

Cell-Level Model to Predict the Spatiotemporal Dynamics of Neurodegenerative Disease

Shih-Huan Huang (黃士桓)^{1,2} Matthew W. Cotton^{1,2} Tuomas P. J. Knowles,^{1,3}
David Klenerman^{1,2} and Georg Meisl^{1,2,*}

¹Yusuf Hamied Department of Chemistry, *University of Cambridge*, Cambridge, United Kingdom

²UK Dementia Research Institute, *University of Cambridge*, Cambridge, United Kingdom

³Cavendish Laboratory, *University of Cambridge*, Cambridge, United Kingdom



(Received 22 August 2025; accepted 14 January 2026; published 17 February 2026)

A central challenge in modeling neurodegenerative diseases is connecting cellular-level mechanisms to tissue-level pathology, in particular to determine whether pathology is driven primarily by cell-autonomous triggers or by propagation from cells that are already in a pathological, runaway aggregation state. To bridge this gap, we develop here a bottom-up physical model that explicitly incorporates these two fundamental cell-level drivers of protein aggregation dynamics. We show that our model naturally explains the characteristic long, slow development of pathology followed by a rapid acceleration, a hallmark of many neurodegenerative diseases. Furthermore, the model reveals the existence of a critical switch point at which the system's dynamics transition from being dominated by slow, spontaneous formation of diseased cells to being driven by fast propagation. We explore the different limiting behaviours of this model, derive approximate analytical solutions for several observables, and demonstrate the parallels to models used in population epidemiology. This framework offers a method to simulate disease propagation and intervention *in silico* and provides a robust physical foundation for interpreting pathological data.

DOI: [10.1103/f9hz-xvpr](https://doi.org/10.1103/f9hz-xvpr)

I. INTRODUCTION

Current understanding of neurodegenerative diseases is limited by the challenge of connecting the microscopic mechanisms of protein aggregation to the macroscopic patterns of pathology observed in patients. While the general link between protein aggregation and disease is well-established [1], the physical principles governing the emergence of disease-specific patterns, such as the distinct spatial patterns or the characteristic long, slow initial phase followed by rapid progression [2], remain poorly understood, hindering the development of rationally designed therapies [3].

This difficulty stems from the fundamental multiscale nature of the problem [Fig. 1(a)]. Current kinetic theories describe protein filament assembly at the molecular level [4–6], and network models capture phenomenological spreading at the organ level [7,8], but the crucial mesoscopic, or tissue, scale is left without a first-principles framework. Thus, there currently is no theory that connects the behavior of individual cells to the emergent aggregation patterns observed in patient tissue.

This theoretical gap is particularly problematic as it hinders our ability to resolve a central mechanistic question: does pathology arise primarily from cell-autonomous triggers

within vulnerable cells, or is the major driver a spreading mechanism from cells that are already in a pathological, runaway aggregation state [9,10]? The challenge in distinguishing the contributions of these two fundamental mechanistic pathways from pathological data has been a major barrier to progress in the field [11] as effective therapies should target fundamentally different processes in the two scenarios.

To bridge this gap, we develop a bottom-up physical multiscale model connecting molecular, cellular, and tissue levels. Our framework explicitly incorporates both cell-autonomous triggers and cell-to-cell propagation to simulate the stochastic evolution of aggregation at the single-cell level. We showcase the varied behavior this minimal model gives rise to in different regimes, and we discuss the mathematical relationship to reaction diffusion equations and epidemiological models of the spread of disease in a susceptible population. By deriving analytical expressions for key spatial statistics, we provide a quantitative toolkit to infer the dominant aggregation mechanism from static patterns of aggregates, culminating in the derivation of a critical switch fraction that predicts when the system transitions from being cell-autonomous to propagation-dominated.

II. A CELL-LEVEL MODEL FOR NEURODEGENERATIVE DISEASES

To bridge the gap between molecular events and tissue-level pathology, we developed a biophysical model to describe the spread of disease within a tissue. We model the tissue as an ensemble of discrete cells, the fundamental unit of biological organization [13]. Each cell i is treated as a pointlike compartment at position $\mathbf{x}_i$ and is described by a single binary

*Contact author: gm373@cam.ac.uk

Published by the American Physical Society under the terms of the [Creative Commons Attribution 4.0 International](https://creativecommons.org/licenses/by/4.0/) license. Further distribution of this work must maintain attribution to the author(s) and the published article's title, journal citation, and DOI.

