

Figure 3 – figure supplement 1

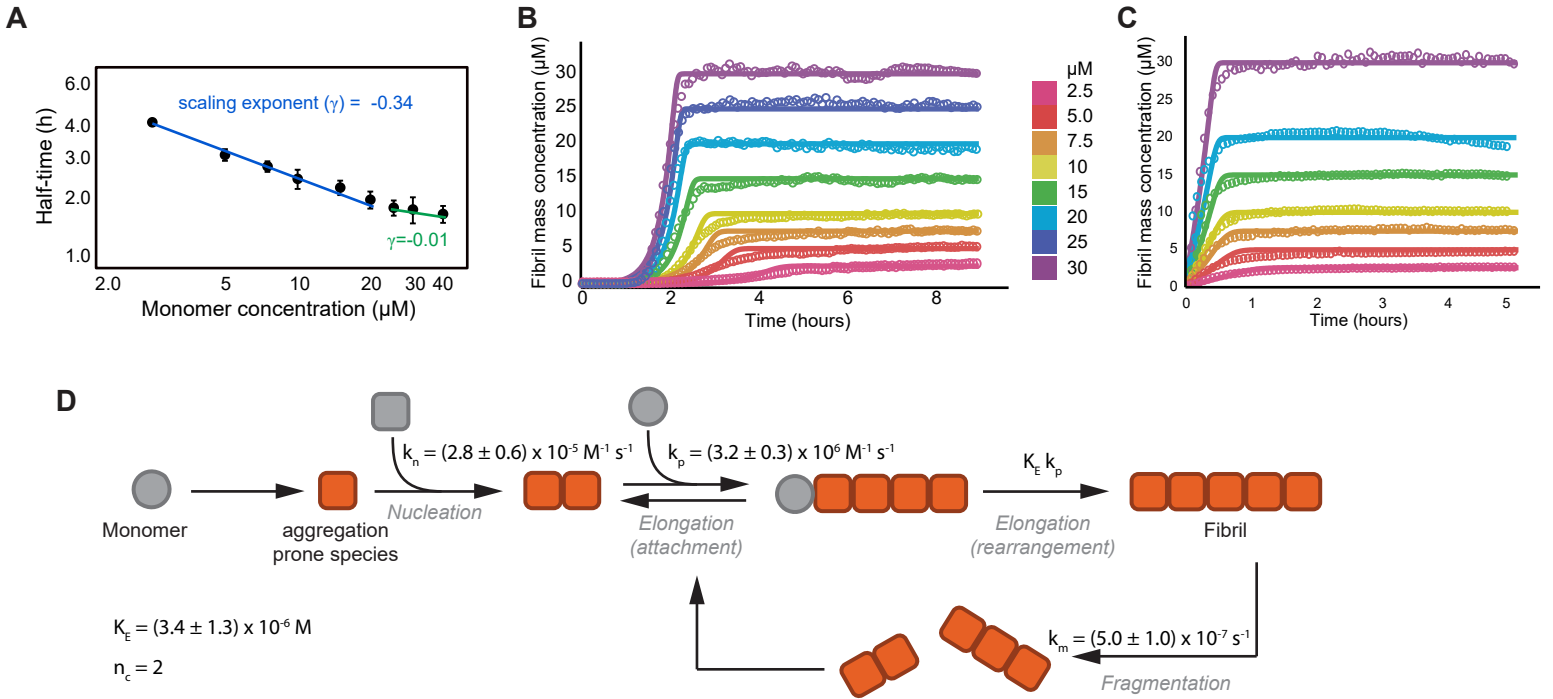


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Global fitting of tau aggregation data. (A) A plot of the aggregation reaction half-times versus the initial monomer concentration, used to narrow down the aggregation mechanism of tau (45). Half-times were calculated from 3 independent experiments of unseeded tau aggregation, as shown in B. To extract the scaling factor (γ), the half-times ($t_{1/2}$) of the aggregation reaction were plotted versus the tau monomer concentration on a double logarithmic plot with the slope of this plot providing the scaling exponent ($\log(t_{1/2}) = \gamma \log(m_0) + \text{constant}$). By using the rate laws for the time evolution of aggregate mass, γ can be related to the reaction orders for each of the models. The scaling factor for tau aggregation was calculated to be -0.34 ± 0.04 , with $-0.5 < \gamma < 0$ indicating primary nucleation and fragmentation as the correct model. Furthermore, the deviation of the points from a straight line shows that γ is dependent on the monomer concentration, with positive curvature indicating the presence of saturating elongation (45). **(B-C)** Kinetic profiles of the concentration-dependent aggregation of tau^{4R} at concentrations of 2.5, 5, 7.5, 10, 15, 20, and 30 μM , initiated by the addition of 0.5 molar equivalents of heparin (B) or 1% seeds (C), and monitored by ThT fluorescence (open circles). Continuous lines represent the global fitting of the data to the integrated rate laws (see equations in the methods section). **(D)** Schematic of microscopic steps during tau aggregation and their corresponding rate constants as obtained from the fits (see methods for detail). k_n is the rate of nucleation, k_p is the rate of elongation, K_E is the critical concentration for saturated elongation, and k_m is the rate of fibril fragmentation. Nucleus size was assumed to be two ($n_c=2$) (44, 46).