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A generic approach to decipher the mechanistic pathway of heterogeneous protein aggregation kinetics

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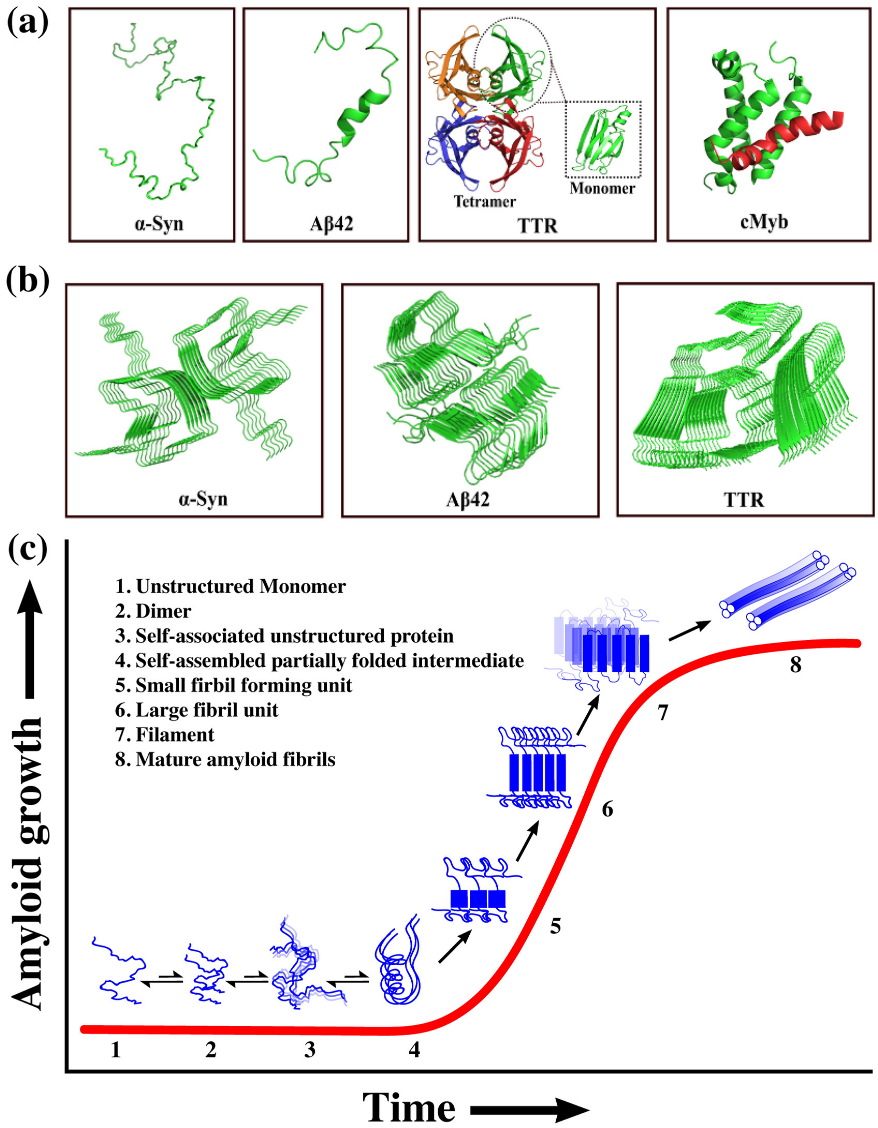


Fig. S1 Visual rendition of the amyloid structure and conversion of disordered structure to amyloid. **(a)** Ensemble structure of α-Syn (PDB ID: PED00024e001), solution structure of Aβ42 protein (PDB ID: 6SZF), crystal structure of TTR (PDB ID: 1DVQ) and structure of cMyb:KIX complex; the backbone of KIX complex and cMyb protein has been shown in green and red colour (PDB ID: 1SB0).[1–4] **(b)** Cryo-EM structure of amyloid fibril of α-Syn (PDB ID: 6A6B), Aβ42 (PDB ID: 5KK3), TTR (PDB ID: 6SDZ), (for cMyb protein final amyloid structure is not available).[5–7] **(c)** Schematics representations of the aggregation dynamics of the natively unstructured protein along the lag and growth phase.

A proposed set of canonical models for the aggregation process of amyloid-forming protein:

The detailed interaction network for each distinct model has been schematized here. The detailed description of each interaction node has been explained and summarized in Section-3.

Model-1A/Model-2A

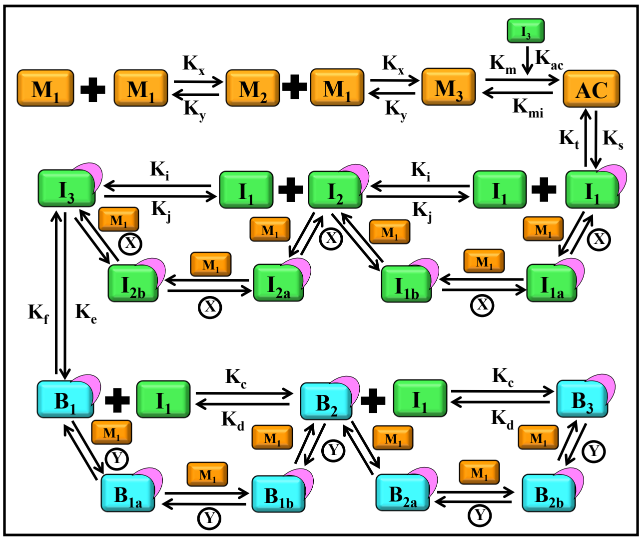


Fig. S2(a) Detail interaction network of one of the proposed Model variants [Model-1A/Model2A]. The reaction nodes are similar for both Model-1A and Model-2A having an equal number of reacting species [19] and ThT bounded complexes [14]. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1A, X represents the forward and backward rate constant as $n \times K_i$ and $n \times K_j$. Y represents the forward and backward rate constant as $n1 \times K_c$ and $n1 \times K_d$, including total of 19 rate constants and one scaling constant. Consequently, for Model-2A, X represents the forward and backward rate constant as K_{i1} and K_{j1}. Y represents the forward and backward rate constant as K_{c1} and K_{d1}, including total of 21 rate constants and one scaling constant. The pink color symbol represents the ThT binding with the secondary structure of the protein.

Model-1B/Model-2B

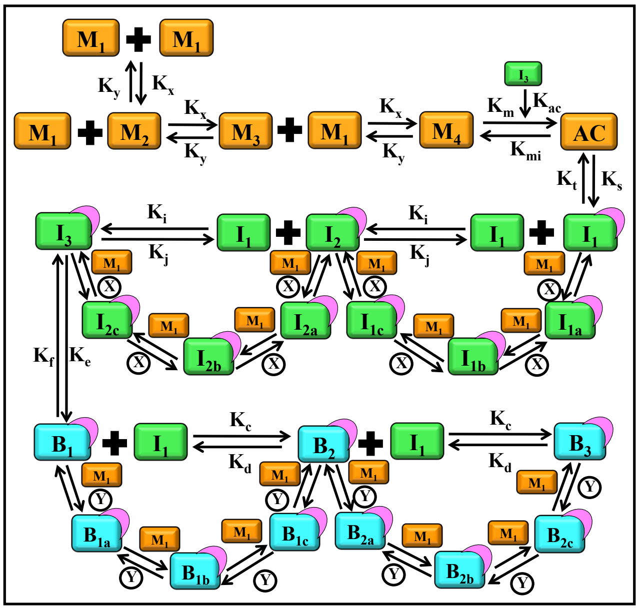


Fig. S2(b) Detail interaction network of one of the proposed Model variants [Model-1B/Model2B]. The reaction nodes are similar for both Model-1B and Model-2B having an equal number of reacting species [24] and ThT bounded complexes [18]. The arrow represents the biochemical reactions. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1B, X represents the forward rate constant as $n \times K_i$ and backward rate constant $n \times K_j$. Y represents forward rate constant as $n1 \times K_c$ and backward rate constant as $n1 \times K_d$, including total of 19 rate constants and one scaling constant. Consequently, for Model-2B, X represents the forward rate constant as K_{i1} and backward rate constant K_{j1}. Y represents the forward rate constant as K_{c1} and backward rate constant K_{d1}. The total number of rate constant involved with the interaction network is 21 including one scaling constant. The pink color symbol represents ThT binding with the secondary structure of the protein.

Model-1C/Model-2C

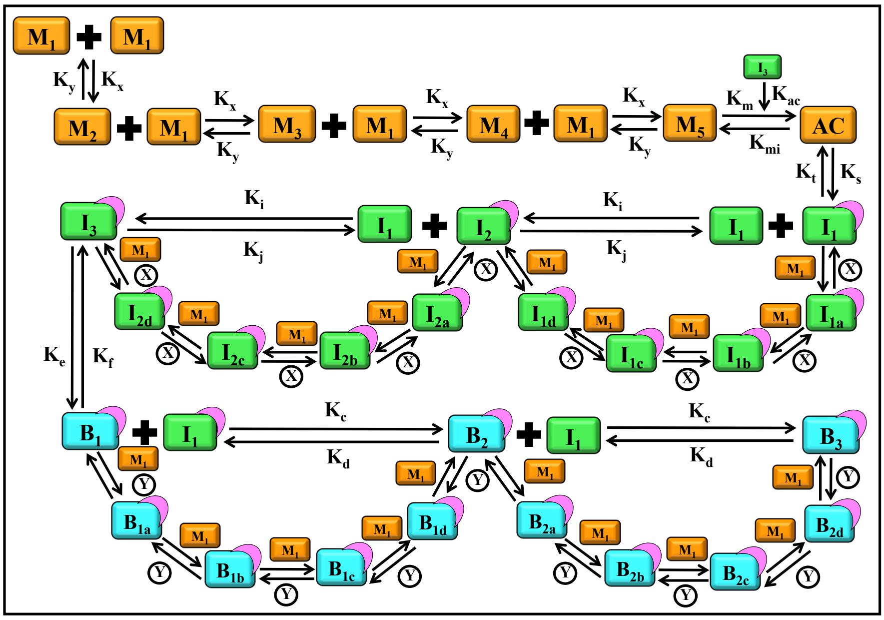


Fig. S2(c) Detail interaction network of one of the proposed Model variants [Model-1C/Model2C]. The reaction nodes are similar for both Model-1C and Model-2C having an equal number of reacting species [29] and ThT bounded complexes [22]. The arrow represents the biochemical reactions. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1C, X represents the forward rate constant as $n \times K_i$ and backward rate constant $n \times K_j$. Y represents the forward rate constant as $n1 \times K_c$ and backward rate constant as $n1 \times K_d$. The total number of rate constant associated with the interaction network is 19 including one scaling constant. Consequently, for Model-2C, X represents the forward rate constant as K_{i1} and backward rate constant K_{j1}. Y represents the forward rate constant as K_{c1} and backward rate constant K_{d1}. The total number of rate constant involved with the interaction network is 21 including one scaling constant. The pink color symbol represents the ThT binding with the secondary structure of the protein.

Model-1D/Model-2D

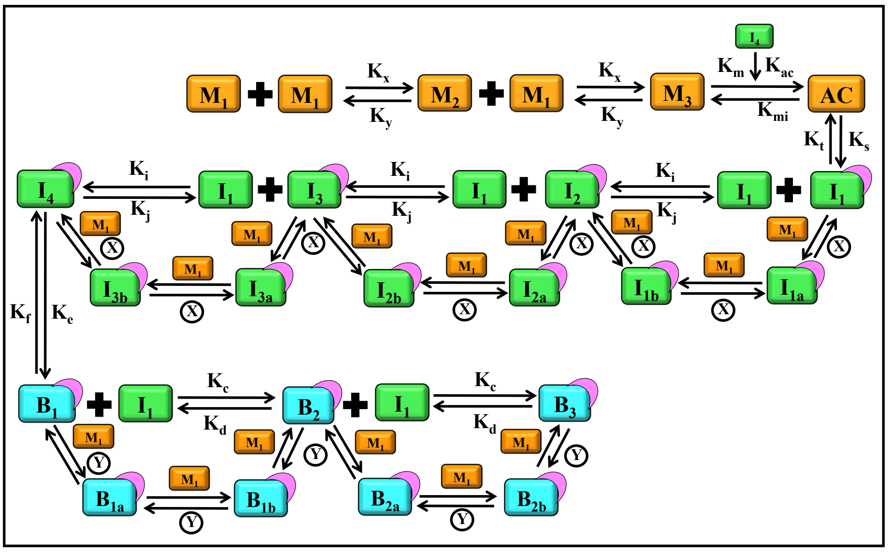


Fig. S2(d) Detail interaction network of one of the proposed Model variants [Model-1D/Model2D]. The reaction nodes are similar for both Model-1D and Model-2D having an equal number of reacting species [22] and ThT bounded complexes [17]. The arrow represents the biochemical reactions. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1D, X represents the forward rate constant as $n \times K_i$ and backward rate constant $n \times K_j$. Y represents the forward rate constant as $n1 \times K_c$ and backward rate constant as $n1 \times K_d$. The total number of rate constant associated with the interaction network is 19 including one scaling constant. Consequently, for Model-2D, X represents the forward rate constant as K_{i1} and backward rate constant K_{j1}. Y represents the forward rate constant as K_{c1} and backward rate constant K_{d1}. The total number of rate constant involved with the interaction network is 21 including one scaling constant. The pink color symbol represents the ThT binding with the secondary structure of the protein.

Model-1E/Model-2E

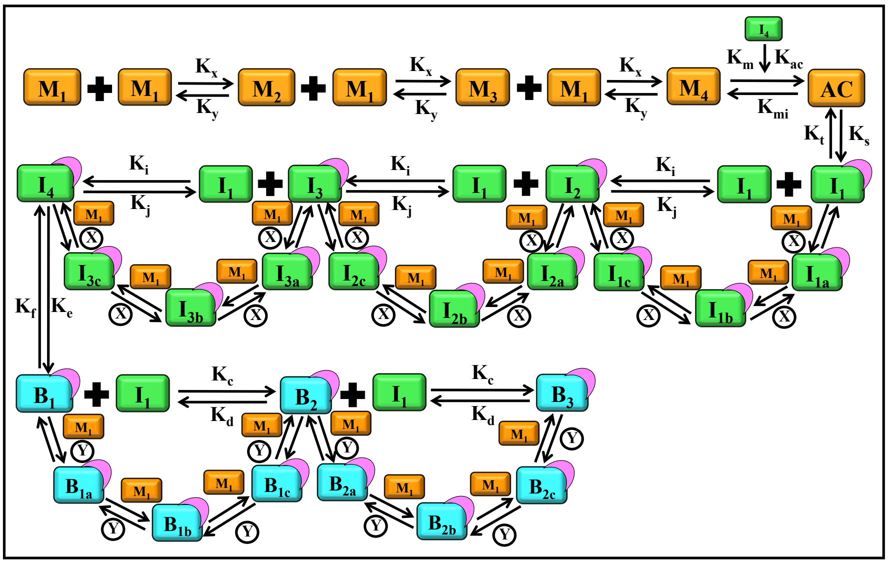


Fig. S2(e) Detail interaction network of one of the proposed Model variants [Model-1E/Model2E]. The reaction nodes are similar for both Model-1E and Model-2E having an equal number of reacting species [28] and ThT bounded complexes [22]. The arrow represents the biochemical reactions. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1E, X represents the forward rate constant as $n \times K_i$ and backward rate constant $n \times K_j$. Y represents the forward rate constant as $n1 \times K_c$ and backward rate constant as $n1 \times K_d$. The total number of rate constant associated with the interaction network is 19 including one scaling constant. Consequently, for Model-2E, X represents the forward rate constant as K_{i1} and backward rate constant K_{j1}. Y represents the forward rate constant as K_{c1} and backward rate constant K_{d1}. The total number of rate constant involved with the interaction network is 21 including one scaling constant. The pink color symbol represents the ThT binding with the secondary structure of the protein.

Model-1F/Model-2F

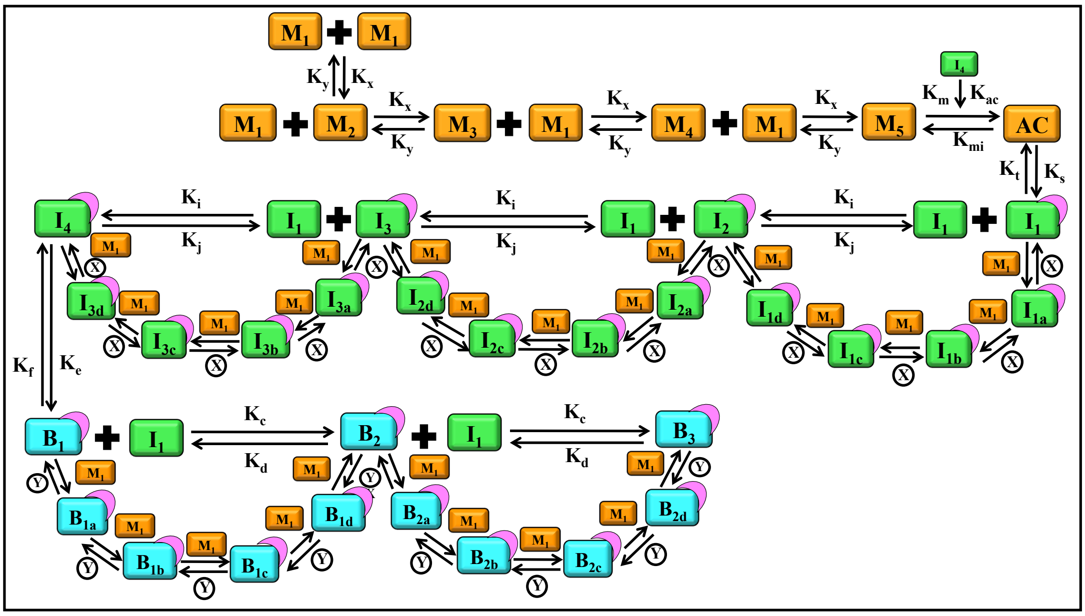


Fig. S2(f) Detail interaction network of one of the proposed Model variants [Model-1F/Model2F]. The reaction nodes are similar for both Model-1F and Model-2F having an equal number of reacting species [34] and ThT bounded complexes [27]. The arrow represents the biochemical reactions. All the variables corresponding to this network are defined in Table S2, all the kinetic rate constants are defined in Table S3, all the reaction events are explained in Section-3 and the differential equations corresponding to each variable are shown in Section-4. Here, for Model-1F, X represents the forward rate constant as $n \times K_i$ and backward rate constant $n \times K_j$. Y represents the forward rate constant as $n1 \times K_c$ and backward rate constant as $n1 \times K_d$. The total number of rate constant associated with the interaction network is 19 including one scaling constant. Consequently, for Model-2F, X represents the forward rate constant as K_{i1} and backward rate constant K_{j1}. Y represents the forward rate constant as K_{c1} and backward rate constant K_{d1}. The total number of rate constant involved with the interaction network is 21 including one scaling constant. The pink color symbol represents the ThT binding with the secondary structure of the protein.

Detail interaction network for ThT binding with the secondary structure of the protein:

Interaction of the ThT molecule with the secondary structure of the protein has been schematized here. The reaction node has been described in Section-3 [STEP-9 & 10].

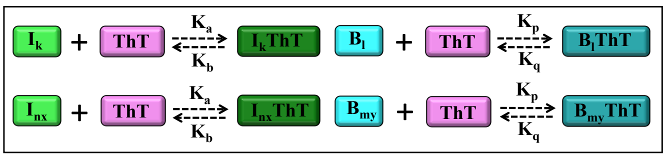


Fig. S3 Detail interaction network of ThT with secondary structure of protein. The indices represents as *k=1,2,3,4; n=1,2,3; x=a,b,c,d; l=1,2,3; m=1,2; y=a,b,c,d*. All the variable corresponding to this network has been described in Table S2 and the corresponding parameter has been described in Table S3.

Classification of the proteins as (Class-1) and (Class-2):

To make an inclusive model so that all type of amyloid forming protein based on their existing kinetic data can be fitted into our proposed model, we introduced two categories for proteins. The classification of the respective proteins as (Case-1) and (Case-2) used to establish the proposed general amyloid framework has been signified based on the available experimental data to study the aggregation kinetics for the respective proteins (Table S1). Once the protein has been classified in the category of (Case-1) or (Case-), only the interpretation of the molecular entity and molecular events to describe the aggregation mechanism varies (Table 1), but the core structure of the model remains similar.

Table S1: Distinguishing the class of the proteins before fitting the kinetic data using our generic modeling approach.

(Case-1)	(Case-2)
• Scientist has often observed the evolution of the partially folded intermediate while following the aggregation kinetics for the proteins under investigation. For such proteins (e.g. α-Syn), experimental data is available for Thioflavin-T data of total aggregates simultaneously measured with the kinetic data of the intermediates. We classified this type of protein as Case-1 protein, where both kinds of data are available to optimize the kinetic parameters.	• On the other hand, the partially folded intermediate has not been identified for many proteins (e.g. c-Myb) during the aggregation study. • The experimental data of partially folded intermediates is available, but the kinetic data for the intermediate was not simultaneously measured with the ThT data of amyloid formation (e.g. Aβ42 and TTR). • We have categories both of these two kinds of proteins as Case-2 proteins.