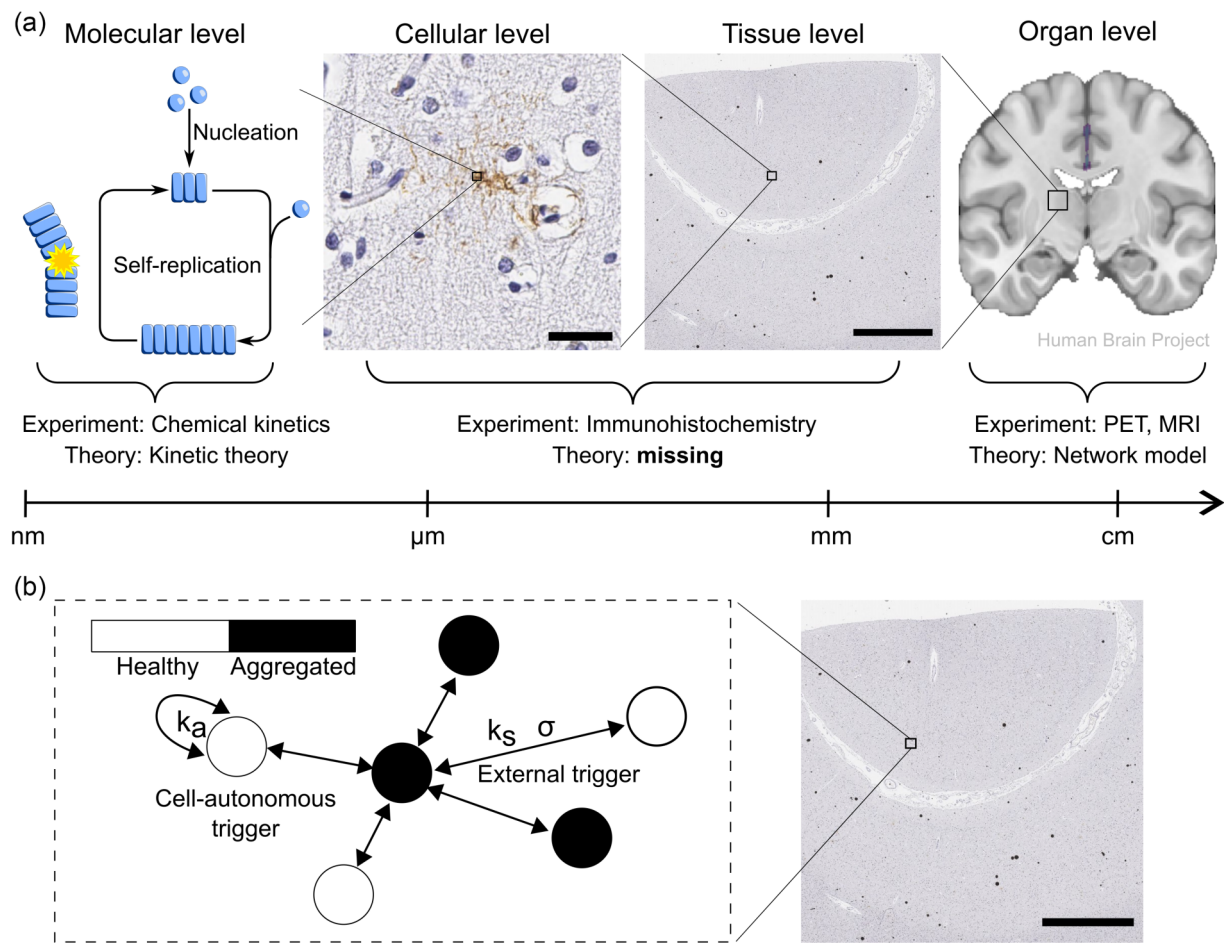


FIG. 1. Model description. (a) A central problem in neurodegenerative research is the lack of theory that can describe different systems across a wide range of temporal and spatial scales. Scale bar: cellular level: $30\ \mu\text{m}$; tissue level: 2 mm. The images for the cellular and tissue levels are examples of immunohistochemistry from the human frontal cortex, acquired from the Cambridge Brain Bank. The tissue is stained for protein aggregates (brown, DAB) and counterstained for cell nuclei (purple, hematoxylin). The brain image is adapted from the Human Brain Project [12]. (b) In our model, the fundamental unit is a cell. Aggregation can begin autonomously within a cell at a rate k_a (in units of time^{-1}). Additionally, cells that have already aggregated can trigger aggregation in neighboring cells. This interaction depends on the spatial coupling strength k_s (in units of time^{-1}) and a length-dependent factor characterized by σ (in units of length). Scale bar: 2 mm.

state variable, ϕ_i . This variable denotes whether the cell is “healthy” ($\phi_i = 0$) or has transitioned to a state of pathological protein aggregation ($\phi_i = 1$). In our model, cells are considered stationary, allowing us to focus purely on the change of their state from healthy to aggregated. This is a well-justified approximation for the biological context of most adult-onset neurodegenerative diseases in which the primarily affected cells are stationary cells such as neurons.

We simulate the evolution of tissue by prescribing ϕ_i for every cell at some initial time, and we proceed in discrete time steps, Δt , during which a healthy cell can transition to the aggregated state through two distinct mechanistic pathways.

The first pathway, the *cell-autonomous triggers*, represents processes that are intrinsic to a single cell and independent of its local environment. Depending on the disease, this cell-autonomous transition could be caused by a stochastic nucleation event, or via overwhelming of the cellular aggregate removal mechanisms [14,15]. The effect of rare nucleation events has been well established *in vitro* [16] and *in vivo* [17], and is likely the key driver of sporadic prion disease. By con-

trast, an overwhelming of aggregate removal mechanisms is a more likely scenario in common neurodegenerative disorders such as Alzheimer’s disease. This process may be driven by factors such as age-related accumulation of somatic mutations in neurons [18], or other stressors leading to a temporary failure of protein homeostasis [19] and ultimately runaway aggregation [20]. We coarse-grain these distinct processes into a single time-independent cell-autonomous rate, k_a (in units of time^{-1}). The probability $p_{a,i}$ that any given healthy cell i spontaneously transitions to the aggregated state in a small time interval Δt is therefore given by

$$p_{a,i} = 1 - \exp(-k_a \Delta t) \approx k_a \Delta t$$

for the short times Δt .

The second pathway, *cell-to-cell triggers*, encompasses all processes that are explicitly dependent on the state of neighboring cells. This can represent various biological processes, including the direct transport of pathogenic protein seeds between cells or the triggering of inflammatory responses [21,22], which in turn can compromise the protein

quality control systems of otherwise healthy cells, increasing their vulnerability to aggregation. If the pathology is still predominantly in stationary cells, (e.g., neurons and oligodendrocytes) but the motion of cells (e.g., microglia) is relevant for pathology, our models will generally capture this behavior by subsuming the cell movement into this cell-to-cell coupling term.

We model this coupling as a radially isotropic interaction function that decays with distance. Specifically, we use a Gaussian kernel for the majority of this work, as it represents a simple, canonical model for a diffusive process, but we also show that the conclusions are robust regardless of the choice of the specific interaction function. The probability, $p_{s,i}$, that a healthy cell i is triggered by its aggregated neighbors during Δt is then

$$p_{s,i} = 1 - e^{-\lambda_i \Delta t},$$

where λ_i is the local “cell-to-cell coupling rate”:

$$\lambda_i = \frac{k_s \sum_j (\phi_j e^{-d_{ij}^2/2\sigma^2})}{2\pi\sigma^2\rho}.$$

Here, d_{ij} is the distance between cell i and cell j , k_s is the spatial coupling strength (in units of time^{-1}), σ is the characteristic lengthscale of the interaction (in units of length), and ρ is the density of cells. The sum runs over all cells, but the nonzero contributions only come from the aggregated cells (for further details on how this functional form was derived, see Appendix A). We note that a first-order approximation ($p \approx k_a \Delta t$) is used only for the cell-autonomous pathway. This is possible as k_a is a fixed parameter in our simulations and we can thus choose a small Δt such that the condition $k_a \Delta t \ll 1$ is always satisfied. The local coupling rate λ_i , however, is a variable that can become large as the local density of aggregated cells increases. Therefore, the full exponential form is retained for $p_{s,i}$ to ensure the probability is bounded between 0 and 1. In this work, we have chosen a two-dimensional system for convenience, but the results, such as the emergence of distinct regimes, and the existence of a switch fraction, can trivially be extended to three dimensions.

