WHAT IS CLAIMED IS:

1. A computer implemented method for predicting locations where pathological protein aggregates will develop in the brain of a subject who has a neurological or a neurodegenerative disease, the computer performing steps comprising:

a) receiving an image of the brain of the subject;
b) identifying pathological protein aggregates in the image using a machine learning algorithm;
c) mapping positions of the pathological protein aggregates to neuroanatomical regions;
d) modeling a discretized distribution of the pathological protein aggregates in each neuroanatomical region as a set of differential equations using a Smoluchowski network model;
e) using regional gene density maps for each neuroanatomical region to calculate a distribution of gene effects on regional spreading and decay of the pathological protein aggregates;
f) predicting changes in regional density of the pathological protein aggregates as a function of time by modeling spreading, aggregation, decay, and the spatial gene expression of the pathological protein aggregates throughout the neuroanatomical regions, wherein spreading is assumed to occur retrogradely between anatomically interconnected neuroanatomical regions, wherein spreading is modeled as diffusion through a weighted directed graph connecting the neuroanatomical regions of the brain of the subject; and
g) predicting past locations, present locations, and future locations of the pathological protein aggregates based on said modeling.

2. The computer implemented method of claim 1, further comprising adjusting one or more programmed neurostimulation parameters based on said predicting the changes in regional density of the pathological protein aggregates as a function of time.

3. The computer implemented method of claim 2, wherein the one or more programmed neurostimulation parameters are selected from duration, amplitude, frequency, pulse width, and location of the neurostimulation.

4. The computer implemented method of any one of claims 1-3, further comprising instructing a neurostimulation device to apply neurostimulation to locations of the brain where

pathological protein aggregates are predicted to be present in order to treat the neurological or neurodegenerative disease in the subject.

5. The computer implemented method of claim 4, further comprising instructing the neurostimulation device to apply electrical stimulation to locations of the brain where pathological protein aggregates are not yet present but are predicted to occur at a future time based on said predicting changes in the regional density of the pathological protein aggregates as a function of time.

6. The computer implemented method of claim 1, further comprising:

performing image registration to a coordinate space comprising a plurality of voxels, wherein each voxel is represented as a cubic volumetric element centered at a coordinate in the coordinate space;

identifying positions in x, y, z coordinates of each pathological protein aggregate in the coordinate space;

measuring volumes of each pathological protein aggregate from total number of voxels occupied by each pathological protein aggregate;

calculating aggregate density for each voxel, wherein the aggregate density for each voxel is determined from total number of pathological protein aggregates having centers within the same voxel;

calculating total aggregate size for each voxel, wherein the total aggregate size is the total size of all the pathological protein aggregates having centers within the same voxel;

calculating mean aggregate size for each voxel as the total aggregate size divided by the aggregate density for each voxel;

calculating total signal intensity for each voxel from the total intensity of all the pathological protein aggregates having centers within the same voxel; and

calculating mean signal intensity for each voxel as the total signal intensity divided by the aggregate density for each voxel.

7. The computer implemented method of claim 1, wherein said modeling the discretized distribution of the pathological protein aggregates in each neuroanatomical region as a set of differential equations using a Smoluchowski network model comprises using the following set of differential equations:

$$\frac{dc_{1,j}}{dt} = -\alpha \sum_{k=1}^{V} L_{jk}\, c_{1,k} - \mu_{1,j} c_{1,j} - 2c_{1,j}^{2}\left(\kappa_j + \xi \sum_{k=2}^{N} k c_{2,k}\right) - c_{1,j} \sum_{k=2}^{N} c_{k,j},$$

$$\frac{dc_{2,j}}{dt} = -2^{-\eta}\alpha\sum_{k=1}^{V} L_{jk}\, c_{2,k} - 2^{\lambda}\mu_{2,j}c_{2,j} + c_{1,j}^{2}\left(\kappa_j + \xi\sum_{k=2}^{N} kc_{2,k}\right) - c_{1,j}c_{2,j},$$

$$\frac{dc_{i,j}}{dt} = -i^{-\eta}\alpha\sum_{k=1}^{V} L_{jk}\, c_{i,k} - i^{\lambda}\mu_{i,j}c_{i,j} + c_{1,j}\left(c_{i-1,j} - ci,j\right), \text{ and}$$

$$\frac{dc_{N,j}}{dt} = -N^{\lambda}\mu_{N,j}c_{N,j} + c_{1,j}c_{N-1,j},$$

wherein $c_{i,j}$ represents the total count of pathological protein aggregates in a discretized size-bin indexed by *I*, in a brain region indexed by *j*, wherein an *L* matrix represents the Laplacian matrix of the weighted directed graph connecting the neuroanatomical regions of the brain, wherein η is chosen as a hyperparameter that slows the spread of large aggregates as the inverse power of the size, and wherein λ is chosen as a hyperparameter that accelerates the decay of pathological protein aggregates proportionally to the power of their size.

8. The computer implemented method of claim 7, wherein initial values for α and μ are fit by sweeping through a 2-dimensional-grid and selecting values that result in a lowest mean-squared error between predicted and actual counts of the pathological protein aggregates.

9. The computer implemented method of claim 7, wherein the initial value of $\mu = 0$, the initial value of $k = 0$, $\xi = 0$, and *c* is a one-dimensional size vector, wherein the set of differential equations simplifies to a standard network diffusion model.