Table S2: Abbreviated name of the species involved in the model

Model variables representing the concentrations of various species are defined below:

Symbol	Description
$\boldsymbol{ThT}$	The concentration of Thioflavin T dye
$\boldsymbol{M_1}$	Monomer of the non-fibrillar random coil state, which linearly assembled into long-chain fibril. (For simplicity we defined the monomer as the minimum unit of the random coil state of natively unstructured protein.[8–14] The assumption also holds good if the monomeric unit is the smallest unit of the natively folded protein undergoing self-association.[15] We defined oligomer as any polymer rather than monomer that can be any type of structure (primary, secondary or tertiary structure of the protein).
$\boldsymbol{M_2}$	Dimer of the non-fibrillar random coil state produced from the linear combination of the monomeric unit (M_1)
$\boldsymbol{M_3}$	Trimer of the non-fibrillar random coil state produced from the linear combination of the monomeric unit (M_1) with dimer (M_2)
$\boldsymbol{M_4}$	Tetramer of the non-fibrillar random coil state produced from the linear combination of the monomeric unit (M_1) with trimer (M_3)
$\boldsymbol{M_5}$	Pentamer of the non-fibrillar random coil state produced from the linear combination of the monomeric unit (M_1) with tetramer (M_4)

$\boldsymbol{AC}$	A critical assemble of the amyloidogenic protein which on the verge of transitioning into either partially folded intermediate (Case-1) or lower order minimal fibrillar unit (Case-2)
$\boldsymbol{I_1}$	Basic (minimum) structural unit for lower-order fibril (Case-2) or basic (minimum) structural unit for partially folded intermediate structure (Case-1)
$\boldsymbol{I_2}$	Next higher-order elongation unit after (I_1)
$\boldsymbol{I_3}$	Next higher-order elongation unit after (I_2)
$\boldsymbol{I_4}$	Next higher-order elongation unit after (I_3). The association-dissociation mechanism can continue up to various degrees of elongation unit before undergoing the next transition. To simplify our model we have assumed that this is the highest order of the structural degree can be attained for any particular protein in this state.
$\boldsymbol{I_{ni}}$ ***n*** **=1,2,3 and** ***i*** **=a,b,c,d**	Monomer mediated elongation unit for lower order fibrillar structure (Case-2) or elongation unit for partially folded intermediate structure (Case-1), generated through the combination of monomeric unit (M_1) with $(I_n, n = 1,2,3)$.
$\boldsymbol{I_{ni}ThT}$, ***n*** **=1,2,3 ;** ***i*** **=a,b,c,d** **and** $\boldsymbol{I_kThT}$ **k=1,2,3,4**	ThT bounded complex of the corresponding units
$\boldsymbol{B_1}$	Basic (minimum) fibrillar unit of mature fibril
$\boldsymbol{B_2}$	Next higher-ordered fibrillar unit after (B_1)
$\boldsymbol{B_3}$	Next higher-ordered fibril unit after (B_2). The fibrillar unit can vary up to any certain degree; we have assumed that the fibril structure can't go beyond this structural degree to maintain simplicity in building our model.
$\boldsymbol{B_{mi}}$ ***m*** **=1,2 and** ***i*** **=a,b,c,d**	Fibril unit produced from secondary nucleation process
$\boldsymbol{B_{mi}ThT}$ ***m*** **=1,2 and** ***i*** **=a,b,c,d** and $\boldsymbol{B_lThT}$ ***l*** **=1,2,3**	ThT bounded complex of the corresponding fibril units

Table S3: Description of all parameters involved in proposed canonical Models

Symbol	Description	Unit	Comment
$\mathbf{K_x}$	Primary nucleation rate or association rate of random coil (or any other structural) state of protein	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_y}$	The dissociation rate of random coil state of protein	(t^{-1})	Fitted
$\mathbf{K_m}$	Conformational transition rate from the final structure of the random coil state of the protein $(M_x, x = 3,4,5)$ to a critical assembled structure or the activated state (AC)	(t^{-1})	Fitted
$\mathbf{K_{mi}}$	Conformational transition rate from the activated state (AC) to the final structure of the oligomeric random coil state of the protein $(M_x, x = 3,4,5)$	(t^{-1})	Fitted
$\mathbf{K_{ac}}$	Feedback rate of the final structure of the random coil state of the protein $(M_x, x = 3,4,5)$ converted to the activated state (AC) facilitated by the highest ordered elongation unit $(I_{k,} k = 3,4)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_s}$	Conversion rate of the critical assembled state (AC) to basic minimum oligomeric partially folded intermediate (Case-1) unit (I_1) or to basic minimal lower-order (Case-2) fibrillar unit (I_1)	(t^{-1})	Fitted
$\mathbf{K_t}$	Conversion rate of the basic minimum oligomeric partially	(t^{-1})	Fitted
	folded intermediate (Case-1) unit (I_1) to critical assembled state (AC) or basic minimal lower-order (Case-2) fibrillar unit (I_1) to critical assembled state (AC)		
$\mathbf{K_i}$	Self-association rate of the different units of $(I_{k,} k = 1,2,3)$ with (I_1)	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_j}$	Dissociation rate of the different units of $(I_{k,} k = 2,3,4)$, which formed from the self-association process	(t^{-1})	Fitted
$\mathbf{n} \times \boldsymbol{K_i}$ ***or*** $\boldsymbol{K_{i1}}$	Monomer (M_1) mediated growth rate of the different unit of $(I_{k,} k = 1,2,3)$ and $(I_{ni}, n = 1,2,3; i = a, b, c, d)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{n} \times \boldsymbol{K_j}$ ***or*** $\boldsymbol{K_{j1}}$	Dissociation rate of the different unit of $(I_{k,} k = 2,3,4)$ and $(I_{ni}, n = 1,2,3; i = a, b, c, d)$, which produced from the monomer mediated process	(t^{-1})	Fitted
$\mathbf{K_a}$	Binding rate of the ThT with all type of unit of $(I_{k,} k = 1,2,3,4)$ and $(I_{ni}, n = 1,2,3; i = a, b, c, d)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_b}$	Dissociation rate of the ThT bounded complex of the corresponding unit of $(I_k ThT, k = 1,2,3,4)$ and $(I_{ni}ThT, n = 1,2,3; i = a, b, c, d)$	(t^{-1})	Fitted
$\mathbf{K_e}$	Transition rate of the highest-order intermediate unit $(I_k, k = 3,4)$ to basic minimum fibrillar (Case-1) unit (B_1) or transition rate of the lower-order fibrillar unit $(I_k, k = 3,4)$ to higher-order fibrillar (Case-2) unit (B_1)	(t^{-1})	Fitted

$\mathbf{K_f}$	Transition rate of the basic minimum fibrillar unit (B_1) to higher-order intermediate (Case-1) unit $(I_k, k = 3,4)$ or transition rate of the higher-order fibrillar unit (B_1) to lower-order fibrillar (Case-2) unit $(I_k, k = 3,4)$	(t^{-1})	Fitted
$\mathbf{K_c}$	Association rate of the minimum intermediate unit (I_l) with higher-order fibrillar (Case-1) unit $(B_l, l = 1,2)$ or self-assemble rate of minimum lower-order fibrillar unit (I_l) with higher order fibrillar (Case-2) unit $(B_l, l = 1,2)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_d}$	Dissociation rate of different fibrillar unit $(B_l, l = 2,3)$	(t^{-1})	Fitted
$\mathbf{n1 \times K_c}$ $\boldsymbol{or\ K_{c1}}$	Association rate or Secondary nucleation rate of the different fibrillar unit $(B_l, l = 1,2)\ and\ (B_{mi}, m = 1,2; i = a, b, c, d)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{n1 \times K_d}$ $\boldsymbol{or\ K_{d1}}$	Dissociation rate of the different fibrillar units $(B_{mi}, m = 1,2; i = a, b, c, d)$, which produced from secondary nucleation process	(t^{-1})	Fitted
$\mathbf{K_p}$	Binding rate of the ThT with all different fibrillar unit $(B_l, l = 1,2,3)$	$(\mu mol^{-1}t^{-1})$	Fitted
$\mathbf{K_q}$	Dissociation rate of the ThT bounded complex of the corresponding fibrillar unit $(B_l ThT, l = 1,2,3)$ and $(B_{mi} ThT, m = 1,2; i = a, b, c)$	(t^{-1})	Fitted
$\mathbf{F}$	Scaling factor that converts concentration of all species into the intensity	$(AU/\mu mol)$	Fitted
$\mathbf{S}$	Scaling factor that converts total concentration of species into the percentage of species	-	Fixed
$\mathbf{P}_{total}$	The total amount of protein concentration.	(μmol)	Fixed
$\mathbf{ThT}_{total}$	The total amount of Thioflavin T concentration.	(μmol)	Fixed

Table S4: Description of all parameters values of the best-fitted model optimized from proposed canonical models for each corresponding protein

Parameters	Lower bound	Upper bound	α-Syn [Model-1F]	Aβ42 [Model-2C]	Myb [Model-1C]	TTR [Model-1D]
K_x	0.0001	10000	4.548	1.39	1.9	1.216
K_y	0.0001	10000	0.0838	34.76	0.0056	0.311
K_{ac}	0.0001	10000	75.397	23.73	208.72	2.16
K_m	0.0001	10000	1.922	1.088	16.86	21.685
K_{mi}	0.0001	10000	343.0	10.7	16.59	1.653
K_s	0.0001	10000	1.065	5.92	1.73	35.3
K_t	0.0001	10000	1.88	2.83	31.77	8.954
K_i	0.0001	10000	34.09	18.68	22.23	3.47
K_j	0.0001	10000	2.925	7.745	2.034	3.44
K_{i1}	0.0001	10000	-	4.59	-	-
K_{j1}	0.0001	10000	-	0.639	-	-
K_e	0.0001	10000	0.418	5.16	139.4	1.547
K_f	0.0001	10000	0.174	4.25	3.62	0.411
K_c	0.0001	10000	172.85	1.02	11.13	10.893
K_d	0.0001	10000	79.52	0.833	4.32	0.88
K_{c1}	0.0001	10000	-	4.59	-	-
K_{d1}	0.0001	10000	-	8.14	-	-
K_a	0.0001	10000	0.986	12.48	38.105	1.315
K_b	0.0001	10000	797.78	7.674	228.26	28.32
K_p	0.0001	10000	0.86	1.23	12.24	1.4
K_q	0.0001	10000	38.39	35.38	3.87	1.354
n	0.0001	10000	0.56	-	18.27	0.308
n1	0.0001	10000	1.8	-	2.95	1.9
F	0.0001	1	0.0835	0.906	0.911	0.301
S	-	-	0.33	10	5	1.562
P_{total}	-	-	300	10	20	64
ThT_{total}	-	-	1000	10	25	10

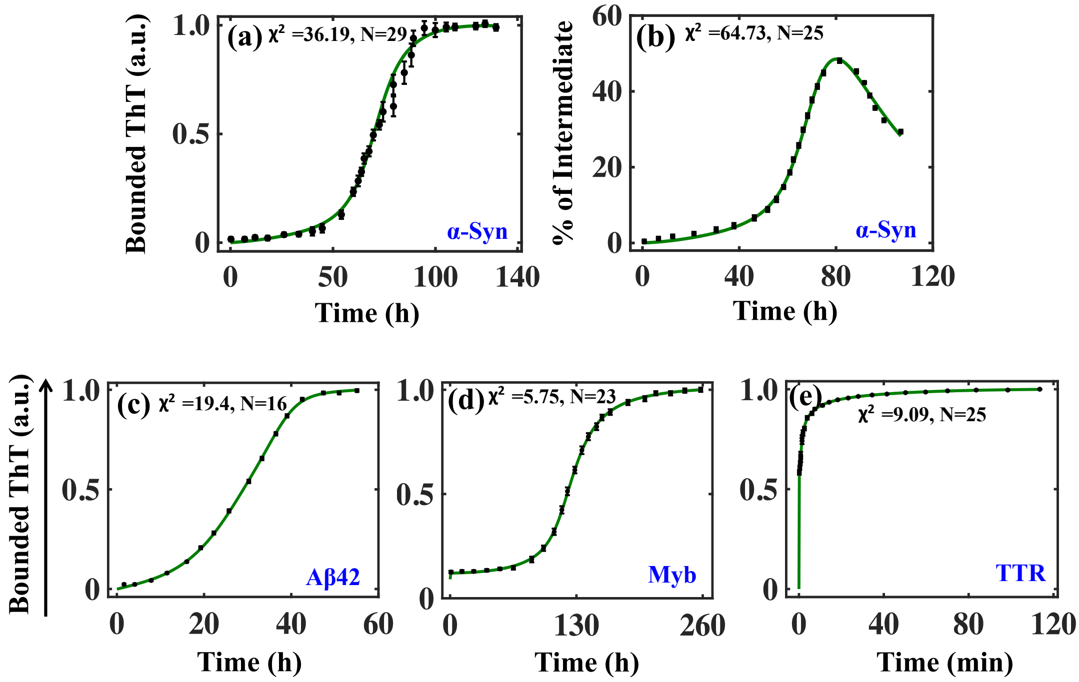


Fig. S4 Calibration of the best-optimized (~3000 fits) model variants with the experimental data set for each corresponding protein. The green solid lines represent the fitted trajectory and the black dots represents the experimental data set with error bars, the N indicates the total number of experimental data points. (a) The best-fitted trajectory ($\chi^2 = 100.92, AIC = 240.17$) of the total ThT bounded aggregates and (b) the time profile of the % of total partially folded intermediate aggregates, when Model-1F has been mapped simultaneously with the experimental data for α-Syn protein (300μM).[12] Fig (c) represents the simulated ThT bounded profile when Model-2C has been optimized ($\chi^2 = 19.39, AIC = 92.8$) taking protein aggregate data of Aβ42 protein (10μM).[9] (d) The best-fitted ($\chi^2 = 5.75, AIC = 88.02$) simulated time course response of the total ThT bounded aggregates obtained by performing global fitting of Model-1C with the experimental data points in case of Myb protein (20μM).[8] (e) The best-fitted trajectory ($\chi^2 = 9.09, AIC = 95.04$) of the total ThT bounded aggregates when Model-1D has been simulated with the experimental data of TTR protein (64μM).[11] For each case, the best-fitted trajectory has been obtained by calibrating corresponding model with ~ 3000 fit sequences (For more details see Section-2).

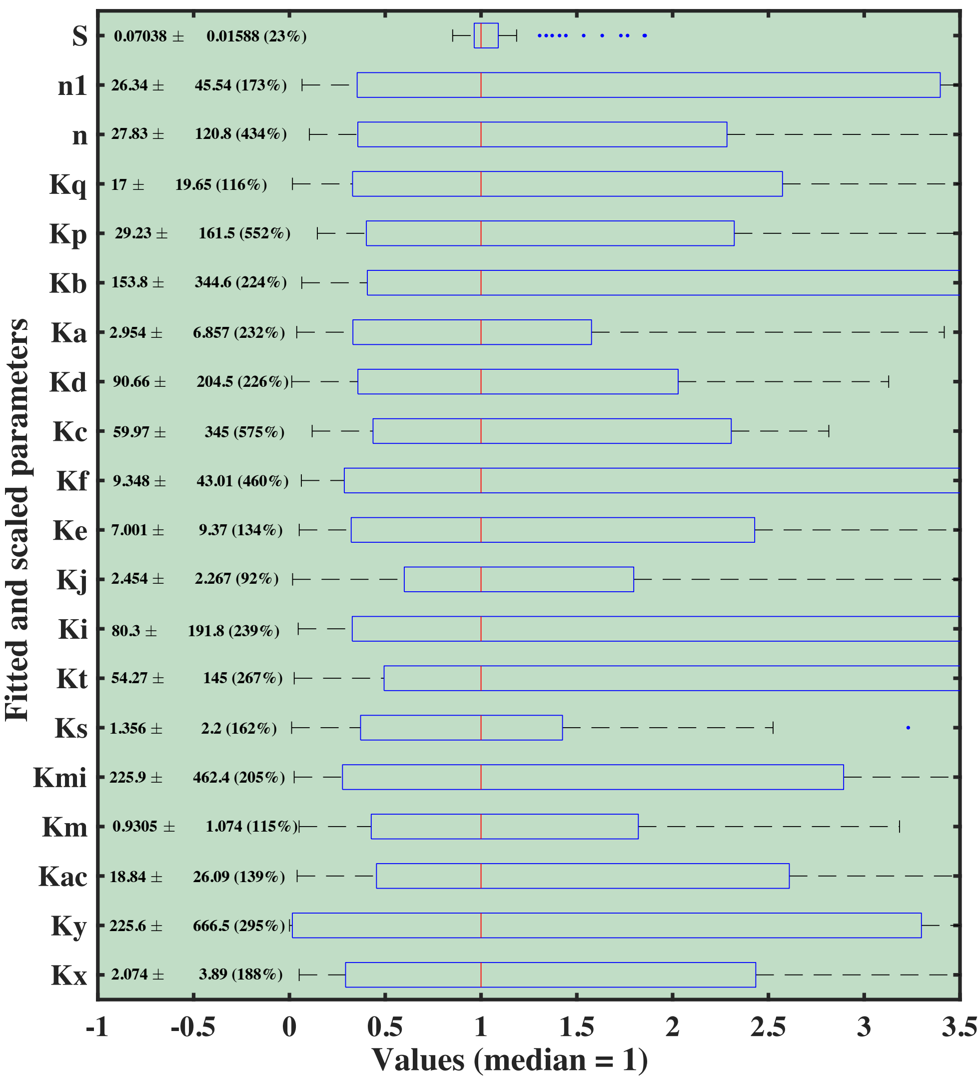


Fig. S5 Variance of the estimated parameters for α-Syn protein from fitting variant Model-1F. The boxplot of the parameter set of 2% best fits from ~3000 fits with median 1.

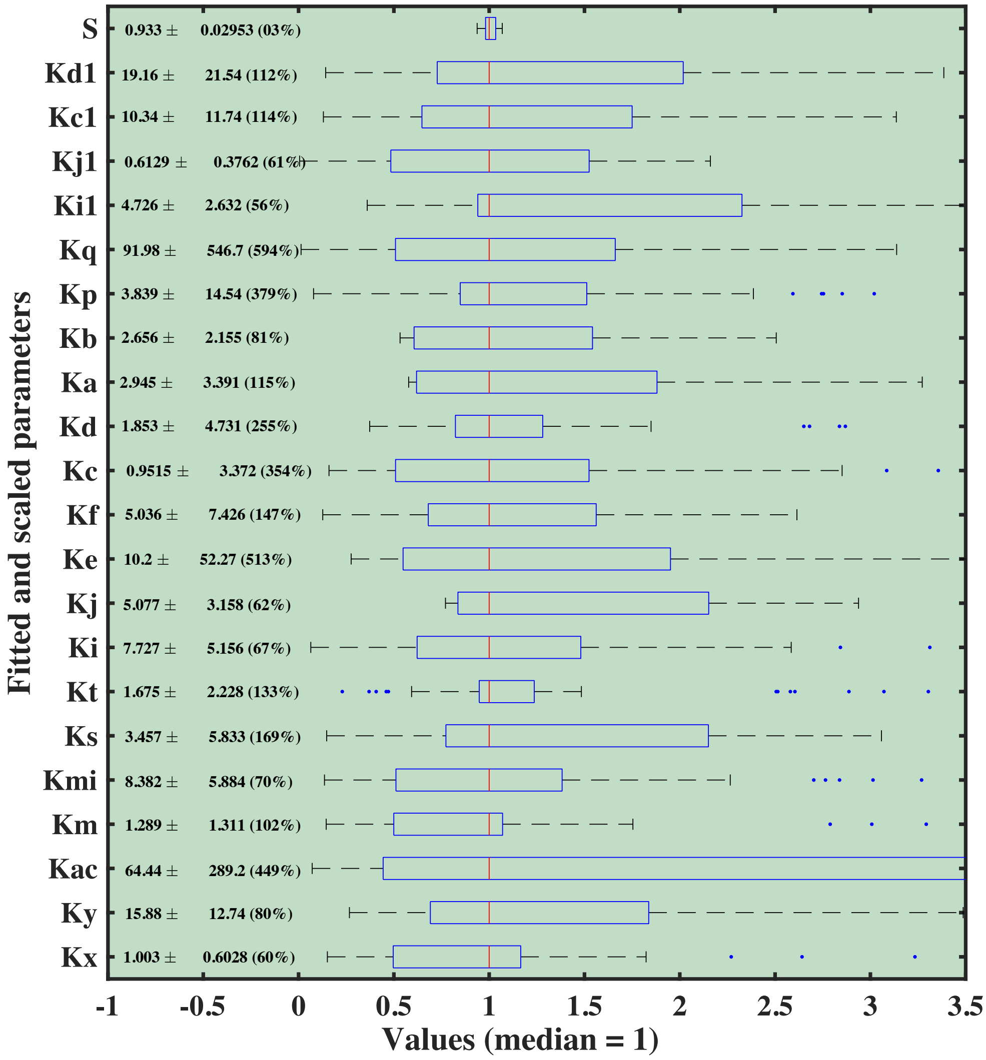


Fig. S6 Variance of the estimated parameters for Aβ42 protein from fitting variant Model-2C. The boxplot of the parameter set of 2% best fits from ~3000 fits with median 1. .

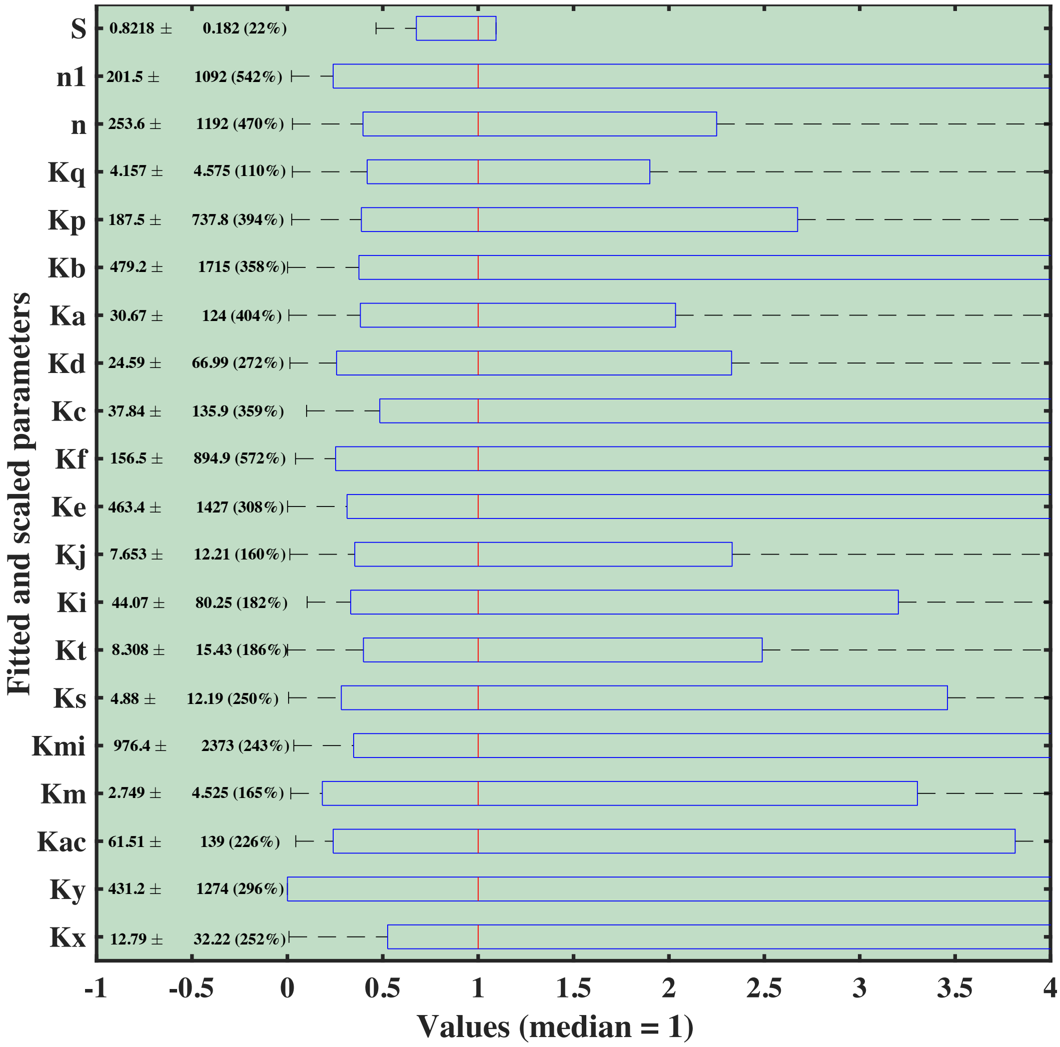


Fig. S7 Variance of the estimated parameters for Myb protein from fitting variant Model-1C. The boxplot of the parameter set of 2% fits from ~3000 fits with median 1.