We evaluate the dynamics of the system numerically using a discrete-time Markov chain: the state of every cell is updated at each time step Δt (see the Supplemental Material [23] for validation of convergence, Figs. S1A and S1B). A healthy cell i transitions to the aggregated state if it is triggered by either the cell-autonomous pathway (with probability $p_{a,i}$) or the cell-to-cell propagation pathway (with probability $p_{s,i}$), which are treated as independent stochastic events. As above, ρ is the two-dimensional density of cells, in units of distance^{-2} . Cell positions were initialized by drawing coordinates from a uniform random distribution within the simulation box, without an excluded volume constraint. The simulations were performed in a square domain with periodic boundary conditions, except for Fig. 5. In this work, we set the density to be constant to compare more easily with analytical results; however, this is not required by our simulation framework, as demonstrated in [24].

To ensure our simulations explore a biologically plausible parameter space, we have based our parameter choices on order-of-magnitude estimates from our own complementary work analyzing post-mortem brain tissue from patients with

Progressive Supranuclear Palsy [24]. In that work, we found that the mean intercellular distance of $27.3 \mu\text{m}$ corresponds to a cell density ρ of approximately 1342 cells/mm^2 . We also found that cell-to-cell-propagation dominates over cell-autonomous processes when more than 0.1% of cells are aggregated, and that the cell-to-cell coupling radius σ has a lower bound of $100 \mu\text{m}$. The parameters used throughout this manuscript are chosen to reflect these data-driven findings. We also note that the time units in our model are arbitrary to avoid overinterpretation. As most detailed experimental datasets are post-mortem, only a pseudo time-course can be assembled [11]. By contrast, the lengthscales and ratio of rates, reflected even in single time-point post-mortem measurements, are chosen to match the values observed in real data where possible [24].

III. RESULTS

To quantitatively characterize the spatial patterns of aggregation produced by our model, we employ three distinct measures, each sensitive to structure on a different length-scale. The *total fraction of aggregated cells* provides a macroscopic view of disease progression, analogous to read-outs from bulk tissue homogenates [25]. For understanding the emerging spatial patterns, we use two measures: The *nearest-neighbour distance (NND) distribution* is the probability distribution of distances from each aggregated cell to the nearest other aggregated cell. The *radial distribution function (RDF)*, $g_{\text{norm}}(r)$, is defined here as the average fraction of cells that are aggregated a distance r away from an aggregated cell. Mathematically, $g_{\text{norm}}(r) = \langle dn_r \rangle / \langle dn_c \rangle$, where dn_r and dn_c are the number of aggregated cells and the number of total cells, respectively, in an annulus of radius r and infinitesimal width, dr , around each aggregated cell. Note that this also captures the overall degree of aggregation in its magnitude and thus differs in its normalization from the standard definition of the radial distribution function in the statistical mechanics literature, where a value of 1 corresponds to a random arrangement at the average density. This definition was chosen to remove the effect from spatial variations in cell density, a common feature of experimental data. Together, these measures provide a comprehensive fingerprint of the aggregation pattern that can be directly compared to experimental data [24].

A. Spontaneous aggregation ($k_s = 0$) results in random spatial patterns

We initially consider the simplest limiting case where aggregation is driven exclusively by cell-autonomous triggers ($k_s = 0$). This scenario corresponds to a hypothetical disease process where cells are entirely independent, and pathology cannot spread between them. The aggregation of polyglutamine in a *C. elegans* model of Huntington’s disease is an example of such behavior [17].

In this limiting case, we predict three signatures: First, the total fraction of aggregated cells, n , increases as healthy cells transition to the aggregated state and is captured well by a simple analytical model of independent events [17]:

$$n(t) = 1 - e^{-k_a t}, \quad (1)$$

where k_a is the rate constant of the cell-autonomous process (see Appendix C for a complete derivation). Second, due to our specific normalization, the RDF should be a constant with a value equal to the total fraction of aggregated cells (see Appendix D for a full derivation), and third, the NND distribution should follow the analytical form for a Poisson point process:

$$P(\text{nearest-neighbor distance at } r \rightarrow r + dr) = 2\pi r D e^{-\pi r^2 D} dr, \quad (2)$$

where D is the density of aggregated cells (see Appendix E for a complete derivation). Here we have $D = \rho n$, where ρ and n is the density of cells, and the total fraction of aggregated cells, respectively.

As shown in the simulation snapshots [Fig. 2(b)], this regime produces a random, spatially uncorrelated scattering of aggregated cells across the tissue at all time points. This observation is confirmed quantitatively by the RDF [Fig. 2(c)], as $g_{\text{norm}}(r)$ is constant and is equal to the total fraction of aggregated cells. In addition, a good match between simulated total cell fraction aggregated and the analytical expression can be seen in Fig. 2(a). Finally, the simulated NND distribution agrees well with the analytical expression in Eq. (2) [Fig. 2(d)]. Note that at early times, the distribution appears noisy due to the low number of aggregated cells.

B. Propagating-only aggregation ($k_a \rightarrow 0$) leads to growing, spatially correlated clusters

In this limiting case, aggregation is driven solely by cell-to-cell propagation from an initial seed ($k_a \approx 0$). This case models a scenario where the disease spreads like an infection from a single starting point, a key feature of prionlike dynamics. The nature of this propagation depends critically on the interaction distance, σ , relative to the intercellular distance, $\rho^{-1/2}$. We therefore analyzed the behavior in two distinct regimes: the short-range and long-range coupling limits.

1. Short-range coupling generates dense clusters

First, we examined the short-range regime, where the interaction distance is comparable to the intercellular distance ($\sigma \sim \rho^{-1/2}$), modeling direct neighbor transmission. In this case, the simulations show the formation of a single cluster of aggregated cells, with a sharp boundary, that grows outwards as neighboring cells are sequentially triggered [Fig. 3(b)]. This dense region of aggregated cells creates two clear quantitative signatures. First, the NND distribution is sharply peaked at the mean intercellular distance and determined by the underlying density of all cells, ρ , not the number of aggregates [Fig. 3(d), Eq. (3)],

$$P(\text{nearest-neighbor distance at } r \rightarrow r + dr) = 2\pi r \rho e^{-\pi r^2 \rho} dr. \quad (3)$$

Second, the RDF shows a strong, sharp boundary, due to the cells forming a dense aggregated cluster [Fig. 3(c)]. In this short-range coupling limit, where the interaction lengthscale σ is comparable to the typical intercellular distance $\rho^{-1/2}$, the shape of the aggregation front is no longer smooth [Fig. 3(b)].

