Supporting Information

The role of annealing and fragmentation in human tau aggregation dynamics

Carol J. Huseby[‡], Ralf Bundschuh[‡,§], and Jeff Kuret[‡,¶,1]

From the [‡]Interdisciplinary Biophysics Graduate Program, The Ohio State University, Columbus, Ohio 43210; [§]Departments of Physics, Internal Medicine, and Chemistry & Biochemistry; The Ohio State University, Columbus, Ohio 43210; [¶]Department of Biological Chemistry & Pharmacology, The Ohio State University, Columbus, Ohio 43210

[1]To whom correspondence should be addressed: Jeff Kuret, Ph.D., The Ohio State University College of Medicine, 1060 Carmack Rd., Columbus, OH 43210, USA, Tel: (614) 688-5899; Fax: (614) 292-5379, E-mail: kuret.3@osu.edu

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$$\frac{dc_1}{dt} = -2\left(k_{n_+}c_1^2 - k_{n\_}c_2\right) - \sum_{i=3}^{N}\left(k_{e_+}c_1c_{i-1} - k_{e\_}c_i\right) - \sum_{i=10}^{N} 2\left(k_{n2_+}ic_ic_1^2 - k_{n2\_}ic_ic_2\right) \tag{S1}$$

$$\frac{dc_2}{dt} = \left(k_{n_+}c_1^2 - k_{n\_}c_2\right) - \left(k_{e_+}c_1c_2 - k_{e\_}c_3\right) + \sum_{i=10}^{N}\left(k_{n2_+}ic_ic_1^2 - k_{n2\_}ic_ic_2\right) \tag{S2}$$

$$\frac{dc_3}{dt} = \left(k_{e_+}c_1c_2 - k_{e\_}c_3\right) - \left(k_{e_+}c_1c_3 - k_{e\_}c_4\right) - k_{an}\left(\frac{3}{N}\right)^{\alpha}\sum_{i=3}^{N-3}2c_3c_i\left(\frac{i}{N}\right)^{\alpha} + k_{fr}2\sum_{i=6}^{N}c_i\left(\frac{i}{N}\right)^{\beta} \tag{S3}$$

$$\frac{dc_4}{dt} = \left(k_{e_+}c_1c_3 - k_{e\_}c_4\right) - \left(k_{e_+}c_1c_4 - k_{e\_}c_5\right) - k_{an}\left(\frac{4}{N}\right)^{\alpha}\sum_{i=3}^{N-4}2c_4c_i\left(\frac{i}{N}\right)^{\alpha} + k_{fr}2\sum_{i=7}^{N}c_i\left(\frac{i}{N}\right)^{\beta} \tag{S4}$$

$$\frac{dc_5}{dt} = \left(k_{e_+}c_1c_4 - k_{e\_}c_5\right) - \left(k_{e_+}c_1c_5 - k_{e\_}c_6\right) - k_{an}\left(\frac{5}{N}\right)^{\alpha}\sum_{i=3}^{N-5}2c_5c_i\left(\frac{i}{N}\right)^{\alpha} + k_{fr}2\sum_{i=8}^{N}c_i\left(\frac{i}{N}\right)^{\beta} \tag{S5}$$

$j = 6{:}\,N-4$

$$\begin{aligned}\frac{dc_j}{dt} = {} & \left(k_{e_+}c_1c_{j-1} - k_{e\_}c_j\right) - \left(k_{e_+}c_1c_j - k_{e\_}c_{j+1}\right) \\ & + k_{an}\sum_{i=3}^{(N-3)-(N-j)}c_ic_{j-i}\left(\frac{i}{N}\right)^{\alpha}\left(\frac{j-i}{N}\right)^{\alpha} - k_{an}\sum_{i=3}^{N-j}2c_jc_i\left(\frac{i}{N}\right)^{\alpha}\left(\frac{j}{N}\right)^{\alpha} \\ & + k_{fr}2\sum_{i=j+3}^{N}c_i\left(\frac{i}{N}\right)^{\beta} - k_{fr}\left(\frac{j}{N}\right)^{\beta}(j-5)c_j\end{aligned} \tag{S6}$$

$$\begin{aligned}\frac{dc_{N-3}}{dt} = {} & \left(k_{e_+}c_1c_{N-4} - k_{e\_}c_{N-3}\right) - \left(k_{e_+}c_1c_{N-3} - k_{e\_}c_{N-2}\right) \\ & + k_{an}\sum_{i=3}^{(N-6)}c_ic_{(N-3)-i}\left(\frac{i}{N}\right)^{\alpha}\left(\frac{(N-3)-i}{N}\right)^{\alpha} - k_{an}2c_{N-3}c_3\left(\frac{3}{N}\right)^{\alpha}\left(\frac{N-3}{N}\right)^{\alpha} \\ & - k_{fr}\left(\frac{N-3}{N}\right)^{\beta}\left((N-3)-5\right)c_{N-3}\end{aligned} \tag{S7}$$