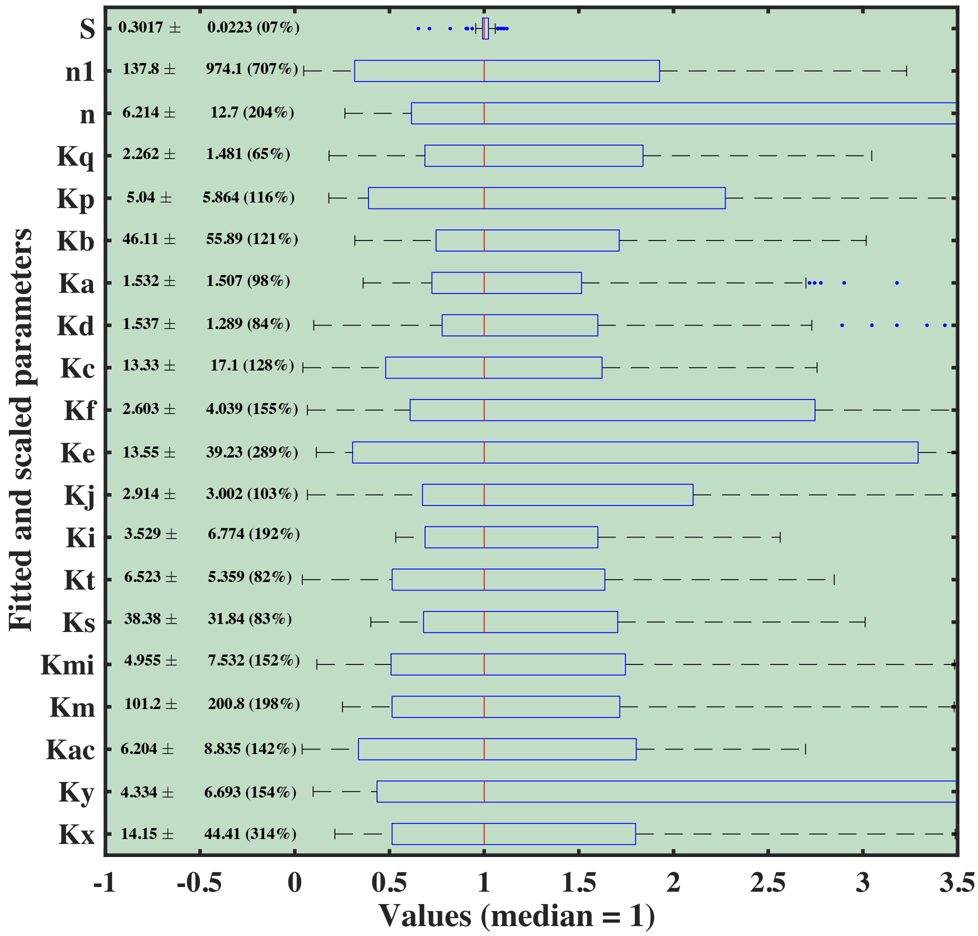


Fig. S8 Variance of the estimated parameters for TTR protein from fitting variant Model-1D. The boxplot of the parameter set of 2% best fits from ~3000 fits with median 1.

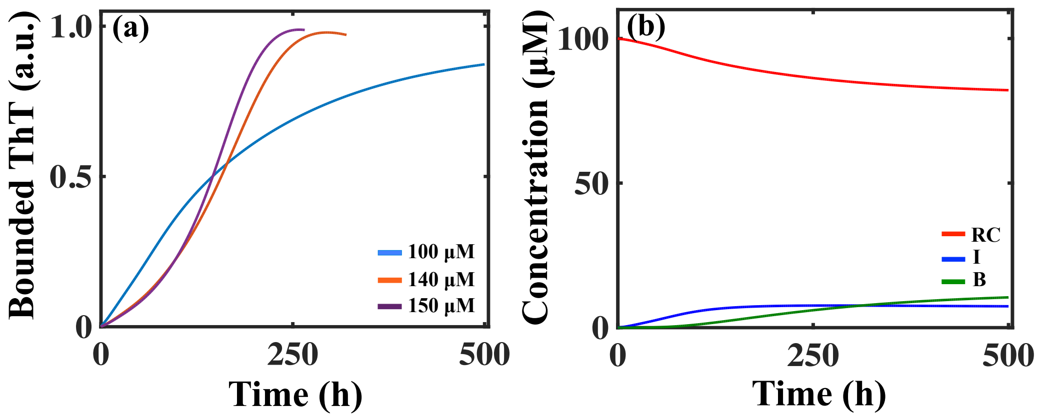


Fig. S9 Numerical analysis of the aggregation dynamics at low initial monomeric protein concentrations in case of α-Syn protein. (a) Time course simulation of Model-1F at $150\mu M, 140\mu M$, and $100\mu M$ total protein concentrations in case of α-Syn. Model simulations predict that for $100\mu M$ concentration, although the simulation has been done keeping the scaling factor at its highest value $F = 0.99$, the amyloid growth profile does not follow sigmoidal kinetics. (b) Model predicted time profile for random coil state (RC), partially folded intermediate (I) and β-sheet rich fibril (B) for $100\mu M$ total monomer protein concentration. The time profile of $(RC), (I) and\ (B)$ indicates that the protein remains mostly in its random coil state throughout the simulation.

This signifies the fact that a minimum concentration (here $140\mu M$ or above) is needed for the protein to drive the process of amyloidogenesis under the parametric condition provided in Table S4.

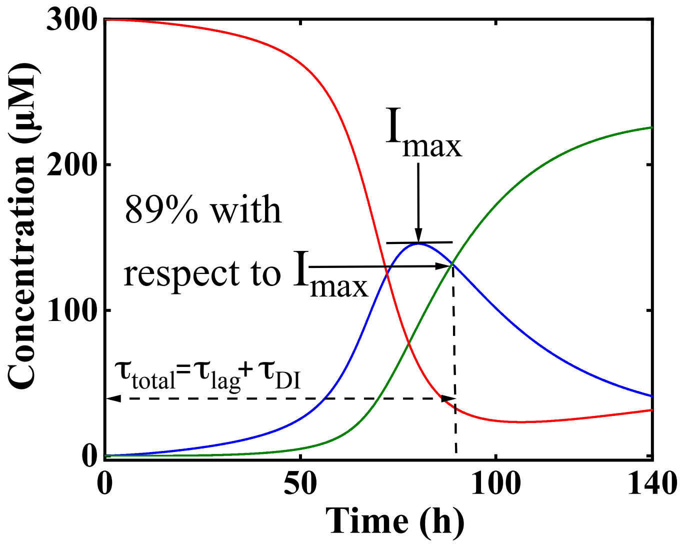


Fig. S10 Standard schematics for the estimation of the duration of the intermediate aggregates at any particular concentration of protein in case of α-Syn. Experimentally, the duration of the lag time (τ_{lag}) and the duration of the helical intermediate (τ_{DI}) for α-Syn protein at a particular protein concentration say, 300 μM, have been quantified by Ghosh *et al.*[12] We have plotted the simulated trajectories of (RC), (I) and (B) from the best-fitted Model-1F at that protein concentration (300 μM), where (RC), (I) and (B) stands for the total random coil state, total intermediate and total fibril like aggregate, respectively. It has been observed that the sum of the experimentally calculated (τ_{DI}) and (τ_{lag}) value i.e. (τ_{total}) corresponds to the time point of the simulated trajectory of intermediate (I), which is consistent with 89% drop with respect to the maximum level of the intermediate (I_{max}). Now, this observation helps us to set a criterion to find out the duration of intermediate (τ_{DI}) at any given concentration. We can simulate the trajectory for (RC), (I) and (B) at any given concentration using the best-fitted Model-1F under the given parametric domain (Table S4), where we can easily find out the (τ_{total}), which is 89% drop of (I_{max}) and consequently can calculate the (τ_{DI}) by subtracting the (τ_{lag}) from (τ_{total}).

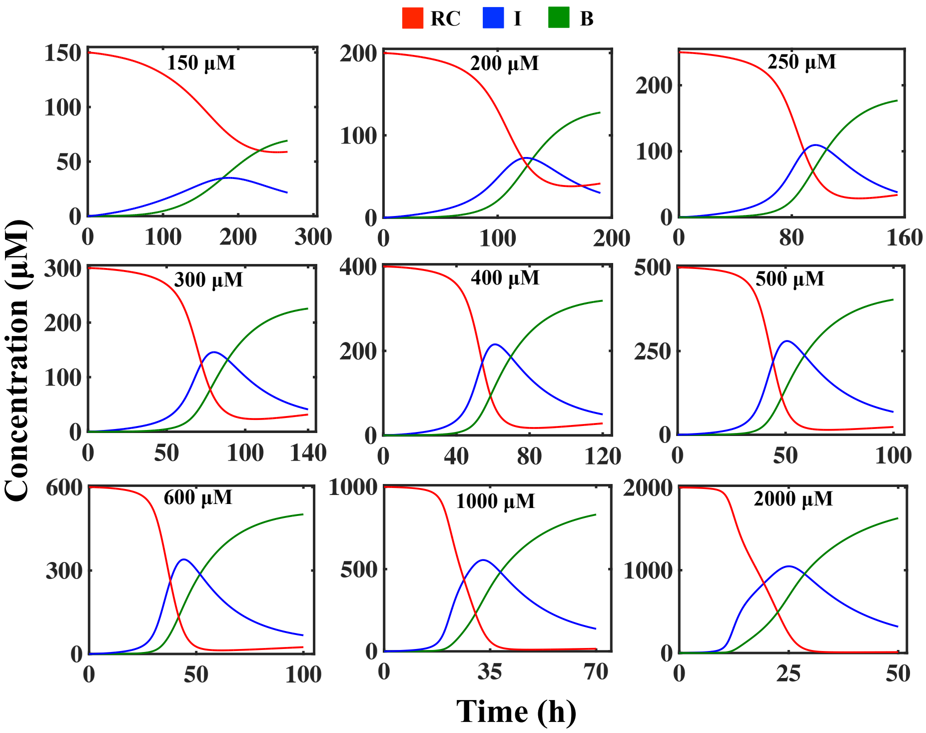


Fig. S11 The dynamical evolution of the (RC), (I), and (B) is rational with respect to total protein concentration in case of α-Syn. Model predicted time profiles of (RC) (random coil), (I) (Intermediate) and (B) (fibril) under different total protein concentrations corresponding to (i) 150 μM, (ii) 200 μM, (iii) 250 μM, (iv) 300 μM, (v) 400 μM, (vi) 500 μM, (vii) 600 μM (viii) 1000 μM and (IX) 2000 μM, respectively. The temporal timing equilibria between the conversions of (RC) to (I) to (B) not only control the phase transition (lag phase to rapid growth to saturation phase) but also maintain that how long the system will sustain in each phase. The time scales of the transformation of the unstructured monomeric unit to mature stable fibril depend totally on this crucial timing balance. Interestingly, from our observation, it has been found that these proportionate equilibria are totally concentration-dependent, and the transient evolution of the intermediate plays a very crucial role here. At low concentration, the intermediate structure assembled slowly at a later time point, which slows down the aggregation process. With increasing concentration, the (RC) rapidly converts to partially folded intermediate, which results sharpe decay of the intermediate aggregates and readily transform into β-sheet rich fibril, thereby enhancing the entire fibrillization mechanism.

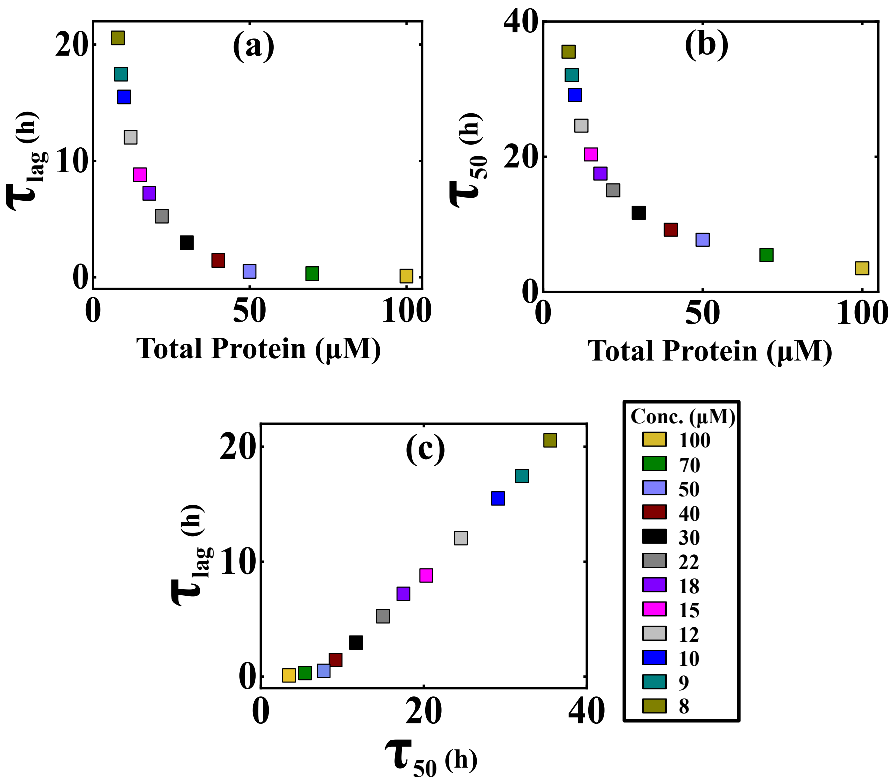


Fig. S12 The variation of (τ_{lag}) and (τ_{50}) and their correlation at different concentrations in case of Aβ42 protein. The (τ_{lag}) and the (τ_{50}) have been calculated for different concentrations by keeping the other rate constant similar as described in (Table S4) for Model-2C. (a) Schematic representation of the variation of (τ_{lag}) as a function of total protein concentration calculated from the model predicted simulated time-courses. The (τ_{lag}) is decreasing with an increment of the initial monomer concentration. (b) The model predicted value of (τ_{50}) with total protein concentration variation showed similar behavior as observed with (τ_{lag}). (c) A plot of (τ_{lag}) vs (τ_{50}) shows a higher degree of linear correlation at any given total protein concentration.

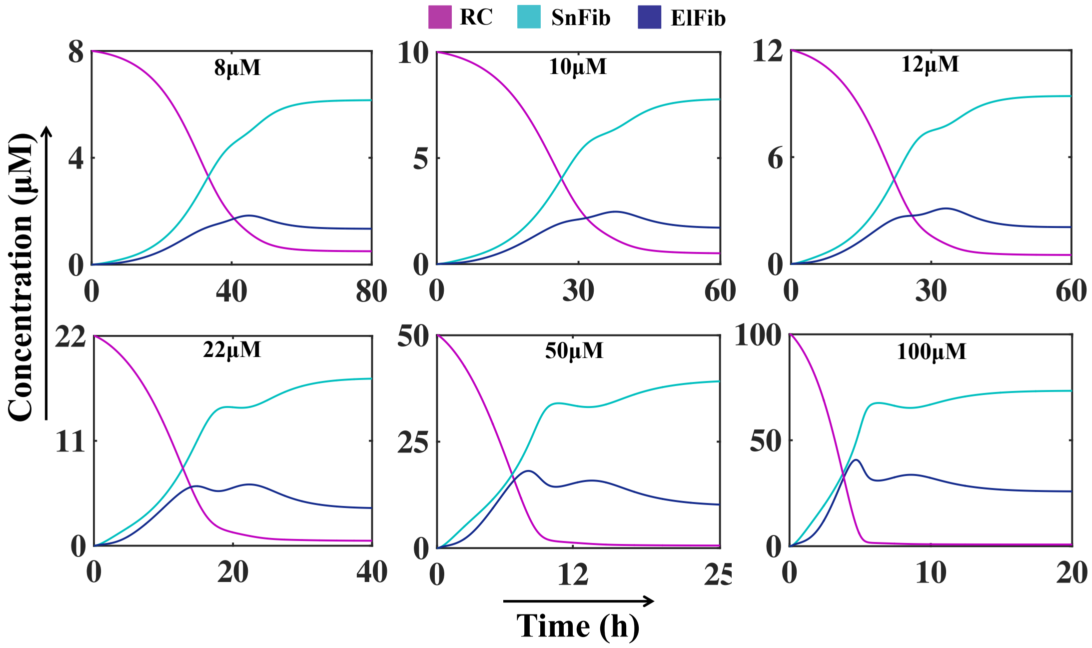


Fig. S13 The time evolution of the RC, SnFib, and ElFib for various total protein concentrations in case of Aβ42. We have plotted the simulated trajectories of RC (random coil structure), SnFib (fibril generated from monomer dependent process) and ElFib (Fibril generated through self-association mechanism) from the best-fitted Model-2C using the corresponding parameter set provided in (Table S4), total protein concentrations corresponding to (i) 8 μM, (ii) 10 μM, (iii) 12 μM, (iv) 22 μM, (v) 50 μM, (vi) 100 μM, respectively. The monomer-mediated fibril generation process predominantly controls the kinetics at any particular total protein concentration.

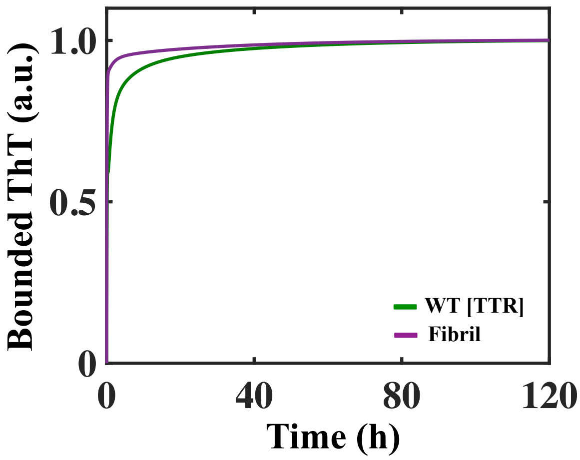


Fig. S14 Seeding effect on the aggregation kinetics of TTR protein. Accelerated kinetics of fibril formation in case of TTR protein when seeded with fibril ($B_1 = 1.0, B_2 = 1.0, B_3 = 1.0$) compared to WT protein. The trajectory was obtained by simulating the best-fitted Model-1D with set of the rate constant described in Table S4.[16]

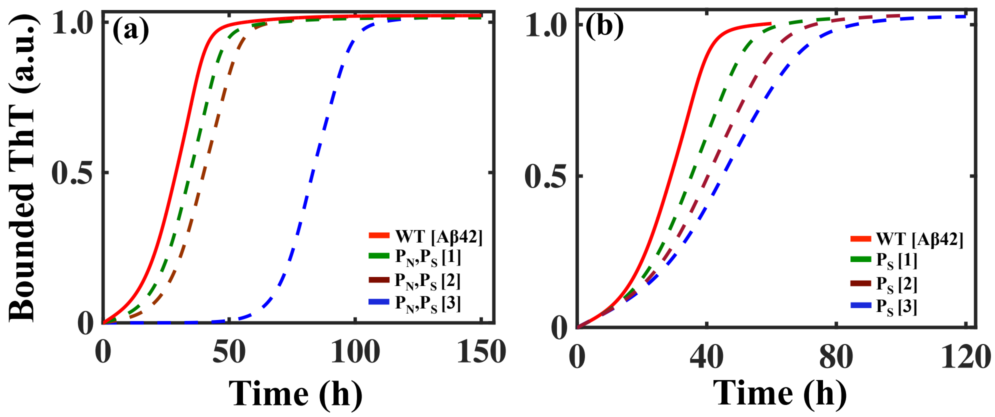


Fig. S15 Inhibition of the aggregation process of Aβ42 protein by the molecular chaperones DNAJB6 and human BRICHOS domain. Molecular chaperon, a natural inhibitor in living system have been known for several decades to have a key role to prevent aggregation mechanism, though the inhibition mechanism by these chaperones is significantly different. (a) The experimentally observed retardation in the Aβ42 protein aggregation in presence of the molecular chaperon DNJB6 can be captured by the model simulation via inhibiting the primary nucleation (P_N, associated rate constant, K_X) and monomer mediated fibril growth process (P_S, associated rate constant, K_{i1}) simultaneously ($\{K_X = 1.0, K_{i1} = 4.0, [1]\}, \{K_X = 0.78, K_{i1} = 3.5, [2]\}, \{K_X = 0.1, K_{i1} = 3.0, [3]\}$) at different extent in comparison to the WT (red solid line). (b) The inhibitory effect of molecular chaperon BRICHOS over Aβ42 protein aggregation can be reproduced via model simulation by specifically inhibiting the secondary nucleation process ($\{K_{i1} = 3.0, [1]\}, \{ K_{i1} = 2.3, [2]\}, \{ K_{i1} = 1.9, [3]\}$) in comparison to the WT (red solid line) scenario. All these findings remarkably corroborate with experimental observations.[17,18]

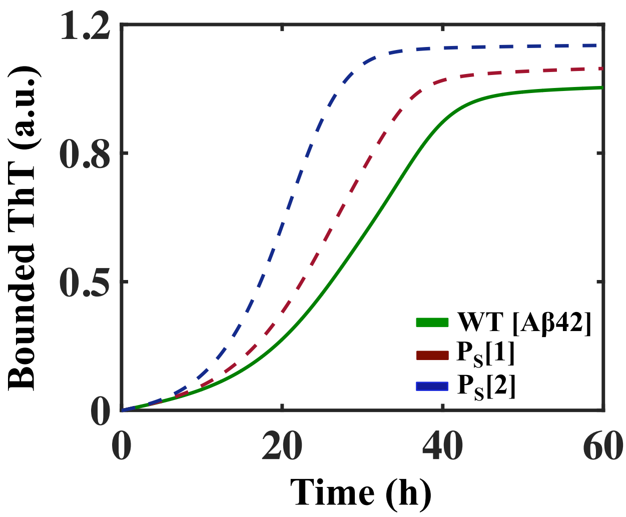


Fig. S16 Model predicts ways to alter the aggregation dynamics by perturbing monomer mediated growth process for Aβ42 protein. The kinetics of amyloid formation accelerates with increasing the rate K_j, $(\{K_j = 2 \times K_j(WT), [1]\}, \{ K_j = 10 \times K_j(WT), [2]\})$, which is the reverse rate of monomer mediated growth process of lower-order fibril K_i. Increasing the K_j, enhances the amount of lower ordered fibril, as a result, both the $(\tau_{50})$and (τ_{lag}) is getting reduced.

Section-2

A global approach to identify a most probable network of amyloidogenesis for different proteins by comparing an ensemble of model configurations by performing statistical analysis:

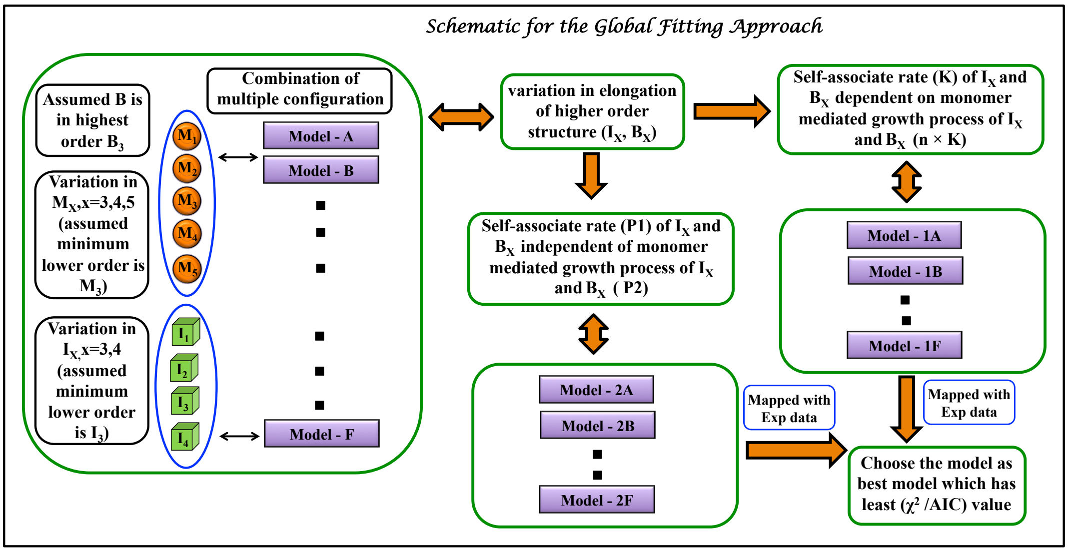


Fig. S17 Schematics for performing the global fitting procedure to identify the best-fitted model. We have considered different ensembles of models (Fig. S2(a-f)) and performed statistical operation by using a software "Potterswheel",[19] with the preferred experimental data set with each comprehensive model separately under the same simulation condition (Initially, each model has been optimized with ~500 fit sequences) and find out the model, which has the least χ^2 value (Table S5-S8). As the model configurations are different along with various rate constants, comparing only the χ^2 value is not sufficient to figure out the best model. So, we searched for an advanced criterion for comparing the competing models and find out the corresponding AIC value for all these variations (Table S5-S8). Thus, the best-fitted model has been sorted out from a set of probable models for each corresponding protein. This particular selected model variant has the highest configuration for the fibrillar unit as B_3, since we have assumed that the protein can have this order of highest degree for mature fibril. Thus with the help of the global fitting method, comparing and analyzing the χ^2 and corresponding AIC value (Table S5-S8), we finally got that Model-1F, Model-2C, Model-1C, and Model-1D is the best-optimized model for α-Syn, Aβ42, Myb, and TTR protein respectively.