Instead, it is affected by the specific, random positions of individual cells. As the discretization matters in this limit, the aggregation pattern is therefore not well-described by a simple continuous model.

2. Long-range coupling gives rise to continuous traveling waves

We then investigated the long-range coupling regime, where the interaction distance is much larger than the intercellular distance ($\sigma \gg \rho^{-1/2}$). This corresponds to propagation beyond direct neighbors and in this limit we expect a continuum approximation to be valid. Here, the aggregation front is no longer sharp, but rather a diffuse boundary, which leads to a broad correlation peak in the RDF (see Fig. 4, where $\sigma/\rho^{-1/2} \approx 15$, compared to $\sigma/\rho^{-1/2} \approx 1.5$ in Fig. 3).

When the lengthscale of interactions is significantly longer than the lengthscale of discretization, a continuous model can be used to approximate the dynamics and derive closed form expressions that describe the evolution of the aggregation patterns. We describe the fraction of aggregated cells in a small volume at position $\mathbf{x}$ at time t as $n(\mathbf{x}, t)$, so that the density of aggregated cells is $\rho(\mathbf{x})n(\mathbf{x}, t)$. In this continuum limit, the cell-to-cell coupling rate at position $\mathbf{x}$ to aggregate is

$$\tilde{\lambda}(\mathbf{x}, t) = \frac{k_s}{2\pi\sigma^2\rho} \int_{\Omega} \rho(\mathbf{x}') n(\mathbf{x}', t) e^{-\frac{(\mathbf{x}-\mathbf{x}')^2}{2\sigma^2}} d^2\mathbf{x}', \quad (4)$$

where the integration is over the entire tissue, Ω , and for the uniform density we have $\rho(\mathbf{x}) = \rho$. Using a Taylor expansion to approximate, $n(\mathbf{x}', t) = n(\mathbf{x}, t) + \nabla n(\mathbf{x}, t)^T (\mathbf{x} - \mathbf{x}') + (1/2)(\mathbf{x} - \mathbf{x}')^T H_n(\mathbf{x}, t)(\mathbf{x} - \mathbf{x}') + \dots$, where $H_n(\mathbf{x}, t)$ is the Hessian matrix of n evaluated at $(\mathbf{x}, t)$, yielding

$$\tilde{\lambda}(\mathbf{x}, t) \approx k_s n(\mathbf{x}, t) + \frac{1}{2} k_s \sigma^2 \nabla^2 n(\mathbf{x}, t). \quad (5)$$

At every point, only the nonaggregated cells can transition to the aggregated state, so the fraction of aggregated cells will increase at a rate proportional to the number of nonaggregated cells, giving

$$\partial n(\mathbf{x}, t) / \partial t = \tilde{\lambda}(\mathbf{x}, t) [1 - n(\mathbf{x}, t)]. \quad (6)$$

Combining with Eq. (5), we obtain a partial differential equation for the fraction of aggregated cells,

$$\frac{\partial n(\mathbf{x}, t)}{\partial t} = \alpha [1 - n(\mathbf{x}, t)] n(\mathbf{x}, t) + \beta [1 - n(\mathbf{x}, t)] \nabla^2 n(\mathbf{x}, t), \quad (7)$$

with $\alpha = k_s$ and $\beta = \frac{1}{2} k_s \sigma^2$. We use numerical integration to obtain the solution to this nonlinear partial differential equation. As shown in Fig. 5(b), there is a close match between our discrete model and the numerical integrated results of Eq. (7).

Equation (7) has the form of a Fisher-KPP reaction-diffusion equation [26], with an additional $(1 - n)$ factor for the spatial term. For low densities where $1 - n \approx 1$, we can therefore obtain the limiting traveling wave speed as the speed of the Fisher wave,

$$v \geq \sqrt{2} k_s \sigma. \quad (8)$$

This analytical form for the wave speed still matches well our numerically integrated results of the traveling wave speed, as demonstrated in Fig. 5(c). A key observation is that, comparing the parameters in our model to those of Fisher-KPP, both the parameter for the local reaction, α , as well as the parameter for “diffusion,” β , depend on the rate of cell-to-cell triggering, via the spatial coupling strength, k_s . In other words, the local reaction term is governed by the same parameter as the longer