$$\begin{aligned}\frac{dc_{N-2}}{dt} = {} & \left(k_{e_+}c_1c_{N-2} - k_{e\_}c_{N-1}\right) - \left(k_{e_+}c_1c_{N-1} - k_{e\_}c_N\right) \\ & + k_{an}\sum_{i=3}^{(N-5)}c_ic_{(N-2)-i}\left(\frac{(N-2)-i}{N}\right)^{\alpha}\left(\frac{i}{N}\right)^{\alpha} - k_{fr}\left(\frac{N-2}{N}\right)^{\beta}\left((N-2)-5\right)c_{N-2}\end{aligned} \tag{S8}$$

$$\begin{aligned}\frac{dc_{N-1}}{dt} = {} & \left(k_{e_+}c_1c_{N-2} - k_{e\_}c_{N-1}\right) - \left(k_{e_+}c_1c_{N-1} - k_{e\_}c_N\right) \\ & + k_{an}\sum_{i=3}^{(N-4)}c_ic_{(N-1)-i}\left(\frac{i}{N}\right)^{\alpha}\left(\frac{(N-1)-i}{N}\right)^{\alpha} - k_{fr}\left(\frac{N-1}{N}\right)^{\beta}\left((N-1)-5\right)c_{N-1}\end{aligned} \tag{S9}$$

$$\frac{dc_N}{dt} = \left(k_{e_+}c_1c_{N-1} - k_{e\_}c_N\right) + k_{an}\sum_{i=3}^{(N-3)}c_ic_{N-i}\left(\frac{i}{N}\right)^{\alpha}\left(\frac{N-i}{N}\right)^{\alpha} - k_{fr}\left(\frac{N}{N}\right)^{\beta}(N-5)c_N \tag{S10}$$

Figure S1. Mathematical model of tau aggregation. The time-dependent evolution of tau filaments of protomer length N was modeled with a system of ordinary differential equations assuming reversible association of monomers. The number of equations was limited to $N = 900$. The model included terms for the primary processes of nucleation and elongation (black font), and the secondary processes of secondary nucleation (green font), end-to-end annealing (blue font) and fragmentation (red font). The final model incorporating terms for all three secondary processes is termed "NEAFS".

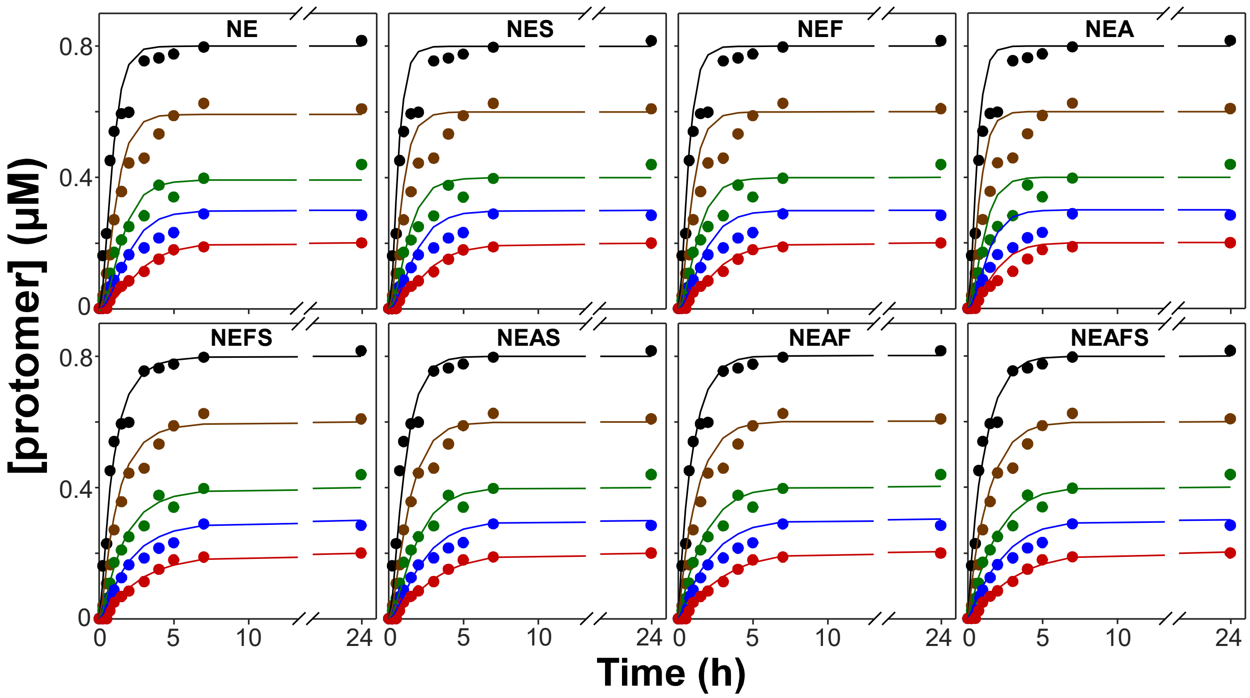

Figure S2. Fits of mathematical models to protomer concentration time series. Mathematical models composed of nucleation-elongation (NE) and either one (NES, NEF, NEA), two (NEFS, NEAS, NEAF) or three (NEAFS) secondary processes were simultaneously fit to protomer concentration and length distribution time series (*i.e.*, the same data as shown in **Fig. 6A**). Each point represents protomer concentration as a function of time (0 – 24 h at 37°C) and starting bulk 2N4R tau concentration (0.4 μM, red; 0.5 μM, blue; 0.6 μM, green; 0.8 μM, brown; 1 μM, black), whereas solid lines depict a simulation of the best fit of each model to the data points.