Another key aspect in the protein aggregation event till now to be questioned whether the fibril elongation through self-association process and the fibril growth mechanism based on monomer mediated process is dependent or independent on each other. If these processes depend on each other, then whether there exists any correlation among these events. Also, we need to understand whether this is a generic property for protein. These probabilistic hypotheses have not been explored in the literature till now. We tried to enlighten these issues while searching for an optimum network model of amyloidogenesis. Hence, we tried to shed light on these aspects by focusing on the reaction fluxes of these different aggregation processes along with the configuration variation in the models that we considered in (Fig. S2(a-f)). In few instances, we assumed that the monomer dependent process $(K_{i1}/K_{j1}, K_{c1}/K_{d1})$ and the self-associated processes $(K_i/K_j, K_c/K_d)$ are totally independent ($(P1, P2)$ of Table S5-S8) of each other which has been depicted in different models $(Model - 2A, 2B, 2C, 2D, 2E, 2F)$. In other cases, we have approached that the monomer dependent process relies on the self-associated processes ($(n \times K)$ of Table S5-S8). To correlate these two process, we have fixed the rate constant for the self-associated process $(K_i/K_j, K_c/K_d)$ and described the rate constant of the monomer dependent processes by multiplying with another rate constant $(n, n1)$ with the rate constants of self-association process$(n \times K_i/n \times K_j, n1 \times K_c/n1 \times K_d)$. This allows the system to chooses the rate constant $(n, n1)$ such that it will always depend on the $(K_i/K_j, K_c/K_d)$, which has been described in $(Model - 1A, 1B, 1C, 1D, 1E, 1F)$. Crucially, it turns out that when the two different processes are mutually correlated, then models for α-Syn, Myb and TTR protein produce least χ^2 value, whereas the opposite phenomena is observed for Aβ42 protein, indicating that this is not a generic property.

Table S5: Probable set of combination of all models and their corresponding statistical perimeter for α-Syn protein

	Configuration variation						Reaction rate variation		χ^2 value	AIC value
	M_3	M_4	M_5	I_3	I_4	B_3	n × K	P1, P2		
Model-1A	✔	✖	✖	✔	✖	✔	✔	✖	185.32	324.56
Model-1B	✔	✔	✖	✔	✖	✔	✔	✖	178.1	323.35
Model-1C	✔	✔	✔	✔	✖	✔	✔	✖	131.55	270.79
Model-1D	✔	✖	✖	✔	✔	✔	✔	✖	209.94	349.18
Model-1E	✔	✔	✖	✔	✔	✔	✔	✖	141.26	280.5
Model-1F	✔	✔	✔	✔	✔	✔	✔	✖	117.86	257.1
Model-2A	✔	✖	✖	✔	✖	✔	✖	✔	197.35	340.59
Model-2B	✔	✔	✖	✔	✖	✔	✖	✔	193.64	336.88
Model-2C	✔	✔	✔	✔	✖	✔	✖	✔	243.94	387.19
Model-2D	✔	✖	✖	✔	✔	✔	✖	✔	226.89	370.13
Model-2E	✔	✔	✖	✔	✔	✔	✖	✔	206	349.25
Model-2F	✔	✔	✔	✔	✔	✔	✖	✔	151.48	294.73

Table S6: Probable set of combination of all models and their corresponding statistical perimeter for Aβ42 protein

	Configuration variation						Reaction rate variation		χ^2 value	AIC value
	M_3	M_4	M_5	I_3	I_4	B_3	n × K	P1, P2		
Model-1A	✔	✖	✖	✔	✖	✔	✔	✖	22.25	91.65
Model-1B	✔	✔	✖	✔	✖	✔	✔	✖	28.23	97.64
Model-1C	✔	✔	✔	✔	✖	✔	✔	✖	28.6	98
Model-1D	✔	✖	✖	✔	✔	✔	✔	✖	29.06	98.46
Model-1E	✔	✔	✖	✔	✔	✔	✔	✖	31.16	100.57
Model-1F	✔	✔	✔	✔	✔	✔	✔	✖	25.92	95.33
Model-2A	✔	✖	✖	✔	✖	✔	✖	✔	23.27	96.67
Model-2B	✔	✔	✖	✔	✖	✔	✖	✔	26.03	99.44
Model-2C	✔	✔	✔	✔	✖	✔	✖	✔	19.39	92.8
Model-2D	✔	✖	✖	✔	✔	✔	✖	✔	23.97	97.38
Model-2E	✔	✔	✖	✔	✔	✔	✖	✔	26.06	99.47
Model-2F	✔	✔	✔	✔	✔	✔	✖	✔	19.4	92.8

Table S7: Probable set of combination of all models and their corresponding statistical perimeter for Myb protein

	Configuration variation						Reaction rate variation		χ^2 value	AIC value
	M_3	M_4	M_5	I_3	I_4	B_3	n × K	P1, P2		
Model-1A	✔	✖	✖	✔	✖	✔	✔	✖	95.59	177.86
Model-1B	✔	✔	✖	✔	✖	✔	✔	✖	26.87	109.1
Model-1C	✔	✔	✔	✔	✖	✔	✔	✖	5.75	88.02
Model-1D	✔	✖	✖	✔	✔	✔	✔	✖	189.79	272.07
Model-1E	✔	✔	✖	✔	✔	✔	✔	✖	160.5	662.75
Model-1F	✔	✔	✔	✔	✔	✔	✔	✖	168.9	251.2
Model-2A	✔	✖	✖	✔	✖	✔	✖	✔	101.34	187.6
Model-2B	✔	✔	✖	✔	✖	✔	✖	✔	28.71	114.98
Model-2C	✔	✔	✔	✔	✖	✔	✖	✔	69.95	156.223
Model-2D	✔	✖	✖	✔	✔	✔	✖	✔	111.45	197.72
Model-2E	✔	✔	✖	✔	✔	✔	✖	✔	118.46	204.73
Model-2F	✔	✔	✔	✔	✔	✔	✖	✔	122.44	208.72

Table S8: Probable set of combination of all models and their corresponding statistical perimeter for TTR protein

	Configuration variation						Reaction rate variation		χ^2 value	AIC value
	M_3	M_4	M_5	I_3	I_4	B_3	n × K	P1, P2		
Model-1A	✔	✖	✖	✔	✖	✔	✔	✖	10.43	96.38
Model-1B	✔	✔	✖	✔	✖	✔	✔	✖	10.3	96.25
Model-1C	✔	✔	✔	✔	✖	✔	✔	✖	14.1	100.05
Model-1D	✔	✖	✖	✔	✔	✔	✔	✖	9.09	95.04
Model-1E	✔	✔	✖	✔	✔	✔	✔	✖	16.69	102.64
Model-1F	✔	✔	✔	✔	✔	✔	✔	✖	14.24	100.2
Model-2A	✔	✖	✖	✔	✖	✔	✖	✔	10.45	100.4
Model-2B	✔	✔	✖	✔	✖	✔	✖	✔	13.33	103.28
Model-2C	✔	✔	✔	✔	✖	✔	✖	✔	15.2	105.15
Model-2D	✔	✖	✖	✔	✔	✔	✖	✔	9.89	99.8
Model-2E	✔	✔	✖	✔	✔	✔	✖	✔	11.37	101.32
Model-2F	✔	✔	✔	✔	✔	✔	✖	✔	13.91	103.9

Section-3

Description of the different microscopic processes involved in the aggregation mechanism

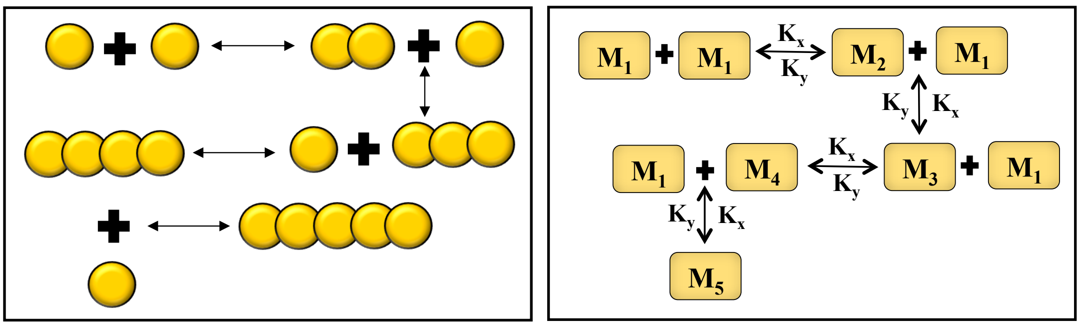
The first step in the protein aggregation processes is the nucleation which mainly occurs in the lag phase, where natively structured or unstructured protein slowly self-associates to form the nucleus which is the critical unit for fibril formation.[10] This step is slow because it is a thermodynamically unfavorable process. The subsequent step is the elongation phase, where elongation nuclei readily convert to fibril through monomer addition to the nuclei or association of the fibril nuclei itself. The third step is the stationary phase where the fibril formation process almost gets completed. The probable interaction network (Fig. S2(a-f)) has been converted into sets of the ordinary differential equation using simple mass-action kinetics, which has been described in **Section-4**. Here, we have assumed that the filament or fibril size could change by only association or dissociation reaction. Experimentally, it has been found that most of the intrinsically disordered protein can remain as natively unfolded structure under various physiological conditions and can slowly get converted into different form of oligomeric structures upon incubation for longer time. Thus, the total protein concentration can easily be expressed as the sum of all oligomeric states including monomer. The aggregation mechanism involves multi-step processes like nucleation, conformational transition, and elongation. The individual steps of the aggregation mechanism are described below:

STEP-1: Primary Nucleation Process (P_N)

The protein in the solution can exist as natively unfolded random coil structure or any other structure. The first important process in the aggregation is the formation of the nucleus. The monomer of random coil state (M_1) (or initial structure) self-associates to form dimer (M_2), which again binds with monomer (M_1) to form trimer (M_3) and consequently, it can be extended up to pentamer, (M_5). Here, to mention that the protein could attain any structural degree for forming the nucleus. To keep simple our strategy, we have assumed that the highest degree of the nucleus can be trimer, tetramer or pentamer for different ensemble models. This mechanism is quite slow as it is thermodynamically unfavorable process.[20]

STEP-1: Primary Nucleation Process (P_N)

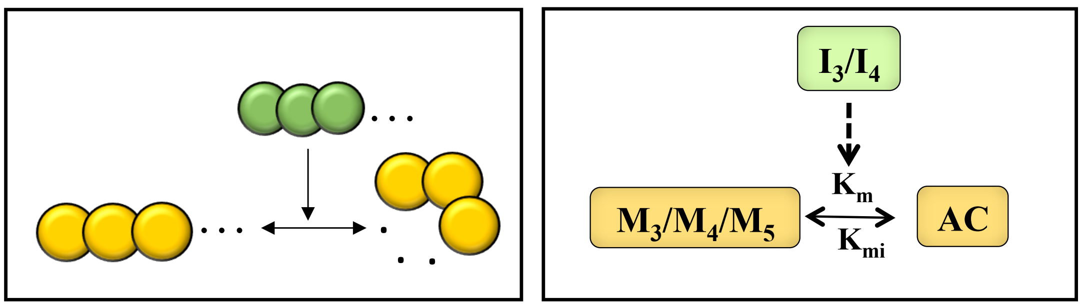
Reversible association of the primary non-fibrillar M_x molecule



STEP-2: Reversible Rearrangement from M_3 /M_4 /M_5 molecule to critical assemble state AC (S_P and S_F)

Until now, we have assumed that the initial self-association of protein occurs without any significant conformational transition (or change in conformation by individual protein structure is very low). Now, the corresponding nucleus (M_3, M_4, M_5) can undergo a reversible structural rearrangement to form a critical state (AC) as reported for both structured as well as natively unstructured protein undergoing amyloidogenesis.[21,22] We termed this as critical assembled state (AC) as it is essential or obligatory for the amyloid formation. The formation of critical assembled state (AC) can be further facilitated (S_F) by the highest ordered elongation unit (maybe (I_3) or (I_4), depends on probable interaction network). This conformational transition is assumed to be faster compared to the nucleation process.[23]

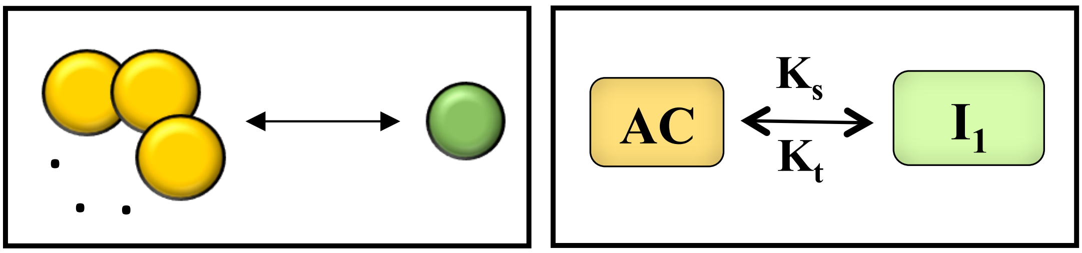
STEP-2: Reversible Rearrangement of the self-assembled random coil structure to a critical assembled state (S_P and S_F)



STEP-3: Reversible conformational transition from AC to either basic intermediate unit or basic fibrillar unit I_1 (T_E)

Previous aggregation studies by various proteins and peptides showed that some native structured and unstructured protein self-associate to form partially folded intermediate before converting to fibrils (Case-1)[12,24], whereas some natively unstructured proteins may transition from random coil to β-sheet rich fibril directly (Case-2)[8,9,11] Our model can be applied for all these kinds of aggregate-prone proteins. Here, to declare that as suitable and simultaneous experimental data set for ThT binding for fibrillation and along with the kinetics data for intermediate is not available, so we took only the ThT kinetic data for the overall fibrillation process for Aβ42 protein. Thereafter, we categorized this protein as Case-2, though experimentally people have identified the presence of intermediate aggregates during aggregation of Aβ42 protein.[25,26] We consider that this critical assembled state (AC), can convert to basic minimal partially folded intermediate unit (I_1) by conformational transition, which can be used as seed for the growth of the fibril (Case-1). For other types of protein (Case-2), the (AC) can transit to form to basic minimal lower-order fibrillar unit I_1. Now, the basic units (I_n) can grow itself through lateral association via (I_1) following the elongation mechanism.

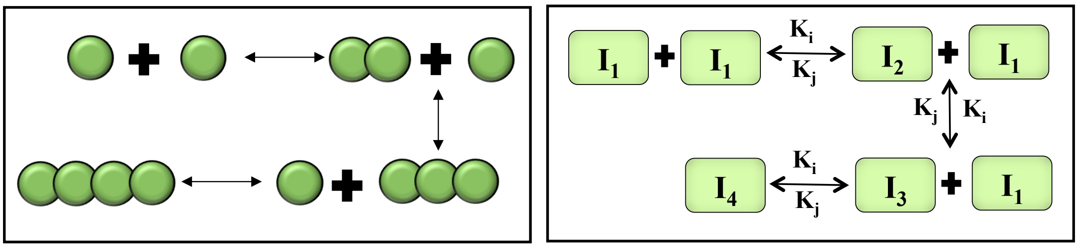
STEP-3: Reversible conformational transition from AC to either basic intermediate unit or basic fibrillar unit, (T_E)



STEP-4: Elongation process of the partially folded intermediate unit (Case-1) or lower ordered fibrillar unit (Case-2) (E_I)

The process of elongation can happen via the self-association mechanism. We first assume that the elongation process initiates when the basic unit (I_1) self-associates to produce the dimer (I_2), which further binds to another basic unit (I_1) to form the trimer (I_3). Finally, the highest order elongation unit (can be (I_3) or (I_4), depends on probable interaction network) has been formed. However, we must emphasize the fact that experimentally it is very difficult to predict up to what extent this kind of self-association of the basic unit will proceed. In our modeling setup, we assume that the highest structural degree could be up to tetrameric form.

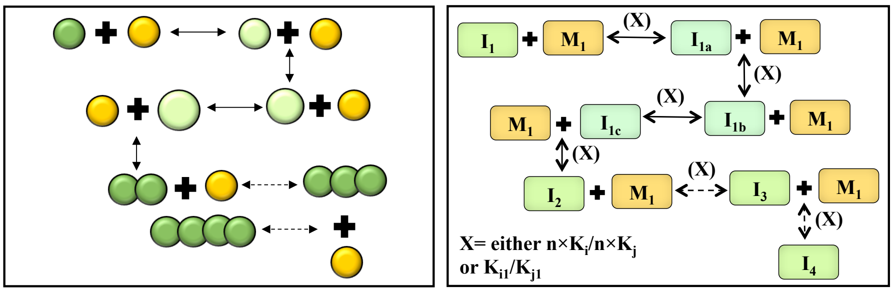
STEP-4: Elongation process of the partially folded intermediate unit (Case-1) or lower ordered fibrillar unit (Case-2) (E_I)



STEP-5: Monomer mediated growth process of the partially folded intermediate unit (Case-1) or lower ordered fibrillar unit (Case-2) (P_S)

Another possible mechanism for the elongation process is that monomer of random coil state (M_1) can bind with the basic intermediate unit or lower-order fibrillar unit (I_1) and start forming the next higher ordered aggregate units. The process begins with the basic unit (I_1) binding with (M_1) to produce the corresponding higher unit (I_{1a}). (I_{1a}) can further associate with (M_1) to give (I_{1a}) and can sequentially produce intermediate structure (I_{1k}) and finally give next higher-order structure (I_2). Similarly, this process can continue for (I_2) and so on (I_{nk}). So, the basic unit (I_n) has two possible ways by which it can form next higher-order unit (I_{n+1}), one via self-association process and another one is binding with monomer (M_1). Here, to mention that how much monomeric units (M_1) will bind with (I_n) that depends on the highest structure of $(M_x, if\ x = 3,\ k = a, b; if\ x = 4, k = a, b, c; if\ x = 5, k = a, b, c, d)$ to keep the mass balance of the system.

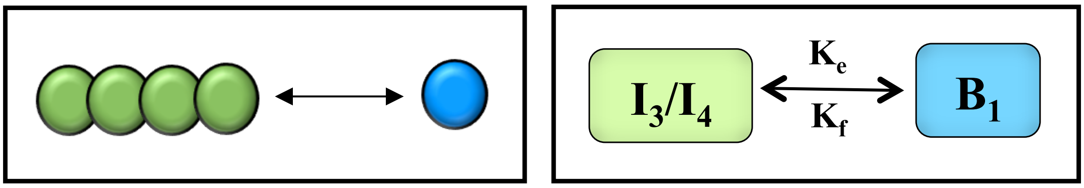
STEP-5: Monomer mediated growth process of the partially folded intermediate unit (Case-1) or lower ordered fibrillar unit (Case-2) (P_S)



STEP-6: Reversible conformational transition to basic minimal fibrillar unit (T_F)

We assumed once the highest ordered elongation unit (I_3/I_4) is formed through self-association process or monomer mediated elongation process, it could transit into a more ordered stable basic minimum unit of mature fibril like conformation (B_1).

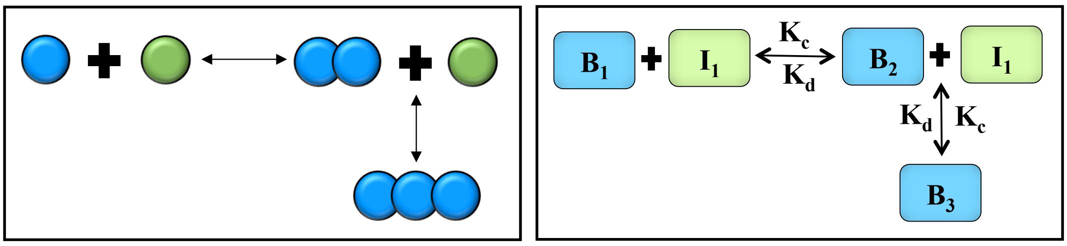
STEP-6: Reversible conformational transition to basic minimal fibrillar unit (T_F)



STEP-7: Elongation process of the fibrillar unit (E_F)

Next, fibril units can laterally associate together and grow in size to form higher-ordered amyloid fibrils. The (B_1) in our model refers to the basic minimum unit of the higher-order fibril. First, this basic fibril unit (B_1) can assemble with the (I_1) to form the higher order-fibrillar unit like (B_2). The (B_2) can further bind with (I_1) and thus can elongate to form higher-ordered thermodynamically most favorable stable fibrillar structure (B_3). We have assumed that (B_3) is the highest structural form of fibril that can be achieved through assembling reaction and every step of this process is reversible.

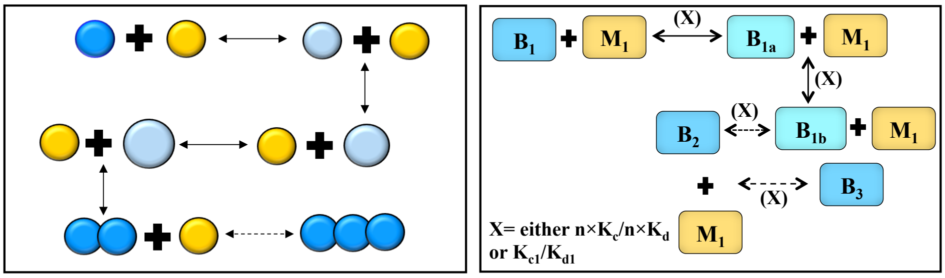
STEP-7: Elongation process of the fibrillar unit (E_F)



STEP-8: Secondary Nucleation process of the Fibril (P_{N2})

In principle, the most important thermodynamically favorable and rapid process that happens during stable fibril-like structure formation is the secondary nucleation process. The secondary nucleation requires the presence of basic minimal unit of fibril (B_1), which can bind to monomer $(M_1)_,$ and thus fibrils can grow in size. In our model, we have incorporated this phenomenon as well. We assumed that the monomer of random coil (M_1) can associate with the basic fibril unit (B_1) to give rise to an intermediate fibril unit (B_{1k}) that can again bind with the monomer of random coil (M_1) to form (B_{1b}) and so on. Again, to keep the mass balance of the system, how much monomeric units (M_1) will bind with (B_n) that depends on the highest structure of $(M_x, if\ x = 3,\ \ k = a, b; if\ x = 4, k = a, b, c; if\ x = 5, k = a, b, c, d)$. A similar kind of elongation mechanism is considered to produce (B_2) from (B_3) via a range of intermediate fibrillar structures. The secondary nucleation process is assumed to be very fast and reversible.