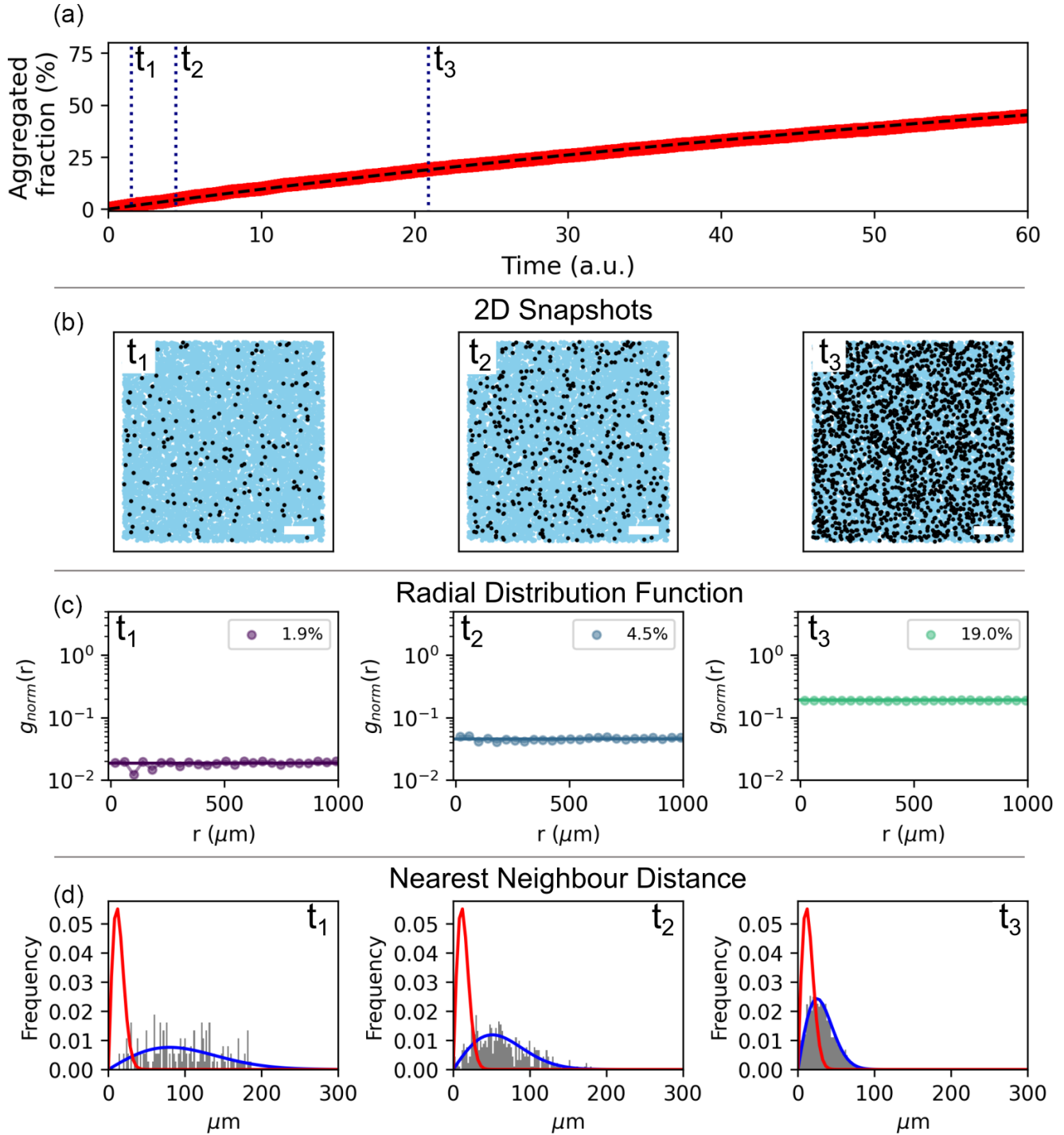


FIG. 2. No spatial coupling case. (a) Temporal evolution of total aggregated fraction. The red dots are simulated points. The black dashed line is the developed analytical theory [Eq. (1)]. (b) Snapshots of simulations of no spatial coupling case at fraction aggregated = 2%, 5%, 20%. Light blue points are nonaggregated cells, black points are aggregated cells. (c) RDF of (b). The flat solid lines correspond to a random arrangement at the average density. (d) Corresponding NND distribution of (b). The gray bars are the histogram of the simulation data. The red curve shows the analytical theory for dense clusters [Eq. (3)], while the blue curve shows the theory for a random Poisson process [Eq. (2)] for comparison. Scale bar on (b): 300 μm . Simulation conditions: total cell number = 10 002, $k_a = 0.01$ a.u.⁻¹, $k_s = 0$ a.u.⁻¹, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0.

range interactions, but the lengthscale σ is only relevant for the longer range interactions.

Note that while deriving Eq. (7), we assume a Gaussian decay coupling, and the results can be generalized for any symmetric, sufficiently rapidly decaying distribution. For

example, changing the coupling term to an exponential decay yields

$$\tilde{\lambda}(\mathbf{x}, t) = \frac{k_s}{2\pi\sigma^2\rho} \int_{\Omega} \rho(\mathbf{x}') n(\mathbf{x}', t) e^{-\frac{|\mathbf{x}-\mathbf{x}'|}{\sigma}} d^2\mathbf{x}'. \quad (9)$$