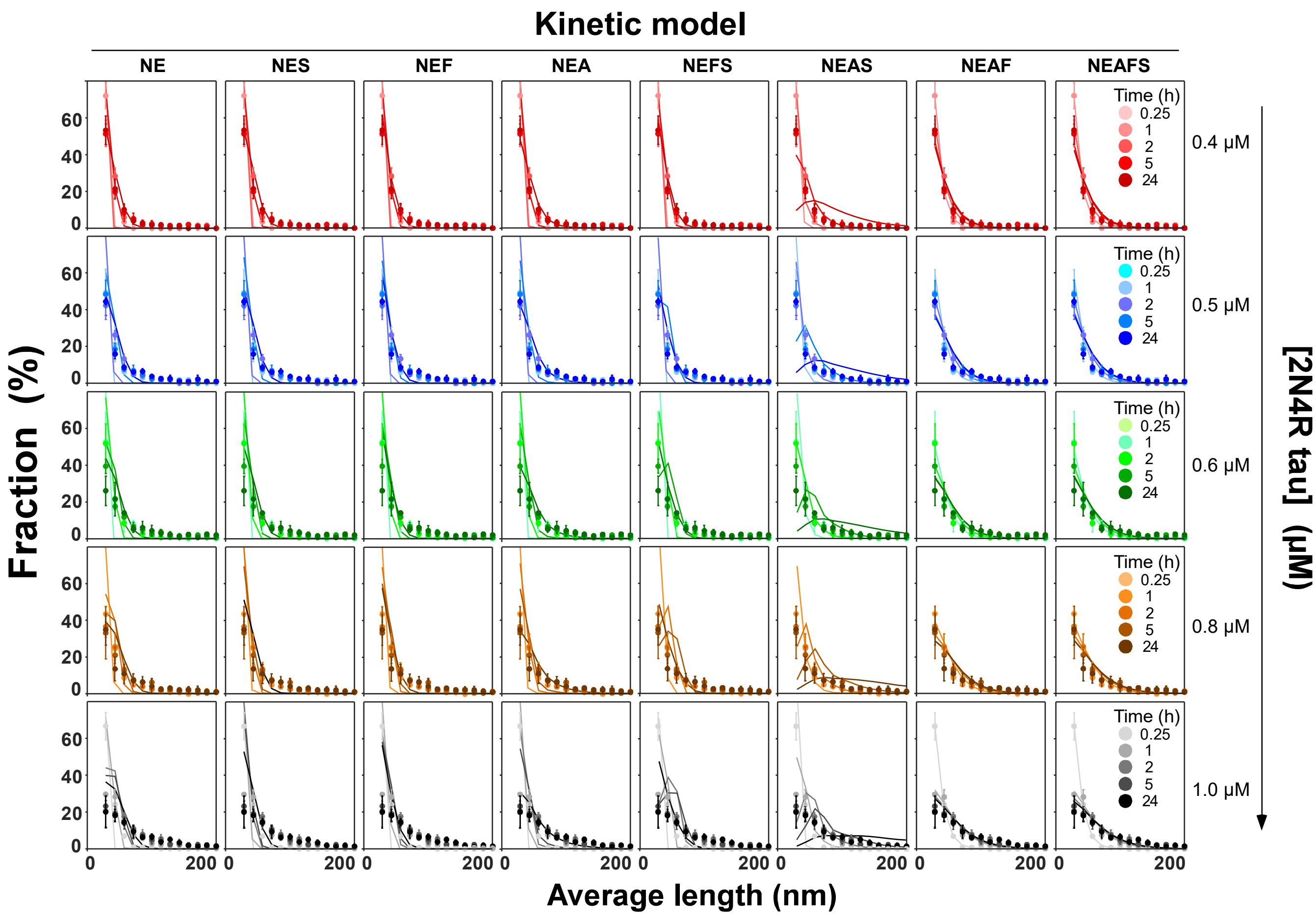

Figure S3. Fits of mathematical models to length distribution time series. Mathematical models composed of nucleation-elongation (NE) with either one (NES, NEF, NEA), two (NEFS, NEAS, NEAF) or three (NEAFS) secondary processes were simultaneously fit to protomer concentration and length distribution time series (*i.e.*, the same data shown in **Fig. 6B**). Each set of points represents tau filament length distribution as a function of time (0 – 24 h at 37°C) and starting bulk 2N4R tau concentration (0.4 μM, red; 0.5 μM, blue; 0.6 μM, green; 0.8 μM, brown; 1 μM, black), whereas lines depict a simulation of the best fit of each model to the data points.