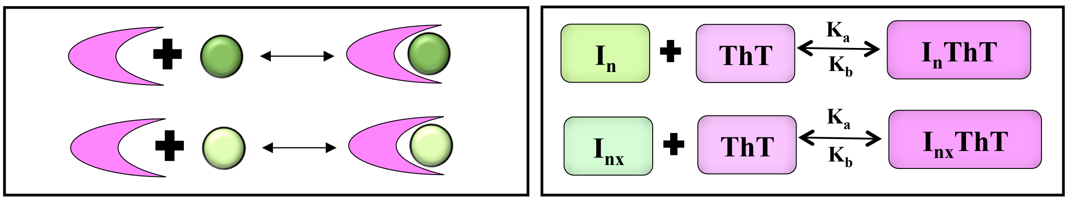
STEP-8: Secondary Nucleation process of the Fibril (P_{N2})



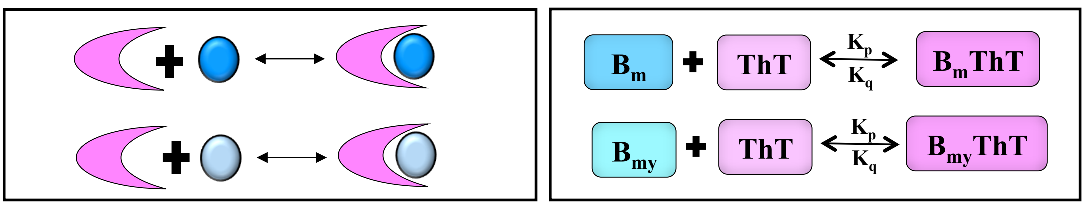
STEP-9 & 10: Reversible Complex formation process between Thioflavin T dye molecule (ThT) with the intermediate unit and fibril unit

There are many biophysical techniques through which many physiological properties like fibril length measurement, secondary structure identification, kinetic study through ThT measurement can be observed that help us to understand and analyze the fibrillation process. As in this work, we mainly focus on the kinetic study and in most cases the sigmoidal kinetic has been followed by Thioflavin T dye (ThT), we have incorporated the ThT interaction with amyloid or intermediate unit in our model. It is well known that ThT can only bind with the secondary structure of the protein (intermediate or fibril), but at which point it starts binding with the structures is not specified. We have considered that ThT can bind reversibly with all the intermediate units and consequently with fibril units. We further assumed that the binding efficiency of ThT with all the types of intermediate or lower-order fibrillar units is same, having the same association (K_a) and dissociation (K_b) rate constant. Similarly, all the mature fibrils bind with the ThT with same efficiency, consisting the same association (K_p) and dissociation (K_q) rate constant though it is different from intermediate or lower-order fibril binding efficiency.

STEP-9: Reversible Complex formation process between the intermediate or lower-order fibril and Thioflavin T dye



STEP-10: Reversible Complex formation process between mature fibril and Thioflavin T dye



Section-4

Ordinary Differential equations for different network configurations (Fig. S2(a-f)):

Ordinary differential equations (ODE) describing the interaction network for different ensemble models.

Model-1A/Model-2A

The Model-1A and Model-2A have similar configuration containing an equal number of ODE (31) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1A

$$\frac{dM_2}{dt} = \left((K_x \times M_1^2) - (K_y \times M_2) - (K_x \times M_1 \times M_2) + (K_y \times M_3)\right) \tag{1}$$

$$\frac{dM_3}{dt} = \left((K_x \times M_1 \times M_2) - (K_y \times M_3) - (K_m \times M_3) + (K_{mi} \times AC) - (K_{ac} \times M_3 \times I_3)\right) \tag{2}$$

$$\frac{dAC}{dt} = ((K_{ac} \times M_3 \times I_3) + (K_m \times M_3) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1)) \tag{3}$$

$$\begin{aligned}\frac{dI_1}{dt} = \Big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) \\ - (n \times K_i \times I_1 \times M_1) + (n \times K_j \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) \\ - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1 ThT)\Big)\end{aligned} \tag{4}$$

$$\begin{aligned}\frac{dI_2}{dt} = \Big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_2 \times M_1) \\ + (n \times K_j \times I_{2a}) + (n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_2) - (K_a \times I_2 \times ThT) \\ + (K_b \times I_2 ThT)\Big)\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{dI_3}{dt} = \Big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_e \times I_3) + (K_f \times B_1) + (n \times K_i \times I_{2b} \times M_1) \\ - (n \times K_j \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\Big)\end{aligned} \tag{6}$$

$$\begin{aligned}\frac{dB_1}{dt} = \Big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) \\ + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\Big)\end{aligned} \tag{7}$$

$$\begin{aligned}\frac{dB_2}{dt} = \Big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1b} \times M_1) \\ - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) \\ + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\Big)\end{aligned} \tag{8}$$

$$\begin{aligned}\frac{dB_3}{dt} = \Big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_3) \\ - (K_p \times B_3 \times ThT) + (K_q \times B_3 ThT)\Big)\end{aligned} \tag{9}$$

$$\begin{aligned}\frac{dI_{1a}}{dt} = \Big((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) \\ - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\Big)\end{aligned} \tag{10}$$

$$\begin{aligned}\frac{dI_{1b}}{dt} = \Big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_2) \\ - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\Big)\end{aligned} \tag{11}$$

$$\begin{aligned}\frac{dI_{2a}}{dt} = \Big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) \\ - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\Big)\end{aligned} \tag{12}$$

	$\frac{dI_{2b}}{dt} = \left((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\right)$	(13)
	$\frac{dB_{1a}}{dt} = \left((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\right)$	(14)
	$\frac{dB_{1b}}{dt} = \left((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\right)$	(15)
	$\frac{dB_{2a}}{dt} = \left((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\right)$	(16)
	$\frac{dB_{2b}}{dt} = \left((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\right)$	(17)
	$\frac{dI_1ThT}{dt} = \left((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\right)$	(18)
	$\frac{dI_2ThT}{dt} = \left((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\right)$	(19)
	$\frac{dI_3ThT}{dt} = \left((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\right)$	(20)
	$\frac{dB_1ThT}{dt} = \left((K_p \times B_1 \times ThT) - (K_q \times B_1ThT)\right)$	(21)
	$\frac{dB_2ThT}{dt} = \left((K_p \times B_2 \times ThT) - (K_q \times B_2ThT)\right)$	(22)
	$\frac{dB_3ThT}{dt} = \left((K_p \times B_3 \times ThT) - (K_q \times B_3ThT)\right)$	(23)
	$\frac{dI_{1a}ThT}{dt} = \left((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\right)$	(24)
	$\frac{dI_{1b}ThT}{dt} = \left((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\right)$	(25)
	$\frac{dI_{2a}ThT}{dt} = \left((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\right)$	(26)
	$\frac{dI_{2b}ThT}{dt} = \left((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\right)$	(27)
	$\frac{dB_{1a}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1a}ThT)\right)$	(28)
	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1b} \times ThT) - (K_q \times B_{1b}ThT)\right)$	(29)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT)\right)$	(30)

	$\frac{dB_{2b}ThT}{dt} = \left(\left(K_p \times B_{2b} \times ThT\right) - \left(K_q \times B_{2b}ThT\right)\right)$	(31)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 3 \times AC + 3 \times I_1 + 3 \times I_1ThT + 4 \times I_{1a} + 4 \times I_{1a}ThT + 5 \times I_{1b} + 5 \times I_{1b}ThT + 6 \times I_2 + 6 \times I_2ThT + 7 \times I_{2a} + 7 \times I_{2a}ThT + 8 \times I_{2b} + 8 \times I_{2b}ThT + 9 \times I_3 + 9 \times I_3ThT + 9 \times B_1 + 9 \times B_1ThT + 10 \times B_{1a} + 10 \times B_{1a}ThT + 11 \times B_{1b} + 11 \times B_{1b}ThT + 12 \times B_2 + 12 \times B_2ThT + 13 \times B_{2a} + 13 \times B_{2a}ThT + 14 \times B_{2b} + 14 \times B_{2b}ThT + 15 \times B_3 + 15 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = F \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_3ThT)$	(1)
	$\%\ of\ I = S \times (3 \times I_1 + 3 \times I_1ThT + 4 \times I_{1a} + 4 \times I_{1a}ThT + 5 \times I_{1b} + 5 \times I_{1b}ThT + 6 \times I_2 + 6 \times I_2ThT + 7 \times I_{2a} + 7 \times I_{2a}ThT + 8 \times I_{2b} + 8 \times I_{2b}ThT + 9 \times I_3 + 9 \times I_3ThT)$	(2)

ODE for Model-2A

	Equations different from Model-1A	
	$\frac{dI_1}{dt} = \left((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + \left(2 \times K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (K_{i1} \times I_1 \times M_1) + \left(K_{j1} \times I_{1a}\right) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\right)$	(4)
	$\frac{dI_2}{dt} = \left((K_i \times I_1^2) - \left(K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (K_{i1} \times I_2 \times M_1) + \left(K_{j1} \times I_{2a}\right) + (K_{i1} \times I_{1b} \times M_1) - \left(K_{j1} \times I_2\right) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\right)$	(5)
	$\frac{dI_3}{dt} = \left((K_i \times I_1 \times I_2) - \left(K_j \times I_3\right) - (K_e \times I_3) + \left(K_f \times B_1\right) + (K_{i1} \times I_{2b} \times M_1) - \left(K_{j1} \times I_3\right) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\right)$	(6)
	$\frac{dB_1}{dt} = \left((K_e \times I_3) - \left(K_f \times B_1\right) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + \left(K_q \times B_1ThT\right)\right)$	(7)
	$\frac{dB_2}{dt} = \left((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + \left(K_q \times B_2ThT\right)\right)$	(8)
	$\frac{dB_3}{dt} = \left((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_3) - \left(K_p \times B_3 \times ThT\right) + \left(K_q \times B_3ThT\right)\right)$	(9)

	$$\frac{dI_{1a}}{dt} = \big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a}ThT)\big)$$	(10)
	$$\frac{dI_{1b}}{dt} = \big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b}ThT)\big)$$	(11)
	$$\frac{dI_{2a}}{dt} = \big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a}ThT)\big)$$	(12)
	$$\frac{dI_{2b}}{dt} = \big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\big)$$	(13)
	$$\frac{dB_{1a}}{dt} = \big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\big)$$	(14)
	$$\frac{dB_{1b}}{dt} = \big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\big)$$	(15)
	$$\frac{dB_{2a}}{dt} = \big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\big)$$	(16)
	$$\frac{dB_{2b}}{dt} = \big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\big)$$	(17)

Model-1B/Model-2B

The Model-1B and Model-2B have similar configuration containing an equal number of ODE (40) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1B

	$$\frac{dM_2}{dt} = \big((K_x \times M_1^2) - (K_y \times M_2) - (K_x \times M_1 \times M_2) + (K_y \times M_3)\big)$$	(1)
	$$\frac{dM_3}{dt} = \big((K_x \times M_1 \times M_2) - (K_y \times M_3) - (K_x \times M_1 \times M_3) + (K_y \times M_4)\big)$$	(2)
	$$\frac{dM_4}{dt} = \big((K_x \times M_1 \times M_3) - (K_y \times M_4) - (K_m \times M_4) + (K_{mi} \times AC) - (K_{ac} \times M_4 \times I_3)\big)$$	(3)
	$$\frac{dAC}{dt} = \big((K_{ac} \times M_4 \times I_3) + (K_m \times M_4) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1)\big)$$	(4)
	$$\frac{dI_1}{dt} = \big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_1 \times M_1) + (n \times K_j \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\big)$$	(5)
	$$\frac{dI_2}{dt} = \big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_2 \times M_1) + (n \times K_j \times I_{2a}) + (n \times K_i \times I_{1c} \times M_1) - (n \times K_j \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\big)$$	(6)

	$\frac{dI_3}{dt} = \Big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_e \times I_3) + (K_f \times B_1) + (n \times K_i \times I_{2c} \times M_1) - (n \times K_j \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\Big)$	(7)
	$\frac{dB_1}{dt} = \Big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\Big)$	(8)
	$\frac{dB_2}{dt} = \Big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1c} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\Big)$	(9)
	$\frac{dB_3}{dt} = \Big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2c} \times M_1) - (n1 \times K_d \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3 ThT)\Big)$	(10)
	$\frac{dI_{1a}}{dt} = \Big((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\Big)$	(11)
	$\frac{dI_{1b}}{dt} = \Big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\Big)$	(12)
	$\frac{dI_{1c}}{dt} = \Big((n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_{1c}) - (n \times K_i \times I_{1c} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\Big)$	(13)
	$\frac{dI_{2a}}{dt} = \Big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\Big)$	(14)
	$\frac{dI_{2b}}{dt} = \Big((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\Big)$	(15)
	$\frac{dI_{2c}}{dt} = \Big((n \times K_i \times I_{2b} \times M_1) - (n \times K_j \times I_{2c}) - (n \times K_i \times I_{2c} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\Big)$	(16)
	$\frac{dB_{1a}}{dt} = \Big((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a} ThT)\Big)$	(17)
	$\frac{dB_{1b}}{dt} = \Big((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b} ThT)\Big)$	(18)
	$\frac{dB_{1c}}{dt} = \Big((n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_{1c}) - (n1 \times K_c \times B_{1c} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c} ThT)\Big)$	(19)
	$\frac{dB_{2a}}{dt} = \Big((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a} ThT)\Big)$	(20)
	$\frac{dB_{2b}}{dt} = \Big((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_{2c}) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b} ThT)\Big)$	(21)

	$\frac{dB_{2c}}{dt} = \left((n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_{2c}) - (n1 \times K_c \times B_{2c} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2c} \times ThT) + (K_q \times B_{2c}ThT)\right)$	(22)
	$\frac{dI_1ThT}{dt} = ((K_a \times I_1 \times ThT) - (K_b \times I_1ThT))$	(23)
	$\frac{dI_2ThT}{dt} = ((K_a \times I_2 \times ThT) - (K_b \times I_2ThT))$	(24)
	$\frac{dI_3ThT}{dt} = ((K_a \times I_3 \times ThT) - (K_b \times I_3ThT))$	(25)
	$\frac{dB_1ThT}{dt} = \left((K_p \times B_1 \times ThT) - (K_q \times B_1ThT)\right)$	(26)
	$\frac{dB_2ThT}{dt} = \left((K_p \times B_2 \times ThT) - (K_q \times B_2ThT)\right)$	(27)
	$\frac{dB_3ThT}{dt} = \left((K_p \times B_3 \times ThT) - (K_q \times B_3ThT)\right)$	(28)
	$\frac{dI_{1a}ThT}{dt} = ((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT))$	(29)
	$\frac{dI_{1b}ThT}{dt} = ((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT))$	(30)
	$\frac{dI_{1c}ThT}{dt} = ((K_a \times I_{1c} \times ThT) - (K_b \times I_{1c}ThT))$	(31)
	$\frac{dI_{2a}ThT}{dt} = ((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT))$	(32)
	$\frac{dI_{2b}ThT}{dt} = ((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT))$	(33)
	$\frac{dI_{2c}ThT}{dt} = ((K_a \times I_{2c} \times ThT) - (K_b \times I_{2c}ThT))$	(34)
	$\frac{dB_{1a}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1a}ThT)\right)$	(35)
	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1b} \times ThT) - (K_q \times B_{1b}ThT)\right)$	(36)
	$\frac{dB_{1c}ThT}{dt} = \left((K_p \times B_{1c} \times ThT) - (K_q \times B_{1c}ThT)\right)$	(37)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT)\right)$	(38)
	$\frac{dB_{2b}ThT}{dt} = \left((K_p \times B_{2b} \times ThT) - (K_q \times B_{2b}ThT)\right)$	(39)
	$\frac{dB_{2c}ThT}{dt} = \left((K_p \times B_{2c} \times ThT) - (K_q \times B_{2c}ThT)\right)$	(40)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 4 \times M_4 + 4 \times AC + 4 \times I_1 + 4 \times I_1ThT + 5 \times I_{1a} + 5 \times I_{1a}ThT + 6 \times I_{1b} + 6 \times I_{1b}ThT + 7 \times I_{1c} + 7 \times I_{1c}ThT + 8 \times I_2 + 8 \times I_2ThT + 9 \times I_{2a} + 9 \times I_{2a}ThT + 10 \times I_{2b} + 10 \times I_{2b}ThT + 11 \times I_{2c} + 11 \times I_{2c}ThT + 12 \times I_3 + 12 \times I_3ThT + 12 \times B_1 + 12 \times B_1ThT + 13 \times B_{1a} + 13 \times B_{1a}ThT + 14 \times B_{1b} + 14 \times B_{1b}ThT + 15 \times B_{1c} + 15 \times B_{1c}ThT + 16 \times B_2 + 16 \times B_2ThT + 17 \times B_{2a} + 17 \times B_{2a}ThT + 18 \times B_{2b} + 18 \times B_{2b}ThT + 19 \times B_{2c} + 19 \times B_{2c}ThT + 20 \times B_3 + 20 \times B_3ThT)$	(1)

	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = F \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_3ThT)$	(1)
	$\%\ of\ I = (4 \times I_1 + 4 \times I_1ThT + 5 \times I_{1a} + 5 \times I_{1a}ThT + 6 \times I_{1b} + 6 \times I_{1b}ThT + 7 \times I_{1c} + 7 \times I_{1c}ThT + 8 \times I_2 + 8 \times I_2ThT + 9 \times I_{2a} + 9 \times I_{2a}ThT + 10 \times I_{2b} + 10 \times I_{2b}ThT + 11 \times I_{2c} + 11 \times I_{2c}ThT + 12 \times I_3 + 12 \times I_3ThT)$	(2)

ODE for Model-2B

	Equations different from Model-1B	
	$\frac{dI_1}{dt} = \Big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_1 \times M_1) + (K_{j1} \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\Big)$	(5)
	$\frac{dI_2}{dt} = \Big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_2 \times M_1) + (K_{j1} \times I_{2a}) + (K_{i1} \times I_{1c} \times M_1) - (K_{j1} \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\Big)$	(6)
	$\frac{dI_3}{dt} = \Big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_e \times I_3) + (K_f \times B_1) + (K_{i1} \times I_{2c} \times M_1) - (K_{j1} \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\Big)$	(7)
	$\frac{dB_1}{dt} = \Big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1ThT)\Big)$	(8)
	$\frac{dB_2}{dt} = \Big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1c} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2ThT)\Big)$	(9)
	$\frac{dB_3}{dt} = \Big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2c} \times M_1) - (K_{d1} \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3ThT)\Big)$	(10)
	$\frac{dI_{1a}}{dt} = \Big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a}ThT)\Big)$	(11)
	$\frac{dI_{1b}}{dt} = \Big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b}ThT)\Big)$	(12)
	$\frac{dI_{1c}}{dt} = \Big((K_{i1} \times I_{1b} \times M_1) - (K_{j1} \times I_{1c}) - (K_{i1} \times I_{1c} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c}ThT)\Big)$	(13)

	$\frac{dI_{2a}}{dt} = \Big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a}ThT)\Big)$	(14)
	$\frac{dI_{2b}}{dt} = \Big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\Big)$	(15)
	$\frac{dI_{2c}}{dt} = \Big((K_{i1} \times I_{2b} \times M_1) - (K_{j1} \times I_{2c}) - (K_{i1} \times I_{2c} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c}ThT)\Big)$	(16)
	$\frac{dB_{1a}}{dt} = \Big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\Big)$	(17)
	$\frac{dB_{1b}}{dt} = \Big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\Big)$	(18)
	$\frac{dB_{1c}}{dt} = \Big((K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_{1c}) - (K_{c1} \times B_{1c} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c}ThT)\Big)$	(19)
	$\frac{dB_{2a}}{dt} = \Big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (K_{d1} \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\Big)$	(20)
	$\frac{dB_{2b}}{dt} = \Big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_{2c}) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\Big)$	(21)
	$\frac{dB_{2c}}{dt} = \Big((K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_{2c}) - (K_{c1} \times B_{2c} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2c} \times ThT) + (K_q \times B_{2c}ThT)\Big)$	(22)

Model-1C/Model-2C

The Model-1C and Model-2C have similar configuration containing an equal number of ODE (49) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1C

	$\frac{dM_2}{dt} = \Big((K_x \times M_1^2) - (K_y \times M_2) - (K_x \times M_1 \times M_2) + (K_y \times M_3)\Big)$	(1)
	$\frac{dM_3}{dt} = \Big((K_x \times M_1 \times M_2) - (K_y \times M_3) - (K_x \times M_1 \times M_3) + (K_y \times M_4)\Big)$	(2)
	$\frac{dM_4}{dt} = \Big((K_x \times M_1 \times M_3) - (K_y \times M_4) - (K_x \times M_1 \times M_4) + (K_y \times M_5)\Big)$	(3)
	$\frac{dM_5}{dt} = \Big((K_x \times M_1 \times M_4) - (K_y \times M_5) - (K_m \times M_5) + (K_{mi} \times AC) - (K_{ac} \times M_5 \times I_3)\Big)$	(4)
	$\frac{dAC}{dt} = ((K_{ac} \times M_5 \times I_3) + (K_m \times M_5) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1))$	(5)
	$\frac{dI_1}{dt} = \Big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_1 \times M_1) + (n \times K_j \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\Big)$	(6)

	$\frac{dI_2}{dt} = \big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_2 \times M_1) + (n \times K_j \times I_{2a}) + (n \times K_i \times I_{1d} \times M_1) - (n \times K_j \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2 ThT)\big)$	(7)
	$\frac{dI_3}{dt} = \big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_e \times I_3) + (K_f \times B_1) + (n \times K_i \times I_{2d} \times M_1) - (n \times K_j \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\big)$	(8)
	$\frac{dB_1}{dt} = \big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\big)$	(9)
	$\frac{dB_2}{dt} = \big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1d} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\big)$	(10)
	$\frac{dB_3}{dt} = \big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2d} \times M_1) - (n1 \times K_d \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_2 ThT)\big)$	(11)
	$\frac{dI_{1a}}{dt} = \big((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\big)$	(12)
	$\frac{dI_{1b}}{dt} = \big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\big)$	(13)
	$\frac{dI_{1c}}{dt} = \big((n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_{1c}) - (n \times K_i \times I_{1c} \times M_1) + (n \times K_j \times I_{1d}) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\big)$	(14)
	$\frac{dI_{1d}}{dt} = \big((n \times K_i \times I_{1c} \times M_1) - (n \times K_j \times I_{1d}) - (n \times K_i \times I_{1d} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1d} \times ThT) + (K_b \times I_{1d} ThT)\big)$	(15)
	$\frac{dI_{2a}}{dt} = \big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\big)$	(16)
	$\frac{dI_{2b}}{dt} = \big((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\big)$	(17)
	$\frac{dI_{2c}}{dt} = \big((n \times K_i \times I_{2b} \times M_1) - (n \times K_j \times I_{2c}) - (n \times K_i \times I_{2c} \times M_1) + (n \times K_j \times I_{2d}) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\big)$	(18)
	$\frac{dI_{2d}}{dt} = \big((n \times K_i \times I_{2c} \times M_1) - (n \times K_j \times I_{2d}) - (n \times K_i \times I_{2d} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2d} \times ThT) + (K_b \times I_{2d} ThT)\big)$	(19)
	$\frac{dB_{1a}}{dt} = \big((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a} ThT)\big)$	(20)
	$\frac{dB_{1b}}{dt} = \big((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b} ThT)\big)$	(21)

	$\frac{dB_{1c}}{dt} = \Big((n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_{1c}) - (n1 \times K_c \times B_{1c} \times M_1) + (n1 \times K_d \times B_{1d}) - (K_p \times B_{1c} \times ThT) + \big(K_q \times B_{1c}ThT\big)\Big)$	(22)
	$\frac{dB_{1d}}{dt} = \Big((n1 \times K_c \times B_{1c} \times M_1) - (n1 \times K_d \times B_{1d}) - (n1 \times K_c \times B_{1d} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1d} \times ThT) + \big(K_q \times B_{1d}ThT\big)\Big)$	(23)
	$\frac{dB_{2a}}{dt} = \Big((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + \big(K_q \times B_{2a}ThT\big)\Big)$	(24)
	$\frac{dB_{2b}}{dt} = \Big((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_{2c}) - (K_p \times B_{2b} \times ThT) + \big(K_q \times B_{2b}ThT\big)\Big)$	(25)
	$\frac{dB_{2c}}{dt} = \Big((n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_{2c}) - (n1 \times K_c \times B_{2c} \times M_1) + (n1 \times K_d \times B_{2d}) - (K_p \times B_{2c} \times ThT) + \big(K_q \times B_{2c}ThT\big)\Big)$	(26)
	$\frac{dB_{2d}}{dt} = \Big((n1 \times K_c \times B_{2c} \times M_1) - (n1 \times K_d \times B_{2d}) - (n1 \times K_c \times B_{2d} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2d} \times ThT) + \big(K_q \times B_{2d}ThT\big)\Big)$	(27)
	$\frac{dI_1ThT}{dt} = \big((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\big)$	(28)
	$\frac{dI_2ThT}{dt} = \big((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\big)$	(29)
	$\frac{dI_3ThT}{dt} = \big((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\big)$	(30)
	$\frac{dB_1ThT}{dt} = \Big(\big(K_p \times B_1 \times ThT\big) - \big(K_q \times B_1ThT\big)\Big)$	(31)
	$\frac{dB_2ThT}{dt} = \Big(\big(K_p \times B_2 \times ThT\big) - \big(K_q \times B_2ThT\big)\Big)$	(32)
	$\frac{dB_3ThT}{dt} = \Big(\big(K_p \times B_3 \times ThT\big) - \big(K_q \times B_3ThT\big)\Big)$	(33)
	$\frac{dI_{1a}ThT}{dt} = \big((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\big)$	(34)
	$\frac{dI_{1b}ThT}{dt} = \big((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\big)$	(35)
	$\frac{dI_{1c}ThT}{dt} = \big((K_a \times I_{1c} \times ThT) - (K_b \times I_{1c}ThT)\big)$	(36)
	$\frac{dI_{1d}ThT}{dt} = \big((K_a \times I_{1d} \times ThT) - (K_b \times I_{1d}ThT)\big)$	(37)
	$\frac{dI_{2a}ThT}{dt} = \big((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\big)$	(38)
	$\frac{dI_{2b}ThT}{dt} = \big((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\big)$	(39)
	$\frac{dI_{2c}ThT}{dt} = \big((K_a \times I_{2c} \times ThT) - (K_b \times I_{2c}ThT)\big)$	(40)