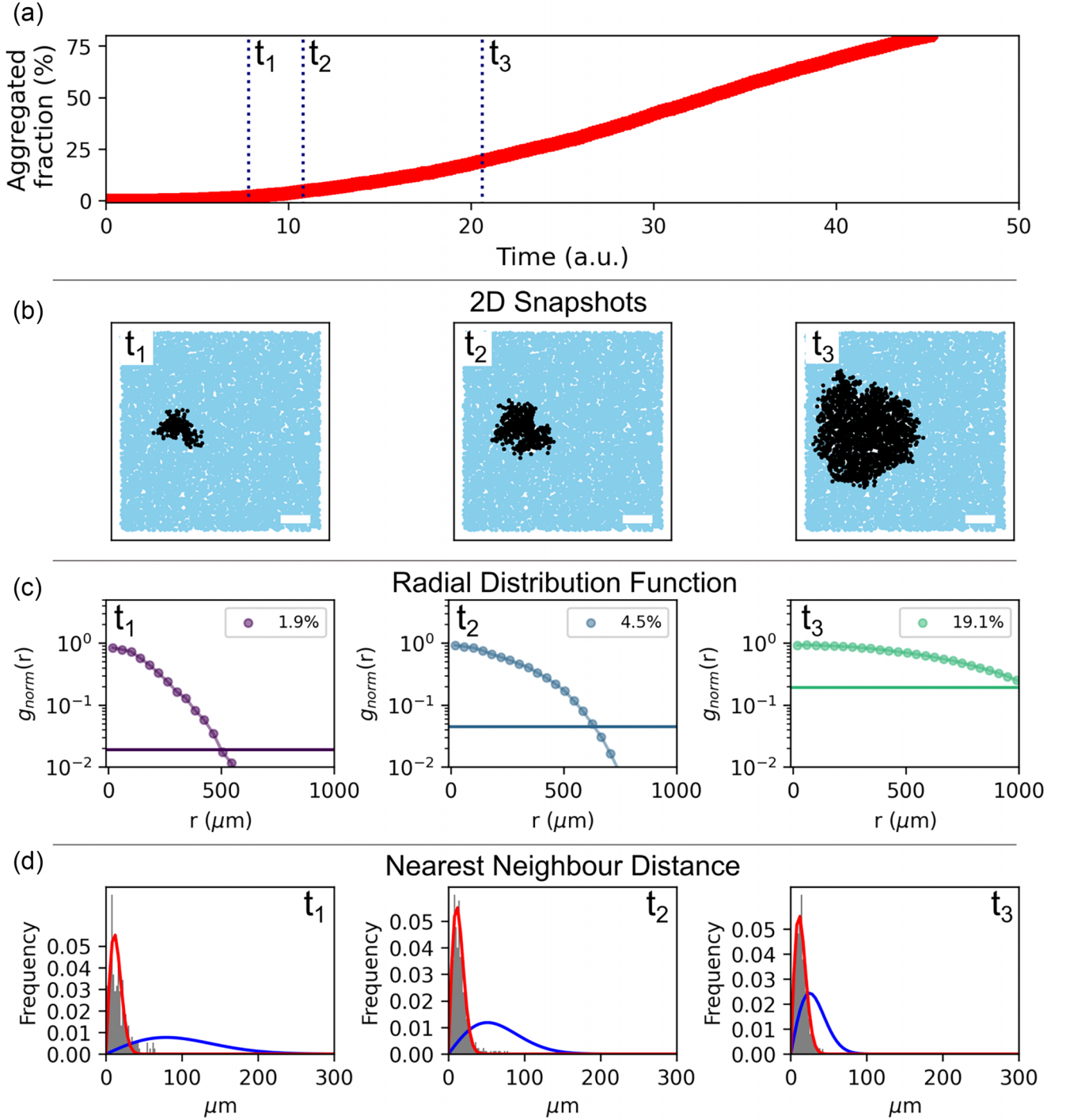


FIG. 3. Short-range coupling case. (a) Temporal evolution of total aggregated fraction. The red dots are simulated points. (b) Snapshots of simulations of the strong spatial coupling case at fraction aggregated = 2%, 5%, 20%. (c) RDF of (b). The flat solid lines correspond to a random arrangement at the average density. (d) Corresponding NND distribution of (b). The gray bars are the histogram of the simulation data. The red curve shows the analytical theory for dense clusters [Eq. (3)], while the blue curve shows the theory for a random Poisson process [Eq. (2)] for comparison. Scale bar on (b): 300 μm . Simulation conditions: total cell number = 10 000, $k_a = 0 \text{ a.u.}^{-1}$, $k_s = 1.0 \text{ a.u.}^{-1}$, $\sigma = 40 \mu\text{m}$, coupling kernel: Gaussian, $\Delta t = 0.1 \text{ a.u.}$, $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 1.

Using the same approach of Taylor expansion [Eq. (5)] and growth dynamics [Eq. (6)], we can arrive at a partial differential equation of a similar form,

$$\frac{\partial n(\mathbf{x}, t)}{\partial t} = \alpha[1 - n(\mathbf{x}, t)]n(\mathbf{x}, t) + \beta'[1 - n(\mathbf{x}, t)]\nabla^2 n(\mathbf{x}, t), \quad (10)$$

with $\alpha = k_s$ and $\beta' = \frac{3}{2}k_s\sigma^2$, the only difference being an additional factor of 3 in the definition of β' . Similarly, the corresponding Fisher traveling wave speed for the exponential decay kernel

$$v = \sqrt{6}k_s\sigma. \quad (11)$$

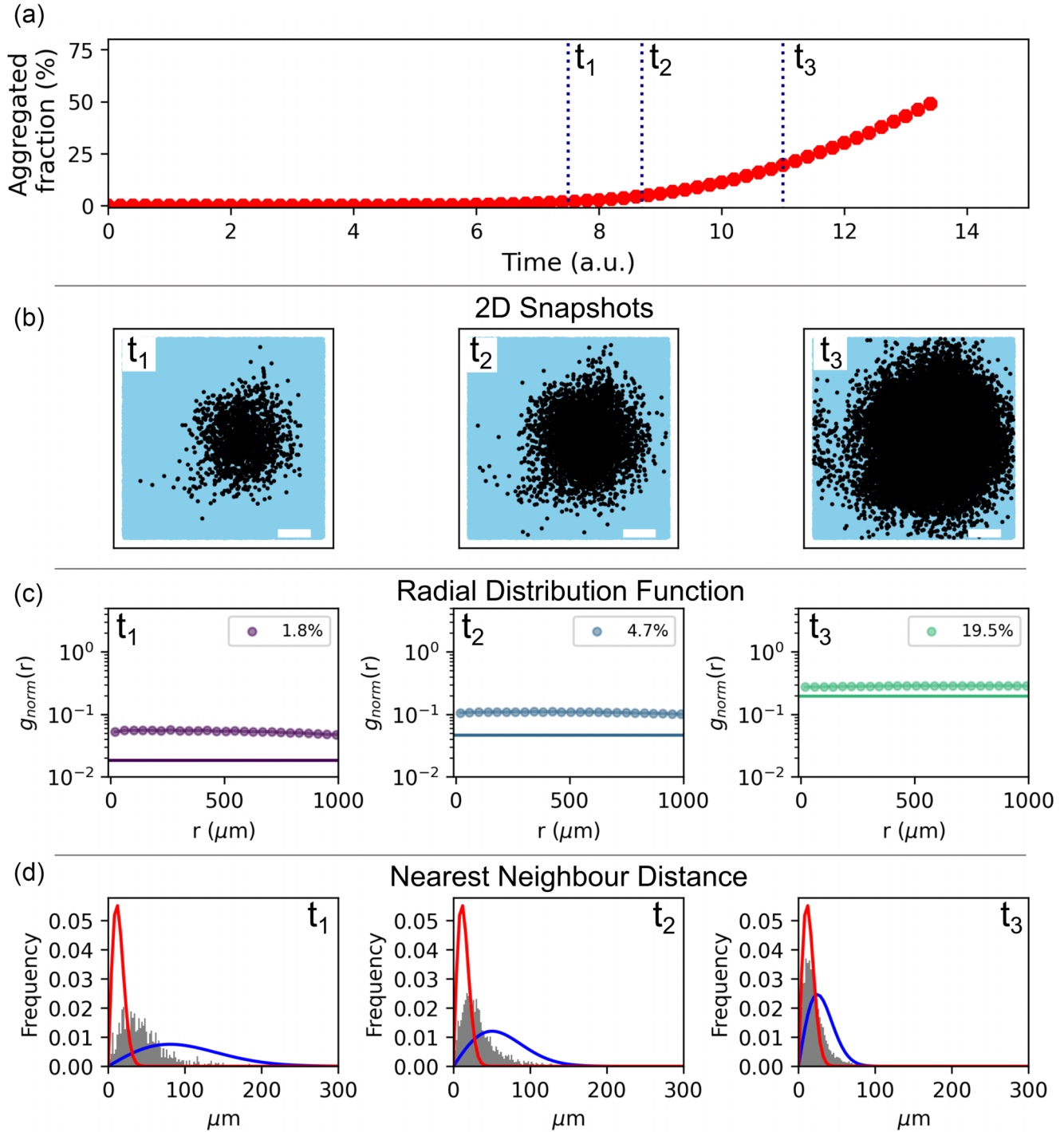


FIG. 4. Long-range spatial coupling. (a) Temporal evolution of total aggregated fraction. The red dots are simulated points. (b) Snapshots of simulations of the strong spatial coupling case at fraction aggregated = 2%, 5%, 20%. (c) RDF of (b). The flat solid lines correspond to a random arrangement at the average density. (d) Corresponding NND distribution of (b). The gray bars are the histogram of the simulation data. The red curve shows the analytical theory for dense clusters [Eq. (3)], while the blue curve shows the theory for a random Poisson process [Eq. (2)] for comparison. Scale bar on (b): 1000 μm . Simulation conditions: total cell number = 90 000, $k_a = 0$ a.u.⁻¹, $k_s = 1.0$ a.u.⁻¹, $\sigma = 400$ μm , coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 1.

