \rightarrow n^*_{free}$	s^{-1}	7.996×10^{-7}	LSR

$\gamma^*_{off,r}$	Kinetic constant describing the rate of transition $n^*_{r0} \rightarrow n^*_{free}$	s^{-1}	2.833×10^{-9}	LSR
$\gamma^*_{free\rightarrow st}$	Kinetic constant describing the rate of transition $n^*_{free} \rightarrow n^*_{st}$	s^{-1}	9.978×10^{-6}	LSR
$\gamma^*_{st\rightarrow free}$	Kinetic constant describing the rate of transition $n^*_{st} \rightarrow n^*_{free}$	s^{-1}	1.651×10^{-5}	LSR
$\gamma^*_{free\rightarrow dif}$	Kinetic constant describing the rate of transition $n^*_{free} \rightarrow n^*_{dif}$	s^{-1}	4.395×10^{-6}	LSR
$\gamma^*_{dif\rightarrow free}$	Kinetic constant describing the rate of transition $n^*_{dif} \rightarrow n^*_{free}$	s^{-1}	2.167×10^{-3}	LSR
$\gamma^*_{dif\rightarrow st}$	Kinetic constant describing the rate of transition $n^*_{dif} \rightarrow n^*_{st}$	s^{-1}	7.924×10^{-7}	LSR
$\gamma^*_{st\rightarrow dif}$	Kinetic constant describing the rate of transition $n^*_{st} \rightarrow n^*_{dif}$	s^{-1}	8.586×10^{-6}	LSR

[a] $j_{tot,tau,x=0} = \frac{j^*_{tot,tau,x=0}}{n^*_{tot,x=0} v^*_a}$.

[b] $n_{free,x=0} = \frac{n^*_{free,x=0}}{n^*_{tot,x=0}}$.

[c] $n_{dif,x=0} = \frac{n^*_{dif,x=0}}{n^*_{tot,x=0}}$.

[d] Because proteins transported by slow axonal transport (such as tau) on average move anterogradely, they cannot be returned to the soma for degradation. Their concentration depends on their half-lives, in the axon and in the synapse, which are not necessarily the same [79].

[e] In the F-W model, misfolded tau represents many different fibril sizes, which may have different half-lives. Due to a lack of published experimental data, as a first approximation we assigned $T^*_{1/2,mis}$ the same value as to the half-life of free monomeric tau. This assumption may

need to be critically reevaluated later, in particular because misfolded tau aggregates may disrupt proteasome function [19] resulting in a longer half-life of tau aggregates.

Table S4. Dependent variables in the model of APP transport.

Symbol	Definition	Units
c_+^*	Concentration of anterogradely transported APP	μm^{-1}
c_-^*	Concentration of retrogradely transported APP	μm^{-1}
c_0^*	Concentration of free APP (not actively transported by motors on MTs)	μm^{-1}

Table S5. Parameters characterizing APP transport and their estimated values.

Symbol	Definition	Units	Estimated value	Reference or estimation method
$c_{-,x=L}$ [a]	Ratio of retrogradely running APP at the end of the axon to anterogradely running APP at the beginning of the axon		$0.4\frac{v_+^*}{v_-^*}$	See the analysis leading to Eq. (2.28)
v_+^* [b]	Anterograde velocity of APP-transporting vesicles propelled by kinesin motors	μm/s	1.74	[60]
v_-^* [b]	Retrograde velocity of APP-transporting vesicles propelled by dynein motors	μm/s	1.51	[60]
α_+^* [c]	Kinetic constant describing the rate of transition $c_0^* \to c_+^*$	s^{-1}	1	[57]
α_-^* [c]	Kinetic constant describing the rate of transition $c_0^* \to c_-^*$	s^{-1}	1	[57]
$\alpha_+'^*$ [c]	Kinetic constant describing the rate of transition $c_+^* \to c_0^*$	s^{-1}	0.4609	[57]

$\alpha_{-}^{\prime *}$ [c]	Kinetic constant describing the rate of transition $c_{-}^{*} \rightarrow c_{0}^{*}$	s^{-1}	1	[57]
β	A parameter in Eq. (3.2) that characterizes how quickly $\alpha_{+}^{\prime *}$ increases when misfolded tau is produced		8×10^{3}	The value 8×10^{3} was found by performing numerical experiments so that the maximum value that $\alpha_{+}^{\prime *}$ takes at steady-state equals twice the value that $\alpha_{+}^{\prime *}$ takes at the initial time, when $n_{mis}=0$ (see Fig. 5b)

[a] $c_{-,x=L}=\dfrac{c_{-,x=L}^{*}}{c_{+,x=L}^{*}}$

[b] Although parameters v_{a}^{*} and v_{+}^{*} characterize cargo velocities propelled by kinesin motors, they are not necessarily the same because they describe motion of different cargos; v_{a}^{*} characterizes tau transport and v_{+}^{*} characterizes APP transport. A similar statement applies to v_{r}^{*} and v_{-}^{*}.

[c] Since there is no published data that allow us to estimate values of kinetic constants for APP transport, we relied on [57] and assumed that kinetic constants are of order 1 s^{-1}. We used a value of 1 s^{-1} for α_{-}^{*}, α_{+}^{*}, and $\alpha_{-}^{\prime *}$ and we set $\alpha_{+}^{\prime *}=0.4\dfrac{v_{+}^{*}}{v_{-}^{*}}=0.4609$ s^{-1}.

Measuring the distance between distributions computed with and without tau agglomeration in Figs. 3 and 4

The dimensionless distance between distributions of various observables computed with and without tau agglomeration (Figs. 3a,b and 4a,b) was evaluated by using the L^2 distance [73]. For example, for the total dimensionless tau concentration (Fig. 3a) this distance is defined as:

$$d\left(n_{tot,no\ aggl},n_{tot,with\ aggl}\right)=\frac{1}{L^{*}}\sqrt{\int_{0}^{L^{*}}\left[n_{tot,no\ aggl}\left(x^{*}\right)-n_{tot,with\ aggl}\left(x^{*}\right)\right]^{2}dx^{*}}\,. \qquad \text{(S1)}$$