10. The computer implemented method of claim 7, further comprising quantifying sensitivity of the model to specific neuroanatomical pathways in the brain, wherein a Jacobian matrix is calculated by taking a partial derivative of the model's output with respect to the weight of the anatomical connection strength between two neuroanatomical regions encoded into the model, wherein an element of the Jacobian matrix represents relative contribution of the anatomical connection between the two neuroanatomical regions to the spreading of pathological protein aggregates to a specific region of the brain.

11. The computer implemented method of claim 7, further comprising using the model to produce a ranking of candidate seed locations for a given pathological state c at $t = T$ months post-injection (MPI) by a method comprising:

using each of the neuroanatomical regions as separate seed locations at $t = 0$ within the model and simulated forward in time to $t = T$ MPI, wherein each of the simulation results for the different neuroanatomical regions are compared with an observed state c using a pairwise

similarity metric, wherein the similarity metric is a correlation coefficient between total regional aggregate counts across observed and simulated states; and

using the similarity metric values to sort the seed locations for the neuroanatomical regions as likely sites that lead to the observed pathological state c, wherein the ranking of candidate seed locations for the given pathological state c at $t = T$ MPI is produced.

12. The computer implemented method of claim 11, further comprising predicting the time since seeding $t = T$ MPI for a given pathological state c by a method comprising:

comparing the whole-brain distribution of aggregate sizes for state c with simulated distributions at various t using a pairwise similarity metric without taking the seed location into account, wherein the distribution of simulated aggregate sizes across the whole brain is assumed to be invariant with respect to which neuroanatomical region is used as the seed location at $t = 0$; and

calculating the mean squared error between the stimulated and observed distributions, wherein when deciding among several candidate t values, the mean squared errors are inverted and normalized to sum to 1 to provide a prediction probability for each t being the correct estimate of T for the given pathological state c.

13. The computer implemented method of claim 7, wherein the gene effects on regional spreading and decay of the pathological protein aggregates are determined by a method comprising:

assuming that α (spreading) and μ (decay) parameters are regionally dependent, wherein the spreading from a specific neuroanatomical region is proportional to the gene density in that region;

normalizing all genes to the same range so that only the regional distribution of gene expression relative to that gene's total whole-brain expression is compared, wherein α is a vector, and the product of α with the Laplacian connectivity matrix L has the effect of modifying the regional connectivity encoded into the model; and

normalizing each gene vector to have a mean of 1 and a standard deviation Σ that is empirically set to preserve a correlation between predicted and observed whole-brain aggregate count, wherein the normalization is chosen so that the product has the effect of maintaining the trace of the original Laplacian connectivity matrix *L*.

14. The computer implemented method of claim 13, wherein derivation of the normalization for maintaining the trace of the original Laplacian connectivity matrix *L* comprises:

assuming the vector *s* is sampled from a multivariate normal distribution with mean-value 1 and standard deviation Σ, wherein $s \sim N(1, \Sigma)$;

using a definition of the matrix trace and representing *s* as a diagonal square matrix *S*, wherein the trace of the product of *S* and the Laplacian connectivity matrix *L* results in the following:

$$Tr(SL) = Tr\left(\begin{bmatrix} s_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & s_V \end{bmatrix} L\right) = \sum_{i=1}^{V} s_i L_{ii} = s \cdot \mathrm{diag}(L) = s \cdot l,$$

wherein *l* represents the diagonal of *L*, and wherein the trace is equivalent to the dot product of *s* and *l*, which has an expectation value equivalent to the sum of the entries of *l*, which recovers the definition of the trace of *L* according to the following equations:

$$s \cdot l \sim N(1 \cdot l,\ l\,\Sigma\,l)$$

$$\mathrm{E}[s \cdot l] = \mathrm{Tr}(L),$$

wherein after each gene is encoded into the model;

comparing net effects on the regional correlation between the simulated and actual data to the baseline correlation with no genes; and

providing an ordered list of genes ranked by the relevance of their spatial expression map in improving the regional predictions of the model.

15. The computer implemented method of claim 1, wherein the cubic volumetric element has a width of 100 μm in the coordinate space.

16. The computer implemented method of any one of claims 1, wherein one or more pathological protein aggregates map to a single voxel.

17. The computer implemented method of claim 1, further comprising performing multidimensional Gaussian filtering to account for variations in image registration between different samples.

18. The computer implemented method of claim 1, further comprising:

receiving a second image of the brain, wherein the second image is taken after said neurostimulation is applied to the brain;

repeating steps (b)-(o) using the second image; and

displaying changes in the total aggregate size for each voxel, the volume of each pathological protein aggregate for each voxel, and the aggregate density for each voxel in the image taken after said neurostimulation is applied to the brain of the subject compared to the image taken before said neurostimulation is applied to the brain of the subject.

19. The computer implemented method of claim 1, further comprising:

receiving a second image of the brain, wherein the second image is taken after said neurostimulation is applied to the brain;

repeating steps (b)-(o) using the second image;

modulating one or more programmed neurostimulation parameters based on any changes in the past locations, present locations, or future locations where the pathological protein aggregates are predicted to occur; and

instructing a neurostimulation device to apply modulated neurostimulation to the brain of the subject in order to treat the neurological or neurodegenerative disease in the subject.