	$\frac{dI_{2d}ThT}{dt} = ((K_a \times I_{2d} \times ThT) - (K_b \times I_{2d}ThT))$	(41)
	$\frac{dB_{1a}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1a}ThT)\right)$	(42)
	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1b} \times ThT) - (K_q \times B_{1b}ThT)\right)$	(43)
	$\frac{dB_{1c}ThT}{dt} = \left((K_p \times B_{1c} \times ThT) - (K_q \times B_{1c}ThT)\right)$	(44)
	$\frac{dB_{1d}ThT}{dt} = \left((K_p \times B_{1d} \times ThT) - (K_q \times B_{1d}ThT)\right)$	(45)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT)\right)$	(46)
	$\frac{dB_{2b}ThT}{dt} = \left((K_p \times B_{2b} \times ThT) - (K_q \times B_{2b}ThT)\right)$	(47)
	$\frac{dB_{2c}ThT}{dt} = \left((K_p \times B_{2c} \times ThT) - (K_q \times B_{2c}ThT)\right)$	(48)
	$\frac{dB_{2d}ThT}{dt} = \left((K_p \times B_{2d} \times ThT) - (K_q \times B_{2d}ThT)\right)$	(49)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 4 \times M_4 + 5 \times M_5 + 5 \times AC + 5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT + 15 \times B_1 + 15 \times B_1ThT + 16 \times B_{1a} + 16 \times B_{1a}ThT + 17 \times B_{1b} + 17 \times B_{1b}ThT + 18 \times B_{1c} + 18 \times B_{1c}ThT + 19 \times B_{1d} + 19 \times B_{1d}ThT + 20 \times B_2 + 20 \times B_2ThT + 21 \times B_{2a} + 21 \times B_{2a}ThT + 22 \times B_{2b} + 22 \times B_{2b}ThT + 23 \times B_{2c} + 23 \times B_{2c}ThT + 24 \times B_{2d} + 24 \times B_{2d}ThT + 25 \times B_3 + 25 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = S \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(1)
	$\%\ of\ I = (5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT)$	(2)

ODE for Model-2C

	Equations different from Model-1C	

	$\frac{dI_1}{dt} = \big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_1 \times M_1) + (K_{j1} \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times I_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1 ThT)\big)$	(6)
	$\frac{dI_2}{dt} = \big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_2 \times M_1) + (K_{j1} \times I_{2a}) + (K_{i1} \times I_{1d} \times M_1) - (K_{j1} \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2 ThT)\big)$	(7)
	$\frac{dI_3}{dt} = \big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_e \times I_3) + (K_f \times B_1) + (K_{i1} \times I_{2d} \times M_1) - (K_{j1} \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\big)$	(8)
	$\frac{dB_1}{dt} = \big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\big)$	(9)
	$\frac{dB_2}{dt} = \big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1d} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\big)$	(10)
	$\frac{dB_3}{dt} = \big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2d} \times M_1) - (K_{d1} \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_2 ThT)\big)$	(11)
	$\frac{dI_{1a}}{dt} = \big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\big)$	(12)
	$\frac{dI_{1b}}{dt} = \big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\big)$	(13)
	$\frac{dI_{1c}}{dt} = \big((K_{i1} \times I_{1b} \times M_1) - (K_{j1} \times I_{1c}) - (K_{i1} \times I_{1c} \times M_1) + (K_{j1} \times I_{1d}) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\big)$	(14)
	$\frac{dI_{1d}}{dt} = \big((K_{i1} \times I_{1c} \times M_1) - (K_{j1} \times I_{1d}) - (K_{i1} \times I_{1d} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1d} \times ThT) + (K_b \times I_{1d} ThT)\big)$	(15)
	$\frac{dI_{2a}}{dt} = \big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\big)$	(16)
	$\frac{dI_{2b}}{dt} = \big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\big)$	(17)
	$\frac{dI_{2c}}{dt} = \big((K_{i1} \times I_{2b} \times M_1) - (K_{j1} \times I_{2c}) - (K_{i1} \times I_{2c} \times M_1) + (K_{j1} \times I_{2d}) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\big)$	(18)
	$\frac{dI_{2d}}{dt} = \big((K_{i1} \times I_{2c} \times M_1) - (K_{j1} \times I_{2d}) - (K_{i1} \times I_{2d} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2d} \times ThT) + (K_b \times I_{2d} ThT)\big)$	(19)

	$\frac{dB_{1a}}{dt} = \Big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + \big(K_q \times B_{1a}ThT\big)\Big)$	(20)
	$\frac{dB_{1b}}{dt} = \Big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_{1c}) - (K_p \times B_{1b} \times ThT) + \big(K_q \times B_{1b}ThT\big)\Big)$	(21)
	$\frac{dB_{1c}}{dt} = \Big((K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_{1c}) - (K_{c1} \times B_{1c} \times M_1) + (K_{d1} \times B_{1d}) - (K_p \times B_{1c} \times ThT) + \big(K_q \times B_{1c}ThT\big)\Big)$	(22)
	$\frac{dB_{1d}}{dt} = \Big((K_{c1} \times B_{1c} \times M_1) - (K_{d1} \times B_{1d}) - (K_{c1} \times B_{1d} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1d} \times ThT) + \big(K_q \times B_{1d}ThT\big)\Big)$	(23)
	$\frac{dB_{2a}}{dt} = \Big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (K_{d1} \times B_{2b}) - (K_p \times B_{2a} \times ThT) + \big(K_q \times B_{2a}ThT\big)\Big)$	(24)
	$\frac{dB_{2b}}{dt} = \Big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_{2c}) - (K_p \times B_{2b} \times ThT) + \big(K_q \times B_{2b}ThT\big)\Big)$	(25)
	$\frac{dB_{2c}}{dt} = \Big((K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_{2c}) - (K_{c1} \times B_{2c} \times M_1) + (K_{d1} \times B_{2d}) - (K_p \times B_{2c} \times ThT) + \big(K_q \times B_{2c}ThT\big)\Big)$	(26)
	$\frac{dB_{2d}}{dt} = \Big((K_{c1} \times B_{2c} \times M_1) - (K_{d1} \times B_{2d}) - (K_{c1} \times B_{2d} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2d} \times ThT) + \big(K_q \times B_{2d}ThT\big)\Big)$	(27)

Model-1D/Model-2D

The Model-1D and Model-2D have similar configuration containing an equal number of ODE (37) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1D

	$\frac{dM_2}{dt} = \Big((K_x \times M_1^2) - \big(K_y \times M_2\big) - (K_x \times M_1 \times M_2) + \big(K_y \times M_3\big)\Big)$	(1)
	$\frac{dM_3}{dt} = \Big((K_x \times M_1 \times M_2) - \big(K_y \times M_3\big) - (K_m \times M_3) + (K_{mi} \times AC) - (K_{ac} \times M_3 \times I_4)\Big)$	(2)
	$\frac{dAC}{dt} = \big((K_{ac} \times M_3 \times I_4) + (K_m \times M_3) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1)\big)$	(3)
	$\frac{dI_1}{dt} = \Big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + \big(2 \times K_j \times I_2\big) - (K_i \times I_1 \times I_2) + \big(K_j \times I_3\big) - (K_i \times I_1 \times I_3) + \big(K_j \times I_4\big) - (n \times K_i \times I_1 \times M_1) + \big(n \times K_j \times I_{1a}\big) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\Big)$	(4)
	$\frac{dI_2}{dt} = \Big((K_i \times I_1^2) - \big(K_j \times I_2\big) - (K_i \times I_1 \times I_2) + \big(K_j \times I_3\big) - (n \times K_i \times I_2 \times M_1) + \big(n \times K_j \times I_{2a}\big) + (n \times K_i \times I_{1b} \times M_1) - \big(n \times K_j \times I_2\big) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\Big)$	(5)
	$\frac{dI_3}{dt} = \Big((K_i \times I_1 \times I_2) - \big(K_j \times I_3\big) - (K_i \times I_1 \times I_3) + \big(K_j \times I_4\big) - (n \times K_i \times I_3 \times M_1) + \big(n \times K_j \times I_{3a}\big) + (n \times K_i \times I_{2b} \times M_1) - \big(n \times K_j \times I_3\big) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\Big)$	

	$\frac{dI_4}{dt} = \left((K_i \times I_1 \times I_3) - (K_j \times I_4) - (K_e \times I_4) + (K_f \times B_1) + (n \times K_i \times I_{3b} \times M_1) - (n \times K_j \times I_4) - (K_a \times I_4 \times ThT) + (K_b \times I_4ThT)\right)$	(7)
	$\frac{dB_1}{dt} = \left((K_e \times I_4) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1ThT)\right)$	(8)
	$\frac{dB_2}{dt} = \left((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2ThT)\right)$	(9)
	$\frac{dB_3}{dt} = \left((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3ThT)\right)$	(10)
	$\frac{dI_{1a}}{dt} = \left((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a}ThT)\right)$	(11)
	$\frac{dI_{1b}}{dt} = \left((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b}ThT)\right)$	(12)
	$\frac{dI_{2a}}{dt} = \left((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a}ThT)\right)$	(13)
	$\frac{dI_{2b}}{dt} = \left((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\right)$	(14)
	$\frac{dI_{3a}}{dt} = \left((n \times K_i \times I_3 \times M_1) - (n \times K_j \times I_{3a}) - (n \times K_i \times I_{3a} \times M_1) + (n \times K_j \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a}ThT)\right)$	(15)
	$\frac{dI_{3b}}{dt} = \left((n \times K_i \times I_{3a} \times M_1) - (n \times K_j \times I_{3b}) - (n \times K_i \times I_{3b} \times M_1) + (n \times K_j \times I_4) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b}ThT)\right)$	(16)
	$\frac{dB_{1a}}{dt} = \left((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\right)$	(17)
	$\frac{dB_{1b}}{dt} = \left((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\right)$	(18)
	$\frac{dB_{2a}}{dt} = \left((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\right)$	(19)
	$\frac{dB_{2b}}{dt} = \left((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\right)$	(20)
	$\frac{dI_1ThT}{dt} = \left((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\right)$	(21)
	$\frac{dI_2ThT}{dt} = \left((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\right)$	(22)

	$\frac{dI_3ThT}{dt} = \left((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\right)$	(23)
	$\frac{dI_4ThT}{dt} = \left((K_a \times I_4 \times ThT) - (K_b \times I_4ThT)\right)$	(24)
	$\frac{dB_1ThT}{dt} = \left((K_p \times B_1 \times ThT) - (K_q \times B_1ThT)\right)$	(25)
	$\frac{dB_2ThT}{dt} = \left((K_p \times B_2 \times ThT) - (K_q \times B_2ThT)\right)$	(26)
	$\frac{dB_3ThT}{dt} = \left((K_p \times B_3 \times ThT) - (K_q \times B_3ThT)\right)$	(27)
	$\frac{dI_{1a}ThT}{dt} = \left((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\right)$	(28)
	$\frac{dI_{1b}ThT}{dt} = \left((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\right)$	(29)
	$\frac{dI_{2a}ThT}{dt} = \left((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\right)$	(30)
	$\frac{dI_{2b}ThT}{dt} = \left((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\right)$	(31)
	$\frac{dI_{3a}ThT}{dt} = \left((K_a \times I_{3a} \times ThT) - (K_b \times I_{3a}ThT)\right)$	(32)
	$\frac{dI_{3b}ThT}{dt} = \left((K_a \times I_{3b} \times ThT) - (K_b \times I_{3b}ThT)\right)$	(33)
	$\frac{dB_{1a}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1a}ThT)\right)$	(34)
	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1b} \times ThT) - (K_q \times B_{1b}ThT)\right)$	(35)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT)\right)$	(36)
	$\frac{dB_{2b}ThT}{dt} = \left((K_p \times B_{2b} \times ThT) - (K_q \times B_{2b}ThT)\right)$	(37)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 3 \times AC + 3 \times I_1 + 3 \times I_1ThT + 4 \times I_{1a} + 4 \times I_{1a}ThT + 5 \times I_{1b} + 5 \times I_{1b}ThT + 6 \times I_2 + 6 \times I_2ThT + 7 \times I_{2a} + 7 \times I_{2a}ThT + 8 \times I_{2b} + 8 \times I_{2b}ThT + 9 \times I_3 + 9 \times I_3ThT + 10 \times I_{3a} + 10 \times I_{3a}ThT + 11 \times I_{3b} + 11 \times I_{3b}ThT + 12 \times I_4 + 12 \times I_4ThT + 12 \times B_1 + 12 \times B_1ThT + 13 \times B_{1a} + 13 \times B_{1a}ThT + 14 \times B_{1b} + 14 \times B_{1b}ThT + 15 \times B_2 + 15 \times B_2ThT + 16 \times B_{2a} + 16 \times B_{2a}ThT + 17 \times B_{2b} + 17 \times B_{2b}ThT + 18 \times B_3 + 18 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_4ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = F \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_4ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_3ThT)$	(1)
	$\%\ of\ I = S \times (3 \times I_1 + 3 \times I_1ThT + 4 \times I_{1a} + 4 \times I_{1a}ThT + 5 \times I_{1b} + 5 \times I_{1b}ThT + 6 \times I_2 + 6 \times I_2ThT + 7 \times I_{2a} + 7 \times I_{2a}ThT + 8 \times I_{2b} + 8 \times I_{2b}ThT + 9 \times I_3 + 9 \times I_3ThT + 10 \times I_{3a} + 10 \times I_{3a}ThT + 11 \times I_{3b} + 11 \times I_{3b}ThT + 12 \times I_4 + 12 \times I_4ThT)$	(2)

ODE for Model-2D

	Equations different from Model-1D	
	$\frac{dI_1}{dt} = \big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (K_{i1} \times I_1 \times M_1) + (K_{j1} \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1 ThT)\big)$	(4)
	$\frac{dI_2}{dt} = \big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_2 \times M_1) + (K_{j1} \times I_{2a}) + (K_{i1} \times I_{1b} \times M_1) - (K_{j1} \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2 ThT)\big)$	(5)
	$\frac{dI_3}{dt} = \big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (K_{i1} \times I_3 \times M_1) + (K_{j1} \times I_{3a}) + (K_{i1} \times I_{2b} \times M_1) - (K_{j1} \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\big)$	(6)
	$\frac{dI_4}{dt} = \big((K_i \times I_1 \times I_3) - (K_j \times I_4) - (K_e \times I_4) + (K_f \times B_1) + (K_{i1} \times I_{3b} \times M_1) - (K_{j1} \times I_4) - (K_a \times I_4 \times ThT) + (K_b \times I_4 ThT)\big)$	(7)
	$\frac{dB_1}{dt} = \big((K_e \times I_3) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\big)$	(8)
	$\frac{dB_2}{dt} = \big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\big)$	(9)
	$\frac{dB_3}{dt} = \big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3 ThT)\big)$	(10)
	$\frac{dI_{1a}}{dt} = \big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\big)$	(11)
	$\frac{dI_{1b}}{dt} = \big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\big)$	(12)
	$\frac{dI_{2a}}{dt} = \big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\big)$	(13)
	$\frac{dI_{2b}}{dt} = \big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\big)$	(14)
	$\frac{dI_{3a}}{dt} = \big((K_{i1} \times I_3 \times M_1) - (K_{j1} \times I_{3a}) - (K_{i1} \times I_{3a} \times M_1) + (K_{j1} \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a} ThT)\big)$	(15)
	$\frac{dI_{3b}}{dt} = \big((K_{i1} \times I_{3a} \times M_1) - (K_{j1} \times I_{3b}) - (K_{i1} \times I_{3b} \times M_1) + (K_{j1} \times I_4) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b} ThT)\big)$	(16)

	$\frac{dB_{1a}}{dt} = \Big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\Big)$	(17)
	$\frac{dB_{1b}}{dt} = \Big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\Big)$	(18)
	$\frac{dB_{2a}}{dt} = \Big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\Big)$	(19)
	$\frac{dB_{2b}}{dt} = \Big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\Big)$	(20)

Model-1E/Model-2E

The Model-1E and Model-2E have similar configuration containing an equal number of ODE (48) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1E

	$\frac{dM_2}{dt} = \Big((K_x \times M_1^2) - (K_y \times M_2) - (K_x \times M_1 \times M_2) + (K_y \times M_3)\Big)$	(1)
	$\frac{dM_3}{dt} = \Big((K_x \times M_1 \times M_2) - (K_y \times M_3) - (K_x \times M_1 \times M_3) + (K_y \times M_4)\Big)$	(2)
	$\frac{dM_4}{dt} = \begin{pmatrix}(K_x \times M_1 \times M_3) - (K_y \times M_4) - (K_m \times M_4) + (K_{mi} \times AC) \\ -(K_{ac} \times M_4 \times I_4)\end{pmatrix}$	(3)
	$\frac{dAC}{dt} = \Big((K_{ac} \times M_4 \times I_4) + (K_m \times M_4) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1)\Big)$	(4)
	$\frac{dI_1}{dt} = \Big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (n \times K_i \times I_1 \times M_1) + (n \times K_j \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\Big)$	(5)
	$\frac{dI_2}{dt} = \Big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_2 \times M_1) + (n \times K_j \times I_{2a}) + (n \times K_i \times I_{1c} \times M_1) - (n \times K_j \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\Big)$	(6)
	$\frac{dI_3}{dt} = \Big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (n \times K_i \times I_3 \times M_1) + (n \times K_j \times I_{3a}) + (n \times K_i \times I_{2c} \times M_1) - (n \times K_j \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\Big)$	(7)
	$\frac{dI_4}{dt} = \Big((K_i \times I_1 \times I_3) - (K_j \times I_4) - (K_e \times I_4) + (K_f \times B_1) + (n \times K_i \times I_{3c} \times M_1) - (n \times K_j \times I_4) - (K_a \times I_4 \times ThT) + (K_b \times I_4ThT)\Big)$	(8)

$\frac{dB_1}{dt} = \Big((K_e \times I_4) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\Big)$	(9)
$\frac{dB_2}{dt} = \Big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1c} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\Big)$	(10)
$\frac{dB_3}{dt} = \Big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2c} \times M_1) - (n1 \times K_d \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3 ThT)\Big)$	(11)
$\frac{dI_{1a}}{dt} = \Big((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\Big)$	(12)
$\frac{dI_{1b}}{dt} = \Big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\Big)$	(13)
$\frac{dI_{1c}}{dt} = \Big((n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_{1c}) - (n \times K_i \times I_{1c} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\Big)$	(14)
$\frac{dI_{2a}}{dt} = \Big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\Big)$	(15)
$\frac{dI_{2b}}{dt} = \Big((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\Big)$	(16)
$\frac{dI_{2c}}{dt} = \Big((n \times K_i \times I_{2b} \times M_1) - (n \times K_j \times I_{2c}) - (n \times K_i \times I_{2c} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\Big)$	(17)
$\frac{dI_{3a}}{dt} = \Big((n \times K_i \times I_3 \times M_1) - (n \times K_j \times I_{3a}) - (n \times K_i \times I_{3a} \times M_1) + (n \times K_j \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a} ThT)\Big)$	(18)
$\frac{dI_{3b}}{dt} = \Big((n \times K_i \times I_{3a} \times M_1) - (n \times K_j \times I_{3b}) - (n \times K_i \times I_{3b} \times M_1) + (n \times K_j \times I_{3c}) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b} ThT)\Big)$	(19)
$\frac{dI_{3c}}{dt} = \Big((n \times K_i \times I_{3b} \times M_1) - (n \times K_j \times I_{3c}) - (n \times K_i \times I_{3c} \times M_1) + (n \times K_j \times I_4) - (K_a \times I_{3c} \times ThT) + (K_b \times I_{3c} ThT)\Big)$	(20)
$\frac{dB_{1a}}{dt} = \Big((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a} ThT)\Big)$	(21)
$\frac{dB_{1b}}{dt} = \Big((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b} ThT)\Big)$	(22)
$\frac{dB_{1c}}{dt} = \Big((n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_{1c}) - (n1 \times K_c \times B_{1c} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c} ThT)\Big)$	(23)
$\frac{dB_{2a}}{dt} = \Big((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a} ThT)\Big)$	(24)

	$$\frac{dB_{2b}}{dt} = \Big((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_{2c}) - (K_p \times B_{2b} \times ThT) + \big(K_q \times B_{2b}ThT\big)\Big)$$	(25)
	$$\frac{dB_{2c}}{dt} = \Big((n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_{2c}) - (n1 \times K_c \times B_{2c} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2c} \times ThT) + \big(K_q \times B_{2c}ThT\big)\Big)$$	(26)
	$$\frac{dI_1ThT}{dt} = \big((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\big)$$	(27)
	$$\frac{dI_2ThT}{dt} = \big((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\big)$$	(28)
	$$\frac{dI_3ThT}{dt} = \big((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\big)$$	(29)
	$$\frac{dI_4ThT}{dt} = \big((K_a \times I_4 \times ThT) - (K_b \times I_4ThT)\big)$$	(30)
	$$\frac{dB_1ThT}{dt} = \Big(\big(K_p \times B_1 \times ThT\big) - \big(K_q \times B_1ThT\big)\Big)$$	(31)
	$$\frac{dB_2ThT}{dt} = \Big(\big(K_p \times B_2 \times ThT\big) - \big(K_q \times B_2ThT\big)\Big)$$	(32)
	$$\frac{dB_3ThT}{dt} = \Big(\big(K_p \times B_3 \times ThT\big) - \big(K_q \times B_3ThT\big)\Big)$$	(33)
	$$\frac{dI_{1a}ThT}{dt} = \big((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\big)$$	(34)
	$$\frac{dI_{1b}ThT}{dt} = \big((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\big)$$	(35)
	$$\frac{dI_{1c}ThT}{dt} = \big((K_a \times I_{1c} \times ThT) - (K_b \times I_{1c}ThT)\big)$$	(36)
	$$\frac{dI_{2a}ThT}{dt} = \big((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\big)$$	(37)
	$$\frac{dI_{2b}ThT}{dt} = \big((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\big)$$	(38)
	$$\frac{dI_{2c}ThT}{dt} = \big((K_a \times I_{2c} \times ThT) - (K_b \times I_{2c}ThT)\big)$$	(39)
	$$\frac{dI_{3a}ThT}{dt} = \big((K_a \times I_{3a} \times ThT) - (K_b \times I_{3a}ThT)\big)$$	(40)
	$$\frac{dI_{3b}ThT}{dt} = \big((K_a \times I_{3b} \times ThT) - (K_b \times I_{3b}ThT)\big)$$	(41)
	$$\frac{dI_{3c}ThT}{dt} = \big((K_a \times I_{3c} \times ThT) - (K_b \times I_{3c}ThT)\big)$$	(42)
	$$\frac{dB_{1a}ThT}{dt} = \Big(\big(K_p \times B_{1a} \times ThT\big) - \big(K_q \times B_{1a}ThT\big)\Big)$$	(43)
	$$\frac{dB_{1b}ThT}{dt} = \Big(\big(K_p \times B_{1b} \times ThT\big) - \big(K_q \times B_{1b}ThT\big)\Big)$$	(44)
	$$\frac{dB_{1c}ThT}{dt} = \Big(\big(K_p \times B_{1c} \times ThT\big) - \big(K_q \times B_{1c}ThT\big)\Big)$$	(45)
	$$\frac{dB_{2a}ThT}{dt} = \Big(\big(K_p \times B_{2a} \times ThT\big) - \big(K_q \times B_{2a}ThT\big)\Big)$$	(46)