The analytical form for the wave speed again matches well our numerically integrated results of the traveling wave speed [Fig. 5(d)], demonstrating robustness of the behavior to the specific choice of the coupling function.

It is interesting to note that our models resemble those used in epidemiology to model the spreading of pathology

between individuals. When assuming there are no recovered or deceased individuals, the description for infectious disease follows similar dynamics to our systems in the propagation-only limit (see [27] and [28]). Accordingly, the above derivation of a continuous model is similar to the integrodifferential equation [Eq. (6)] used in previous

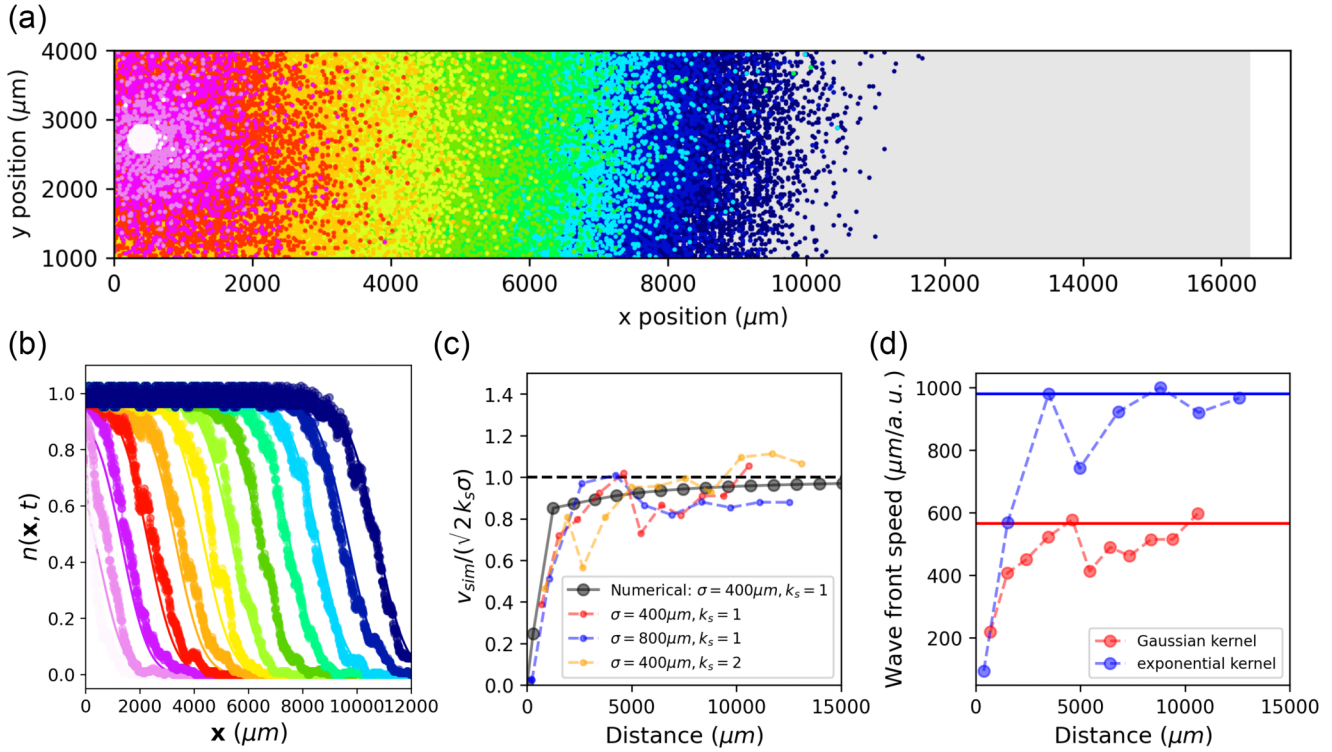


FIG. 5. Wavefront development in long-range coupling cases. (a) 2D snapshots of wavefront development in a strong spatial coupling case over a total time of 20 a.u.. The color represents time, progressing from early (pink) to late (blue). Simulation conditions: total cell number = 120 000, $k_a = 0$ a.u.⁻¹, $k_s = 1.0$ a.u.⁻¹, $\sigma = 400 \mu m$, coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, with an initial condition of a circle of 166 aggregated cells centered at $(409.5 \mu m, 2730 \mu m)$. (b) Profiles of the wavefront from simulations in (a) compared to numerical integration of Eq. (7). For direct comparison, the simulation profiles have been spatially aligned such that the center of the initial seed corresponds to the origin ($x = 0$). The numerical integration was performed using parameters matched to the simulation (k_s, σ, ρ), with no-flux boundary conditions and a step-function initial condition representing a fully aggregated region at the origin. The color scheme is the same as panel (a), with profiles shown at regular time intervals of 2 a.u.. (c) Wave speed comparison for different conditions. Simulation conditions are the same as Fig. 5(a) except for changing k_s and σ . The different conditions are all normalized to the Fisher-KPP propagation speed (black dashed line), which they approach at later times. (d) Wave speed comparison between Gaussian kernel and exponential kernel. Simulation conditions for exponential kernel: the same as Fig. 5(a) with the coupling kernel being exponential decay.

work in epidemiology [29]. Similar reaction-diffusion frameworks have also been developed to model the spatial propagation of protein polymerization in a homogeneous solution *in vitro*, where a Fisher wave emerges in the diffusion-dominated limit [30].

C. Intermediate regime: Switch fraction

Having considered the limiting cases, we now move on to discussing a system in which both cell-autonomous and cell-to-cell triggers drive the progression of the aggregation pattern. This will be the case in many real systems: there is a nonzero probability of a cell switching state spontaneously, as evidenced by the fact that most neurodegenerative diseases are sporadic, with the exception of prion disease [31] and some rare cases of Alzheimer's disease [32,33] where the introduction of infectious material seems to play a role. Additionally, there is also strong evidence that pathology spreads between cells, supporting the presence of cell-to-cell triggers [10,21].