	$\frac{dB_{2b}ThT}{dt} = \left(\left(K_p \times B_{2b} \times ThT\right) - \left(K_q \times B_{2b}ThT\right)\right)$	(47)
	$\frac{dB_{2c}ThT}{dt} = \left(\left(K_p \times B_{2c} \times ThT\right) - \left(K_q \times B_{2c}ThT\right)\right)$	(48)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 4 \times M_4 + 4 \times \mathrm{AC} + 4 \times I_1 + 4 \times I_1ThT + 5 \times I_{1a} + 5 \times I_{1a}ThT + 6 \times I_{1b} + 6 \times I_{1b}ThT + 7 \times I_{1c} + 7 \times I_{1c}ThT + 8 \times I_2 + 8 \times I_2ThT + 9 \times I_{2a} + 9 \times I_{2a}ThT + 10 \times I_{2b} + 10 \times I_{2b}ThT + 11 \times I_{2c} + 11 \times I_{2c}ThT + 12 \times I_3 + 12 \times I_3ThT + 13 \times I_{3a} + 13 \times I_{3a}ThT + 14 \times I_{3b} + 14 \times I_{3b}ThT + 15 \times I_{3c} + 15 \times I_{3c}ThT + 16 \times I_4 + 16 \times I_4ThT + 16 \times B_1 + 16 \times B_1ThT + 17 \times B_{1a} + 17 \times B_{1a}ThT + 18 \times B_{1b} + 18 \times B_{1b}ThT + 19 \times B_{1c} + 19 \times B_{1c}ThT + 20 \times B_2 + 20 \times B_2ThT + 21 \times B_{2a} + 21 \times B_{2a}ThT + 22 \times B_{2b} + 22 \times B_{2b}ThT + 23 \times B_{2c} + 23 \times B_{2c}ThT + 24 \times B_3 + 24 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_4ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = F \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_4ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_3ThT)$	(1)
	$\%\ of\ I = \mathrm{S} \times (4 \times I_1 + 4 \times I_1ThT + 5 \times I_{1a} + 5 \times I_{1a}ThT + 6 \times I_{1b} + 6 \times I_{1b}ThT + 7 \times I_{1c} + 7 \times I_{1c}ThT + 8 \times I_2 + 8 \times I_2ThT + 9 \times I_{2a} + 9 \times I_{2a}ThT + 10 \times I_{2b} + 10 \times I_{2b}ThT + 11 \times I_{2c} + 11 \times I_{2c}ThT + 12 \times I_3 + 12 \times I_3ThT + 13 \times I_{3a} + 13 \times I_{3a}ThT + 14 \times I_{3b} + 14 \times I_{3b}ThT + 15 \times I_{3c} + 15 \times I_{3c}ThT + 16 \times I_4 + 16 \times I_4ThT)$	(2)

ODE for Model-2E

	Equations different from Model-1E	
	$\frac{dI_1}{dt} = \left((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + \left(2 \times K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (K_i \times I_1 \times I_3) + \left(K_j \times I_4\right) - (K_{i1} \times I_1 \times M_1) + \left(K_{j1} \times I_{1a}\right) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\right)$	(5)
	$\frac{dI_2}{dt} = \left((K_i \times I_1^2) - \left(K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (K_{i1} \times I_2 \times M_1) + \left(K_{j1} \times I_{2a}\right) + (K_{i1} \times I_{1c} \times M_1) - \left(K_{j1} \times I_2\right) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\right)$	(6)
	$\frac{dI_3}{dt} = \left((K_i \times I_1 \times I_2) - \left(K_j \times I_3\right) - (K_i \times I_1 \times I_3) + \left(K_j \times I_4\right) - (K_{i1} \times I_3 \times M_1) + \left(K_{j1} \times I_{3a}\right) + (K_{i1} \times I_{2c} \times M_1) - \left(K_{j1} \times I_3\right) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\right)$	(7)
	$\frac{dI_4}{dt} = \left((K_i \times I_1 \times I_3) - \left(K_j \times I_4\right) - (K_e \times I_4) + \left(K_f \times B_1\right) + (K_{i1} \times I_{3c} \times M_1) - \left(K_{j1} \times I_4\right) - (K_a \times I_4 \times ThT) + (K_b \times I_4ThT)\right)$	(8)
	$\frac{dB_1}{dt} = \left((K_e \times I_4) - \left(K_f \times B_1\right) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + \left(K_q \times B_1ThT\right)\right)$	(9)

$\frac{dB_2}{dt} = \big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1c} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\big)$	(10)
$\frac{dB_3}{dt} = \big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2c} \times M_1) - (K_{d1} \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_2 ThT)\big)$	(11)
$\frac{dI_{1a}}{dt} = \big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\big)$	(12)
$\frac{dI_{1b}}{dt} = \big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\big)$	(13)
$\frac{dI_{1c}}{dt} = \big((K_{i1} \times I_{1b} \times M_1) - (K_{j1} \times I_{1c}) - (K_{i1} \times I_{1c} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\big)$	(14)
$\frac{dI_{2a}}{dt} = \big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\big)$	(15)
$\frac{dI_{2b}}{dt} = \big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\big)$	(16)
$\frac{dI_{2c}}{dt} = \big((K_{i1} \times I_{2b} \times M_1) - (K_{j1} \times I_{2c}) - (K_{i1} \times I_{2c} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\big)$	(17)
$\frac{dI_{3a}}{dt} = \big((K_{i1} \times I_3 \times M_1) - (K_{j1} \times I_{3a}) - (K_{i1} \times I_{3a} \times M_1) + (K_{j1} \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a} ThT)\big)$	(18)
$\frac{dI_{3b}}{dt} = \big((K_{i1} \times I_{3a} \times M_1) - (K_{j1} \times I_{3b}) - (K_{i1} \times I_{3b} \times M_1) + (K_{j1} \times I_{3c}) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b} ThT)\big)$	(19)
$\frac{dI_{3c}}{dt} = \big((K_{i1} \times I_{3b} \times M_1) - (K_{j1} \times I_{3c}) - (K_{i1} \times I_{3c} \times M_1) + (K_{j1} \times I_4) - (K_a \times I_{3c} \times ThT) + (K_b \times I_{3c} ThT)\big)$	(20)
$\frac{dB_{1a}}{dt} = \big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a} ThT)\big)$	(21)
$\frac{dB_{1b}}{dt} = \big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b} ThT)\big)$	(22)
$\frac{dB_{1c}}{dt} = \big((K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_{1c}) - (K_{c1} \times B_{1c} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c} ThT)\big)$	(23)
$\frac{dB_{2a}}{dt} = \big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (K_{d1} \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a} ThT)\big)$	(24)
$\frac{dB_{2b}}{dt} = \big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_{2c}) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b} ThT)\big)$	(25)

	$\frac{dB_{2c}}{dt} = \left((K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_{2c}) - (K_{c1} \times B_{2c} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2c} \times ThT) + (K_q \times B_{2c}ThT)\right)$	(26)

Model-1F/Model-2F

The Model-1F and Model-2F have similar configuration containing an equal number of ODE (59) and algebraic relations (2). Only some rate constants for some specific interaction node are different for the two models.

ODE for Model-1F

	$\frac{dM_2}{dt} = \left((K_x \times M_1^2) - (K_y \times M_2) - (K_x \times M_1 \times M_2) + (K_y \times M_3)\right)$	(1)
	$\frac{dM_3}{dt} = \left((K_x \times M_1 \times M_2) - (K_y \times M_3) - (K_x \times M_1 \times M_3) + (K_y \times M_4)\right)$	(2)
	$\frac{dM_4}{dt} = \left((K_x \times M_1 \times M_3) - (K_y \times M_4) - (K_x \times M_1 \times M_4) + (K_y \times M_5)\right)$	(3)
	$\frac{dM_5}{dt} = \left((K_x \times M_1 \times M_4) - (K_y \times M_5) - (K_m \times M_5) + (K_{mi} \times AC) - (K_{ac} \times M_5 \times I_4)\right)$	(4)
	$\frac{dAC}{dt} = \left((K_{ac} \times M_5 \times I_4) + (K_m \times M_5) - (K_{mi} \times AC) - (K_s \times AC) + (K_t \times I_1)\right)$	(5)
	$\frac{dI_1}{dt} = \left((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (n \times K_i \times I_1 \times M_1) + (n \times K_j \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1ThT)\right)$	(6)
	$\frac{dI_2}{dt} = \left((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (n \times K_i \times I_2 \times M_1) + (n \times K_j \times I_{2a}) + (n \times K_i \times I_{1d} \times M_1) - (n \times K_j \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2ThT)\right)$	(7)
	$\frac{dI_3}{dt} = \left((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (n \times K_i \times I_3 \times M_1) + (n \times K_j \times I_{3a}) + (n \times K_i \times I_{2d} \times M_1) - (n \times K_j \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3ThT)\right)$	(8)
	$\frac{dI_4}{dt} = \left((K_i \times I_1 \times I_3) - (K_j \times I_4) - (K_e \times I_4) + (K_f \times B_1) + (n \times K_i \times I_{3d} \times M_1) - (n \times K_j \times I_4) - (K_a \times I_4 \times ThT) + (K_b \times I_4ThT)\right)$	(9)
	$\frac{dB_1}{dt} = \left((K_e \times I_4) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1ThT)\right)$	(10)
	$\frac{dB_2}{dt} = \left((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1d} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2ThT)\right)$	(11)
	$\frac{dB_3}{dt} = \left((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2d} \times M_1) - (n1 \times K_d \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_3ThT)\right)$	(12)

	$\frac{dI_{1a}}{dt} = \Big((n \times K_i \times I_1 \times M_1) - (n \times K_j \times I_{1a}) - (n \times K_i \times I_{1a} \times M_1) + (n \times K_j \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a}ThT)\Big)$	(13)
	$\frac{dI_{1b}}{dt} = \Big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b}ThT)\Big)$	(14)
	$\frac{dI_{1c}}{dt} = \Big((n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_{1c}) - (n \times K_i \times I_{1c} \times M_1) + (n \times K_j \times I_{1d}) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c}ThT)\Big)$	(15)
	$\frac{dI_{1d}}{dt} = \Big((n \times K_i \times I_{1c} \times M_1) - (n \times K_j \times I_{1d}) - (n \times K_i \times I_{1d} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1d} \times ThT) + (K_b \times I_{1d}ThT)\Big)$	(16)
	$\frac{dI_{2a}}{dt} = \Big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a}ThT)\Big)$	(17)
	$\frac{dI_{2b}}{dt} = \Big((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\Big)$	(18)
	$\frac{dI_{2c}}{dt} = \Big((n \times K_i \times I_{2b} \times M_1) - (n \times K_j \times I_{2c}) - (n \times K_i \times I_{2c} \times M_1) + (n \times K_j \times I_{2d}) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c}ThT)\Big)$	(19)
	$\frac{dI_{2d}}{dt} = \Big((n \times K_i \times I_{2c} \times M_1) - (n \times K_j \times I_{2d}) - (n \times K_i \times I_{2d} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2d} \times ThT) + (K_b \times I_{2d}ThT)\Big)$	(20)
	$\frac{dI_{3a}}{dt} = \Big((n \times K_i \times I_3 \times M_1) - (n \times K_j \times I_{3a}) - (n \times K_i \times I_{3a} \times M_1) + (n \times K_j \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a}ThT)\Big)$	(21)
	$\frac{dI_{3b}}{dt} = \Big((n \times K_i \times I_{3a} \times M_1) - (n \times K_j \times I_{3b}) - (n \times K_i \times I_{3b} \times M_1) + (n \times K_j \times I_{3c}) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b}ThT)\Big)$	(22)
	$\frac{dI_{3c}}{dt} = \Big((n \times K_i \times I_{3b} \times M_1) - (n \times K_j \times I_{3c}) - (n \times K_i \times I_{3c} \times M_1) + (n \times K_j \times I_{3d}) - (K_a \times I_{3c} \times ThT) + (K_b \times I_{3c}ThT)\Big)$	(23)
	$\frac{dI_{3d}}{dt} = \Big((n \times K_i \times I_{3c} \times M_1) - (n \times K_j \times I_{3d}) - (n \times K_i \times I_{3d} \times M_1) + (n \times K_j \times I_4) - (K_a \times I_{3d} \times ThT) + (K_b \times I_{3d}ThT)\Big)$	(24)
	$\frac{dB_{1a}}{dt} = \Big((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\Big)$	(25)
	$\frac{dB_{1b}}{dt} = \Big((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\Big)$	(26)
	$\frac{dB_{1c}}{dt} = \Big((n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_{1c}) - (n1 \times K_c \times B_{1c} \times M_1) + (n1 \times K_d \times B_{1d}) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c}ThT)\Big)$	(27)
	$\frac{dB_{1d}}{dt} = \Big((n1 \times K_c \times B_{1c} \times M_1) - (n1 \times K_d \times B_{1d}) - (n1 \times K_c \times B_{1d} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1d} \times ThT) + (K_q \times B_{1d}ThT)\Big)$	(28)

	$\frac{dB_{2a}}{dt} = \left((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + \left(K_q \times B_{2a}ThT\right)\right)$	(29)
	$\frac{dB_{2b}}{dt} = \left((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_{2c}) - (K_p \times B_{2b} \times ThT) + \left(K_q \times B_{2b}ThT\right)\right)$	(30)
	$\frac{dB_{2c}}{dt} = \left((n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_{2c}) - (n1 \times K_c \times B_{2c} \times M_1) + (n1 \times K_d \times B_{2d}) - (K_p \times B_{2c} \times ThT) + \left(K_q \times B_{2c}ThT\right)\right)$	(31)
	$\frac{dB_{2d}}{dt} = \left((n1 \times K_c \times B_{2c} \times M_1) - (n1 \times K_d \times B_{2d}) - (n1 \times K_c \times B_{2d} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2d} \times ThT) + \left(K_q \times B_{2d}ThT\right)\right)$	(32)
	$\frac{dI_1ThT}{dt} = \left((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\right)$	(33)
	$\frac{dI_2ThT}{dt} = \left((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\right)$	(34)
	$\frac{dI_3ThT}{dt} = \left((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\right)$	(35)
	$\frac{dI_4ThT}{dt} = \left((K_a \times I_4 \times ThT) - (K_b \times I_4ThT)\right)$	(36)
	$\frac{dB_1ThT}{dt} = \left(\left(K_p \times B_1 \times ThT\right) - \left(K_q \times B_1ThT\right)\right)$	(37)
	$\frac{dB_2ThT}{dt} = \left(\left(K_p \times B_2 \times ThT\right) - \left(K_q \times B_2ThT\right)\right)$	(38)
	$\frac{dB_3ThT}{dt} = \left(\left(K_p \times B_3 \times ThT\right) - \left(K_q \times B_3ThT\right)\right)$	(39)
	$\frac{dI_{1a}ThT}{dt} = \left((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\right)$	(40)
	$\frac{dI_{1b}ThT}{dt} = \left((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\right)$	(41)
	$\frac{dI_{1c}ThT}{dt} = \left((K_a \times I_{1c} \times ThT) - (K_b \times I_{1c}ThT)\right)$	(42)
	$\frac{dI_{1d}ThT}{dt} = \left((K_a \times I_{1d} \times ThT) - (K_b \times I_{1d}ThT)\right)$	(43)
	$\frac{dI_{2a}ThT}{dt} = \left((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\right)$	(44)
	$\frac{dI_{2b}ThT}{dt} = \left((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\right)$	(45)
	$\frac{dI_{2c}ThT}{dt} = \left((K_a \times I_{2c} \times ThT) - (K_b \times I_{2c}ThT)\right)$	(46)
	$\frac{dI_{2d}ThT}{dt} = \left((K_a \times I_{2d} \times ThT) - (K_b \times I_{2d}ThT)\right)$	(47)
	$\frac{dI_{3a}ThT}{dt} = \left((K_a \times I_{3a} \times ThT) - (K_b \times I_{3a}ThT)\right)$	(48)
	$\frac{dI_{3b}ThT}{dt} = \left((K_a \times I_{3b} \times ThT) - (K_b \times I_{3b}ThT)\right)$	(49)
	$\frac{dI_{3c}ThT}{dt} = \left((K_a \times I_{3c} \times ThT) - (K_b \times I_{3c}ThT)\right)$	(50)

	$\frac{dI_{3d}ThT}{dt} = ((K_a \times I_{3d} \times ThT) - (K_b \times I_{3d}ThT))$	(51)
	$\frac{dB_{1a}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1a}ThT)\right)$	(52)
	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1a} \times ThT) - (K_q \times B_{1b}ThT)\right)$	(53)
	$\frac{dB_{1c}ThT}{dt} = \left((K_p \times B_{1c} \times ThT) - (K_q \times B_{1c}ThT)\right)$	(54)
	$\frac{dB_{1d}ThT}{dt} = \left((K_p \times B_{1d} \times ThT) - (K_q \times B_{1d}ThT)\right)$	(55)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT)\right)$	(56)
	$\frac{dB_{2b}ThT}{dt} = \left((K_p \times B_{2b} \times ThT) - (K_q \times B_{2b}ThT)\right)$	(57)
	$\frac{dB_{2c}ThT}{dt} = \left((K_p \times B_{2c} \times ThT) - (K_q \times B_{2c}ThT)\right)$	(58)
	$\frac{dB_{2d}ThT}{dt} = \left((K_p \times B_{2d} \times ThT) - (K_q \times B_{2d}ThT)\right)$	(59)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 4 \times M_4 + 5 \times M_5 + 5 \times AC + 5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT + 16 \times I_{3a} + 16 \times I_{3a}ThT + 17 \times I_{3b} + 17 \times I_{3b}ThT + 18 \times I_{3c} + 18 \times I_{3c}ThT + 19 \times I_{3d} + 19 \times I_{3d}ThT + 20 \times B_1 + 20 \times B_1ThT + 21 \times B_{1a} + 21 \times B_{1a}ThT + 22 \times B_{1b} + 22 \times B_{1b}ThT + 23 \times B_{1c} + 23 \times B_{1c}ThT + 24 \times B_{1d} + 24 \times B_{1d}ThT + 25 \times B_2 + 25 \times B_2ThT + 26 \times B_{2a} + 26 \times B_{2a}ThT + 27 \times B_{2b} + 27 \times B_{2b}ThT + 28 \times B_{2c} + 28 \times B_{2c}ThT + 29 \times B_{2d} + 29 \times B_{2d}ThT + 30 \times B_3 + 30 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_{3d}ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = S \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_{3d}ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(1)
	$\%\ of\ I = (5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT + 16 \times I_{3a} + 16 \times I_{3a}ThT + 17 \times I_{3b} + 17 \times I_{3b}ThT + 18 \times I_{3c} + 18 \times I_{3c}ThT + 19 \times I_{3d} + 19 \times I_{3d}ThT)$	(2)

ODE for Model-2F

	Equations different from Model-1F	

	$\frac{dI_1}{dt} = \big((K_s \times AC) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + (2 \times K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_1 \times M_1) + (K_{j1} \times I_{1a}) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1 ThT)\big)$	(6)
	$\frac{dI_2}{dt} = \big((K_i \times I_1^2) - (K_j \times I_2) - (K_i \times I_1 \times I_2) + (K_j \times I_3) - (K_{i1} \times I_2 \times M_1) + (K_{j1} \times I_{2a}) + (K_{i1} \times I_{1d} \times M_1) - (K_{j1} \times I_2) - (K_a \times I_2 \times ThT) + (K_b \times I_2 ThT)\big)$	(7)
	$\frac{dI_3}{dt} = \big((K_i \times I_1 \times I_2) - (K_j \times I_3) - (K_i \times I_1 \times I_3) + (K_j \times I_4) - (K_{i1} \times I_3 \times M_1) + (K_{j1} \times I_{3a}) + (K_{i1} \times I_{2d} \times M_1) - (K_{j1} \times I_3) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\big)$	(8)
	$\frac{dI_4}{dt} = \big((K_i \times I_1 \times I_3) - (K_j \times I_4) - (K_e \times I_4) + (K_f \times B_1) + (K_{i1} \times I_{3d} \times M_1) - (K_{j1} \times I_4) - (K_a \times I_4 \times ThT) + (K_b \times I_4 ThT)\big)$	(9)
	$\frac{dB_1}{dt} = \big((K_e \times I_4) - (K_f \times B_1) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (K_{c1} \times B_1 \times M_1) + (K_{d1} \times B_{1a}) - (K_p \times B_1 \times ThT) + (K_q \times B_1 ThT)\big)$	(10)
	$\frac{dB_2}{dt} = \big((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (K_{c1} \times B_{1d} \times M_1) - (K_{d1} \times B_2) - (K_{c1} \times B_2 \times M_1) + (K_{d1} \times B_{2a}) - (K_p \times B_2 \times ThT) + (K_q \times B_2 ThT)\big)$	(11)
	$\frac{dB_3}{dt} = \big((K_c \times B_2 \times I_1) - (K_d \times B_3) + (K_{c1} \times B_{2d} \times M_1) - (K_{d1} \times B_3) - (K_p \times B_3 \times ThT) + (K_q \times B_2 ThT)\big)$	(12)
	$\frac{dI_{1a}}{dt} = \big((K_{i1} \times I_1 \times M_1) - (K_{j1} \times I_{1a}) - (K_{i1} \times I_{1a} \times M_1) + (K_{j1} \times I_{1b}) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\big)$	(13)
	$\frac{dI_{1b}}{dt} = \big((K_{i1} \times I_{1a} \times M_1) - (K_{j1} \times I_{1b}) - (K_{i1} \times I_{1b} \times M_1) + (K_{j1} \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b} ThT)\big)$	(14)
	$\frac{dI_{1c}}{dt} = \big((K_{i1} \times I_{1b} \times M_1) - (K_{j1} \times I_{1c}) - (K_{i1} \times I_{1c} \times M_1) + (K_{j1} \times I_{1d}) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c} ThT)\big)$	(15)
	$\frac{dI_{1d}}{dt} = \big((K_{i1} \times I_{1c} \times M_1) - (K_{j1} \times I_{1d}) - (K_{i1} \times I_{1d} \times M_1) + (K_{j1} \times I_2) - (K_a \times I_{1d} \times ThT) + (K_b \times I_{1d} ThT)\big)$	(16)
	$\frac{dI_{2a}}{dt} = \big((K_{i1} \times I_2 \times M_1) - (K_{j1} \times I_{2a}) - (K_{i1} \times I_{2a} \times M_1) + (K_{j1} \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a} ThT)\big)$	(17)
	$\frac{dI_{2b}}{dt} = \big((K_{i1} \times I_{2a} \times M_1) - (K_{j1} \times I_{2b}) - (K_{i1} \times I_{2b} \times M_1) + (K_{j1} \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b} ThT)\big)$	(18)
	$\frac{dI_{2c}}{dt} = \big((K_{i1} \times I_{2b} \times M_1) - (K_{j1} \times I_{2c}) - (K_{i1} \times I_{2c} \times M_1) + (K_{j1} \times I_{2d}) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c} ThT)\big)$	(19)

	$$\frac{dI_{2d}}{dt} = \Big((K_{i1} \times I_{2c} \times M_1) - (K_{j1} \times I_{2d}) - (K_{i1} \times I_{2d} \times M_1) + (K_{j1} \times I_3) - (K_a \times I_{2d} \times ThT) + (K_b \times I_{2d}ThT)\Big)$$	(20)
	$$\frac{dI_{3a}}{dt} = \Big((K_{i1} \times I_3 \times M_1) - (K_{j1} \times I_{3a}) - (K_{i1} \times I_{3a} \times M_1) + (K_{j1} \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a}ThT)\Big)$$	(21)
	$$\frac{dI_{3b}}{dt} = \Big((K_{i1} \times I_{3a} \times M_1) - (K_{j1} \times I_{3b}) - (K_{i1} \times I_{3b} \times M_1) + (K_{j1} \times I_{3c}) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b}ThT)\Big)$$	(22)
	$$\frac{dI_{3c}}{dt} = \Big((K_{i1} \times I_{3b} \times M_1) - (K_{j1} \times I_{3c}) - (K_{i1} \times I_{3c} \times M_1) + (K_{j1} \times I_{3d}) - (K_a \times I_{3c} \times ThT) + (K_b \times I_{3c}ThT)\Big)$$	(23)
	$$\frac{dI_{3d}}{dt} = \Big((K_{i1} \times I_{3c} \times M_1) - (K_{j1} \times I_{3d}) - (K_{i1} \times I_{3d} \times M_1) + (K_{j1} \times I_4) - (K_a \times I_{3d} \times ThT) + (K_b \times I_{3d}ThT)\Big)$$	(24)
	$$\frac{dB_{1a}}{dt} = \Big((K_{c1} \times B_1 \times M_1) - (K_{d1} \times B_{1a}) - (K_{c1} \times B_{1a} \times M_1) + (K_{d1} \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\Big)$$	(25)
	$$\frac{dB_{1b}}{dt} = \Big((K_{c1} \times B_{1a} \times M_1) - (K_{d1} \times B_{1b}) - (K_{c1} \times B_{1b} \times M_1) + (K_{d1} \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\Big)$$	(26)
	$$\frac{dB_{1c}}{dt} = \Big((K_{c1} \times B_{1b} \times M_1) - (K_{d1} \times B_{1c}) - (K_{c1} \times B_{1c} \times M_1) + (K_{d1} \times B_{1d}) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c}ThT)\Big)$$	(27)
	$$\frac{dB_{1d}}{dt} = \Big((K_{c1} \times B_{1c} \times M_1) - (K_{d1} \times B_{1d}) - (K_{c1} \times B_{1d} \times M_1) + (K_{d1} \times B_2) - (K_p \times B_{1d} \times ThT) + (K_q \times B_{1d}ThT)\Big)$$	(28)
	$$\frac{dB_{2a}}{dt} = \Big((K_{c1} \times B_2 \times M_1) - (K_{d1} \times B_{2a}) - (K_{c1} \times B_{2a} \times M_1) + (K_{d1} \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\Big)$$	(29)
	$$\frac{dB_{2b}}{dt} = \Big((K_{c1} \times B_{2a} \times M_1) - (K_{d1} \times B_{2b}) - (K_{c1} \times B_{2b} \times M_1) + (K_{d1} \times B_{2c}) - (K_p \times B_{2b} \times ThT) + (K_q \times B_{2b}ThT)\Big)$$	(30)
	$$\frac{dB_{2c}}{dt} = \Big((K_{c1} \times B_{2b} \times M_1) - (K_{d1} \times B_{2c}) - (K_{c1} \times B_{2c} \times M_1) + (K_{d1} \times B_{2d}) - (K_p \times B_{2c} \times ThT) + (K_q \times B_{2c}ThT)\Big)$$	(31)
	$$\frac{dB_{2d}}{dt} = \Big((K_{c1} \times B_{2c} \times M_1) - (K_{d1} \times B_{2d}) - (K_{c1} \times B_{2d} \times M_1) + (K_{d1} \times B_3) - (K_p \times B_{2d} \times ThT) + (K_q \times B_{2d}ThT)\Big)$$	(32)

Modification made in the ODE of Model-1F to incorporate the inhibitor effect for α-Syn protein:

Equation changed to incorporate the effect of inhibitor in Model-1F for α-Syn protein.[27]

	$$\frac{dM_2}{dt} = \left(\left(\left[\frac{K_x}{1 + (K_{x1} \times INBA1)}\right] \times M_1^2\right) - (K_y \times M_2) - \left(\left[\frac{K_x}{1 + (K_{x1} \times INBA1)}\right] \times M_1 \times M_2\right) + (K_y \times M_3)\right)$$	(1)

	$\frac{dM_3}{dt} = \left(\left(\left[\frac{K_x}{1+(K_{x1} \times INBA1)}\right] \times M_1 \times M_2\right) - \left(K_y \times M_3\right) - \left(\left[\frac{K_x}{1+(K_{x1} \times INBA1)}\right] \times M_1 \times M_3\right) + \left(K_y \times M_4\right)\right)$	(2)
	$\frac{dM_4}{dt} = \left(\left(\left[\frac{K_x}{1+(K_{x1} \times INBA1)}\right] \times M_1 \times M_3\right) - \left(K_y \times M_4\right) - \left(\left[\frac{K_x}{1+(K_{x1} \times INBA1)}\right] \times M_1 \times M_4\right) + \left(K_y \times M_5\right)\right)$	(3)
	$\frac{dM_5}{dt} = \left(\left(\left[\frac{K_x}{1+(K_{x1} \times INBA1)}\right] \times M_1 \times M_4\right) - \left(K_y \times M_5\right) - (K_m \times M_5) + (K_{mi} \times AC) - (K_{ac} \times M_5 \times I_4)\right)$	(4)
	$\frac{dAC}{dt} = \left((K_{ac} \times M_5 \times I_4) + (K_m \times M_5) - (K_{mi} \times AC) - \left(\left[\frac{K_s}{1+(K_{s1} \times INBA1)}\right] \times AC\right) + (K_t \times I_1)\right)$	(5)
	$\frac{dI_1}{dt} = \left(\left(\left[\frac{K_s}{1+(K_{s1} \times INBA1)}\right] \times AC\right) - (K_t \times I_1) - (2 \times K_i \times I_1^2) + \left(2 \times K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (K_i \times I_1 \times I_3) + \left(K_j \times I_4\right) - (n \times K_i \times I_1 \times M_1) + \left(n \times K_j \times I_{1a}\right) - (K_c \times I_1 \times B_1) + (K_d \times B_2) - (K_c \times I_1 \times B_2) + (K_d \times B_3) - (K_a \times I_1 \times ThT) + (K_b \times I_1 ThT)\right)$	(6)
	$\frac{dI_2}{dt} = \left((K_i \times I_1^2) - \left(K_j \times I_2\right) - (K_i \times I_1 \times I_2) + \left(K_j \times I_3\right) - (n \times K_i \times I_2 \times M_1) + \left(n \times K_j \times I_{2a}\right) + (n \times K_i \times I_{1d} \times M_1) - \left(n \times K_j \times I_2\right) - (K_a \times I_2 \times ThT) + (K_b \times I_2 ThT)\right)$	(7)
	$\frac{dI_3}{dt} = \left((K_i \times I_1 \times I_2) - \left(K_j \times I_3\right) - (K_i \times I_1 \times I_3) + \left(K_j \times I_4\right) - (n \times K_i \times I_3 \times M_1) + \left(n \times K_j \times I_{3a}\right) + (n \times K_i \times I_{2d} \times M_1) - \left(n \times K_j \times I_3\right) - (K_a \times I_3 \times ThT) + (K_b \times I_3 ThT)\right)$	(8)
	$\frac{dI_4}{dt} = \left((K_i \times I_1 \times I_3) - \left(K_j \times I_4\right) - (K_e \times I_4) + \left(K_f \times B_1\right) + (n \times K_i \times I_{3d} \times M_1) - \left(n \times K_j \times I_4\right) - (K_a \times I_4 \times ThT) + (K_b \times I_4 ThT)\right)$	(9)
	$\frac{dB_1}{dt} = \left((K_e \times I_4) - \left(K_f \times B_1\right) - (K_c \times B_1 \times I_1) + (K_d \times B_2) - (n1 \times K_c \times B_1 \times M_1) + (n1 \times K_d \times B_{1a}) - (K_p \times B_1 \times ThT) + \left(K_q \times B_1 ThT\right)\right)$	(10)
	$\frac{dB_2}{dt} = \left((K_c \times B_1 \times I_1) - (K_d \times B_2) - (K_c \times B_2 \times I_1) + (K_d \times B_3) + (n1 \times K_c \times B_{1d} \times M_1) - (n1 \times K_d \times B_2) - (n1 \times K_c \times B_2 \times M_1) + (n1 \times K_d \times B_{2a}) - (K_p \times B_2 \times ThT) + \left(K_q \times B_2 ThT\right)\right)$	(11)
	$\frac{dB_3}{dt} = \left((K_c \times B_2 \times I_1) - (K_d \times B_3) + (n1 \times K_c \times B_{2d} \times M_1) - (n1 \times K_d \times B_3) - \left(K_p \times B_3 \times ThT\right) + \left(K_q \times B_3 ThT\right)\right)$	(12)
	$\frac{dI_{1a}}{dt} = \left((n \times K_i \times I_1 \times M_1) - \left(n \times K_j \times I_{1a}\right) - (n \times K_i \times I_{1a} \times M_1) + \left(n \times K_j \times I_{1b}\right) - (K_a \times I_{1a} \times ThT) + (K_b \times I_{1a} ThT)\right)$	(13)

	$\frac{dI_{1b}}{dt} = \Big((n \times K_i \times I_{1a} \times M_1) - (n \times K_j \times I_{1b}) - (n \times K_i \times I_{1b} \times M_1) + (n \times K_j \times I_{1c}) - (K_a \times I_{1b} \times ThT) + (K_b \times I_{1b}ThT)\Big)$	(14)
	$\frac{dI_{1c}}{dt} = \Big((n \times K_i \times I_{1b} \times M_1) - (n \times K_j \times I_{1c}) - (n \times K_i \times I_{1c} \times M_1) + (n \times K_j \times I_{1d}) - (K_a \times I_{1c} \times ThT) + (K_b \times I_{1c}ThT)\Big)$	(15)
	$\frac{dI_{1d}}{dt} = \Big((n \times K_i \times I_{1c} \times M_1) - (n \times K_j \times I_{1d}) - (n \times K_i \times I_{1d} \times M_1) + (n \times K_j \times I_2) - (K_a \times I_{1d} \times ThT) + (K_b \times I_{1d}ThT)\Big)$	(16)
	$\frac{dI_{2a}}{dt} = \Big((n \times K_i \times I_2 \times M_1) - (n \times K_j \times I_{2a}) - (n \times K_i \times I_{2a} \times M_1) + (n \times K_j \times I_{2b}) - (K_a \times I_{2a} \times ThT) + (K_b \times I_{2a}ThT)\Big)$	(17)
	$\frac{dI_{2b}}{dt} = \Big((n \times K_i \times I_{2a} \times M_1) - (n \times K_j \times I_{2b}) - (n \times K_i \times I_{2b} \times M_1) + (n \times K_j \times I_{2c}) - (K_a \times I_{2b} \times ThT) + (K_b \times I_{2b}ThT)\Big)$	(18)
	$\frac{dI_{2c}}{dt} = \Big((n \times K_i \times I_{2b} \times M_1) - (n \times K_j \times I_{2c}) - (n \times K_i \times I_{2c} \times M_1) + (n \times K_j \times I_{2d}) - (K_a \times I_{2c} \times ThT) + (K_b \times I_{2c}ThT)\Big)$	(19)
	$\frac{dI_{2d}}{dt} = \Big((n \times K_i \times I_{2c} \times M_1) - (n \times K_j \times I_{2d}) - (n \times K_i \times I_{2d} \times M_1) + (n \times K_j \times I_3) - (K_a \times I_{2d} \times ThT) + (K_b \times I_{2d}ThT)\Big)$	(20)
	$\frac{dI_{3a}}{dt} = \Big((n \times K_i \times I_3 \times M_1) - (n \times K_j \times I_{3a}) - (n \times K_i \times I_{3a} \times M_1) + (n \times K_j \times I_{3b}) - (K_a \times I_{3a} \times ThT) + (K_b \times I_{3a}ThT)\Big)$	(21)
	$\frac{dI_{3b}}{dt} = \Big((n \times K_i \times I_{3a} \times M_1) - (n \times K_j \times I_{3b}) - (n \times K_i \times I_{3b} \times M_1) + (n \times K_j \times I_{3c}) - (K_a \times I_{3b} \times ThT) + (K_b \times I_{3b}ThT)\Big)$	(22)
	$\frac{dI_{3c}}{dt} = \Big((n \times K_i \times I_{3b} \times M_1) - (n \times K_j \times I_{3c}) - (n \times K_i \times I_{3c} \times M_1) + (n \times K_j \times I_{3d}) - (K_a \times I_{3c} \times ThT) + (K_b \times I_{3c}ThT)\Big)$	(23)
	$\frac{dI_{3d}}{dt} = \Big((n \times K_i \times I_{3c} \times M_1) - (n \times K_j \times I_{3d}) - (n \times K_i \times I_{3d} \times M_1) + (n \times K_j \times I_4) - (K_a \times I_{3d} \times ThT) + (K_b \times I_{3d}ThT)\Big)$	(24)
	$\frac{dB_{1a}}{dt} = \Big((n1 \times K_c \times B_1 \times M_1) - (n1 \times K_d \times B_{1a}) - (n1 \times K_c \times B_{1a} \times M_1) + (n1 \times K_d \times B_{1b}) - (K_p \times B_{1a} \times ThT) + (K_q \times B_{1a}ThT)\Big)$	(25)
	$\frac{dB_{1b}}{dt} = \Big((n1 \times K_c \times B_{1a} \times M_1) - (n1 \times K_d \times B_{1b}) - (n1 \times K_c \times B_{1b} \times M_1) + (n1 \times K_d \times B_{1c}) - (K_p \times B_{1b} \times ThT) + (K_q \times B_{1b}ThT)\Big)$	(26)
	$\frac{dB_{1c}}{dt} = \Big((n1 \times K_c \times B_{1b} \times M_1) - (n1 \times K_d \times B_{1c}) - (n1 \times K_c \times B_{1c} \times M_1) + (n1 \times K_d \times B_{1d}) - (K_p \times B_{1c} \times ThT) + (K_q \times B_{1c}ThT)\Big)$	(27)
	$\frac{dB_{1d}}{dt} = \Big((n1 \times K_c \times B_{1c} \times M_1) - (n1 \times K_d \times B_{1d}) - (n1 \times K_c \times B_{1d} \times M_1) + (n1 \times K_d \times B_2) - (K_p \times B_{1d} \times ThT) + (K_q \times B_{1d}ThT)\Big)$	(28)
	$\frac{dB_{2a}}{dt} = \Big((n1 \times K_c \times B_2 \times M_1) - (n1 \times K_d \times B_{2a}) - (n1 \times K_c \times B_{2a} \times M_1) + (n1 \times K_d \times B_{2b}) - (K_p \times B_{2a} \times ThT) + (K_q \times B_{2a}ThT)\Big)$	(29)

	$\frac{dB_{2b}}{dt} = \Big((n1 \times K_c \times B_{2a} \times M_1) - (n1 \times K_d \times B_{2b}) - (n1 \times K_c \times B_{2b} \times M_1) + (n1 \times K_d \times B_{2c}) - (K_p \times B_{2b} \times ThT) + \big(K_q \times B_{2b}ThT\big)\Big)$	(30)
	$\frac{dB_{2c}}{dt} = \Big((n1 \times K_c \times B_{2b} \times M_1) - (n1 \times K_d \times B_{2c}) - (n1 \times K_c \times B_{2c} \times M_1) + (n1 \times K_d \times B_{2d}) - (K_p \times B_{2c} \times ThT) + \big(K_q \times B_{2c}ThT\big)\Big)$	(31)
	$\frac{dB_{2d}}{dt} = \Big((n1 \times K_c \times B_{2c} \times M_1) - (n1 \times K_d \times B_{2d}) - (n1 \times K_c \times B_{2d} \times M_1) + (n1 \times K_d \times B_3) - (K_p \times B_{2d} \times ThT) + \big(K_q \times B_{2d}ThT\big)\Big)$	(32)
	$\frac{dI_1ThT}{dt} = \big((K_a \times I_1 \times ThT) - (K_b \times I_1ThT)\big)$	(33)
	$\frac{dI_2ThT}{dt} = \big((K_a \times I_2 \times ThT) - (K_b \times I_2ThT)\big)$	(34)
	$\frac{dI_3ThT}{dt} = \big((K_a \times I_3 \times ThT) - (K_b \times I_3ThT)\big)$	(35)
	$\frac{dI_4ThT}{dt} = \big((K_a \times I_4 \times ThT) - (K_b \times I_4ThT)\big)$	(36)
	$\frac{dB_1ThT}{dt} = \Big(\big(K_p \times B_1 \times ThT\big) - \big(K_q \times B_1ThT\big)\Big)$	(37)
	$\frac{dB_2ThT}{dt} = \Big(\big(K_p \times B_2 \times ThT\big) - \big(K_q \times B_2ThT\big)\Big)$	(38)
	$\frac{dB_3ThT}{dt} = \Big(\big(K_p \times B_3 \times ThT\big) - \big(K_q \times B_3ThT\big)\Big)$	(39)
	$\frac{dI_{1a}ThT}{dt} = \big((K_a \times I_{1a} \times ThT) - (K_b \times I_{1a}ThT)\big)$	(40)
	$\frac{dI_{1b}ThT}{dt} = \big((K_a \times I_{1b} \times ThT) - (K_b \times I_{1b}ThT)\big)$	(41)
	$\frac{dI_{1c}ThT}{dt} = \big((K_a \times I_{1c} \times ThT) - (K_b \times I_{1c}ThT)\big)$	(42)
	$\frac{dI_{1d}ThT}{dt} = \big((K_a \times I_{1d} \times ThT) - (K_b \times I_{1d}ThT)\big)$	(43)
	$\frac{dI_{2a}ThT}{dt} = \big((K_a \times I_{2a} \times ThT) - (K_b \times I_{2a}ThT)\big)$	(44)
	$\frac{dI_{2b}ThT}{dt} = \big((K_a \times I_{2b} \times ThT) - (K_b \times I_{2b}ThT)\big)$	(45)
	$\frac{dI_{2c}ThT}{dt} = \big((K_a \times I_{2c} \times ThT) - (K_b \times I_{2c}ThT)\big)$	(46)
	$\frac{dI_{2d}ThT}{dt} = \big((K_a \times I_{2d} \times ThT) - (K_b \times I_{2d}ThT)\big)$	(47)
	$\frac{dI_{3a}ThT}{dt} = \big((K_a \times I_{3a} \times ThT) - (K_b \times I_{3a}ThT)\big)$	(48)
	$\frac{dI_{3b}ThT}{dt} = \big((K_a \times I_{3b} \times ThT) - (K_b \times I_{3b}ThT)\big)$	(49)
	$\frac{dI_{3c}ThT}{dt} = \big((K_a \times I_{3c} \times ThT) - (K_b \times I_{3c}ThT)\big)$	(50)
	$\frac{dI_{3d}ThT}{dt} = \big((K_a \times I_{3d} \times ThT) - (K_b \times I_{3d}ThT)\big)$	(51)
	$\frac{dB_{1a}ThT}{dt} = \Big(\big(K_p \times B_{1a} \times ThT\big) - \big(K_q \times B_{1a}ThT\big)\Big)$	(52)

	$\frac{dB_{1b}ThT}{dt} = \left((K_p \times B_{1b} \times ThT) - (K_q \times B_{1b}ThT) \right)$	(53)
	$\frac{dB_{1c}ThT}{dt} = \left((K_p \times B_{1c} \times ThT) - (K_q \times B_{1c}ThT) \right)$	(54)
	$\frac{dB_{1d}ThT}{dt} = \left((K_p \times B_{1d} \times ThT) - (K_q \times B_{1d}ThT) \right)$	(55)
	$\frac{dB_{2a}ThT}{dt} = \left((K_p \times B_{2a} \times ThT) - (K_q \times B_{2a}ThT) \right)$	(56)
	$\frac{dB_{2b}ThT}{dt} = \left((K_p \times B_{2b} \times ThT) - (K_q \times B_{2b}ThT) \right)$	(57)
	$\frac{dB_{2c}ThT}{dt} = \left((K_p \times B_{2c} \times ThT) - (K_q \times B_{2c}ThT) \right)$	(58)
	$\frac{dB_{2d}ThT}{dt} = \left((K_p \times B_{2d} \times ThT) - (K_q \times dThT) \right)$	(59)
	Algebraic Equations	
	$P_{total} = (M_1 + 2 \times M_2 + 3 \times M_3 + 4 \times M_4 + 5 \times M_5 + 5 \times AC + 5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT + 16 \times I_{3a} + 16 \times I_{3a}ThT + 17 \times I_{3b} + 17 \times I_{3b}ThT + 18 \times I_{3c} + 18 \times I_{3c}ThT + 19 \times I_{3d} + 19 \times I_{3d}ThT + 20 \times B_1 + 20 \times B_1ThT + 21 \times B_{1a} + 21 \times B_{1a}ThT + 22 \times B_{1b} + 22 \times B_{1b}ThT + 23 \times B_{1c} + 23 \times B_{1c}ThT + 24 \times B_{1d} + 24 \times B_{1d}ThT + 25 \times B_2 + 25 \times B_2ThT + 26 \times B_{2a} + 26 \times B_{2a}ThT + 27 \times B_{2b} + 27 \times B_{2b}ThT + 28 \times B_{2c} + 28 \times B_{2c}ThT + 29 \times B_{2d} + 29 \times B_{2d}ThT + 30 \times B_3 + 30 \times B_3ThT)$	(1)
	$ThT_{total} = (ThT + I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_{3d}ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(2)
	Observables	
	$BoundedThT = S \times (I_1ThT + I_{1a}ThT + I_{1b}ThT + I_{1c}ThT + I_{1d}ThT + I_2ThT + I_{2a}ThT + I_{2b}ThT + I_{2c}ThT + I_{2d}ThT + I_3ThT + I_{3a}ThT + I_{3b}ThT + I_{3c}ThT + I_{3d}ThT + B_1ThT + B_{1a}ThT + B_{1b}ThT + B_{1c}ThT + B_{1d}ThT + B_2ThT + B_{2a}ThT + B_{2b}ThT + B_{2c}ThT + B_{2d}ThT + B_3ThT)$	(1)
	$\%\,of\,I = (5 \times I_1 + 5 \times I_1ThT + 6 \times I_{1a} + 6 \times I_{1a}ThT + 7 \times I_{1b} + 7 \times I_{1b}ThT + 8 \times I_{1c} + 8 \times I_{1c}ThT + 9 \times I_{1d} + 9 \times I_{1d}ThT + 10 \times I_2 + 10 \times I_2ThT + 11 \times I_{2a} + 11 \times I_{2a}ThT + 12 \times I_{2b} + 12 \times I_{2b}ThT + 13 \times I_{2c} + 13 \times I_{2c}ThT + 14 \times I_{2d} + 14 \times I_{2d}ThT + 15 \times I_3 + 15 \times I_3ThT + 16 \times I_{3a} + 16 \times I_{3a}ThT + 17 \times I_{3b} + 17 \times I_{3b}ThT + 18 \times I_{3c} + 18 \times I_{3c}ThT + 19 \times I_{3d} + 19 \times I_{3d}ThT)$	(2)

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