To visualize these competing dynamics, we first simulated the intermediate regime with short-range coupling. The simulations reveal that pathology begins with multiple, spatially random cell-autonomous events that then immediately trigger

the growth of distinct local clusters, as illustrated in the snapshots in Fig. 6(b). As the simulation progresses, these initial clusters expand and begin to merge, creating complex spatial patterns. The immediate impact of the spatial coupling can be seen in the RDF [Fig. 6(c)]. Unlike the purely spontaneous aggregation case [$k_s = 0$, Fig. 2(c)], the RDF here exhibits a distinct peak at short distances even at the earliest time point, t_1 , indicating that the cell-to-cell coupling can affect tissue scale patterning even at early times. As the aggregation fraction increases, this peak grows and broadens, reflecting the expansion and merger of these clusters. At longer distances, a secondary, broader peak can also be observed (e.g., around $600 \mu m$ at time t_1 and t_2); this feature reflects the distance between distinct clusters that were formed by separate, spatially random cell-autonomous events in this particular simulation (see Fig. S2 for repeats). This secondary peak will disappear when clusters are merged as simulation progresses [at time t_3 in Fig. 6(c)], or when simulations are large enough to sample a significant number of distinct clusters, as their location is determined by cell-autonomous events and thus random; see Fig. S2.

We then extended this analysis to the long-range coupling limit to demonstrate how the characteristic lengthscale of

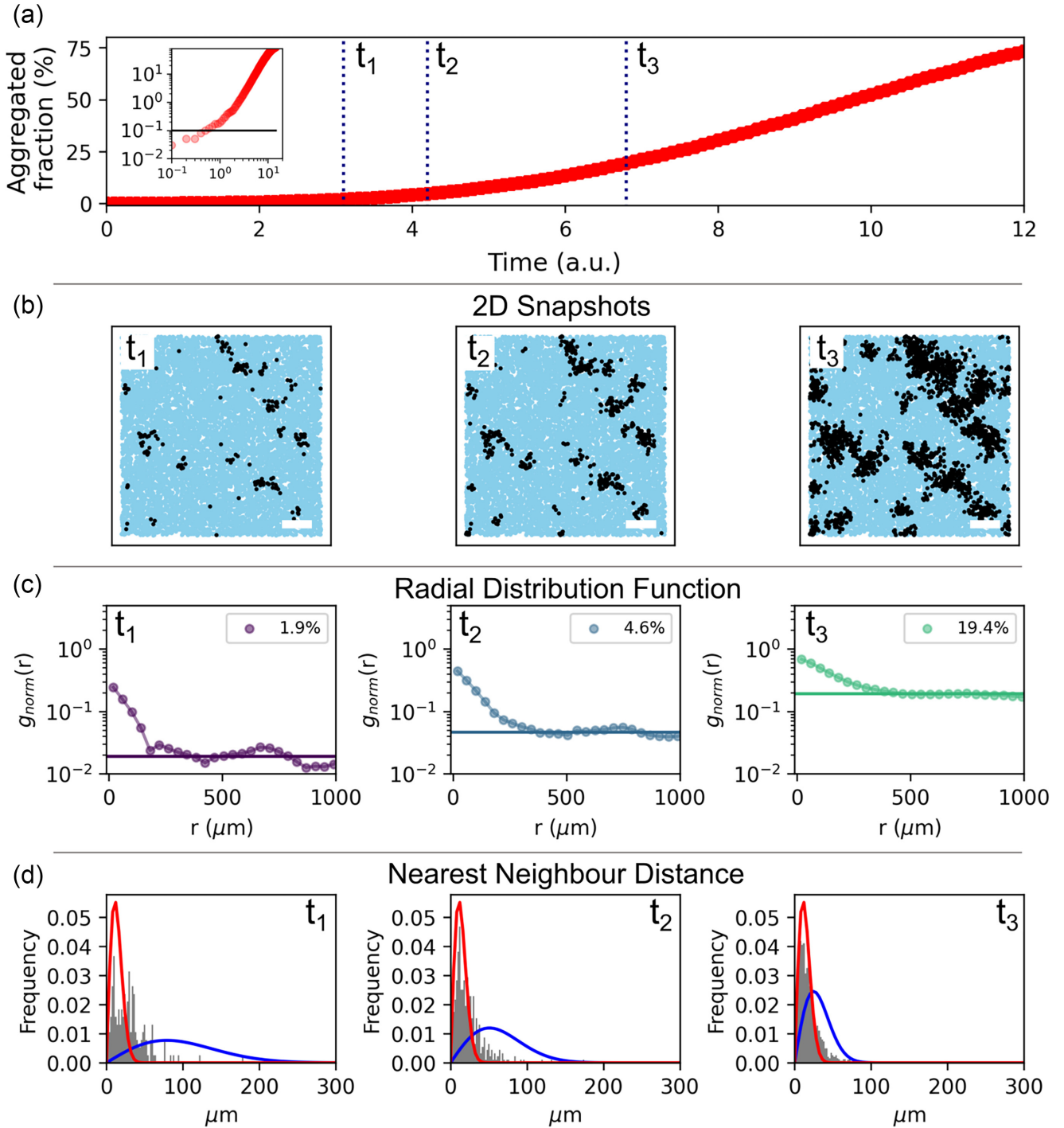


FIG. 6. Intermediate regime—short range coupling. (a) Temporal evolution of total aggregated fraction. The red dots are simulated points. The inset shows the same data plotted on a double logarithmic scale. The solid black line indicates the predicted value of the switch fraction (n_c). (b) Snapshots of simulations of weak spatial coupling case at fraction aggregated = 2%, 5%, 20%. (c) RDF of (b). The flat solid lines correspond to a random arrangement at the average density. (d) Corresponding NND distribution of (b). The gray bars are the histogram of the simulation data. The red curve shows the analytical theory for dense clusters [Eq. (3)], while the blue curve shows the theory for a random Poisson process [Eq. (2)] for comparison. Scale bar on (b): 300 μm . Simulation conditions: total cell number = 10 002, $k_a = 0.001$ a.u. $^{-1}$, $k_s = 1.0$ a.u. $^{-1}$, $\sigma = 40$ μm , coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0.

interactions influences pattern formation. In this regime, the aggregation process is significantly accelerated [Fig. 7(a)]. The resulting clusters are larger, more diffuse, and merge more rapidly than in the short-range case [Fig. 7(b)]. This change in morphology is reflected in the RDF, which shows

a broader correlation peak extending over larger distances [Fig. 7(c)]. Together, these simulations illustrate that the interplay between the cell-autonomous rate (k_a) and the spatial coupling range (σ) creates a rich diversity of aggregation patterns.

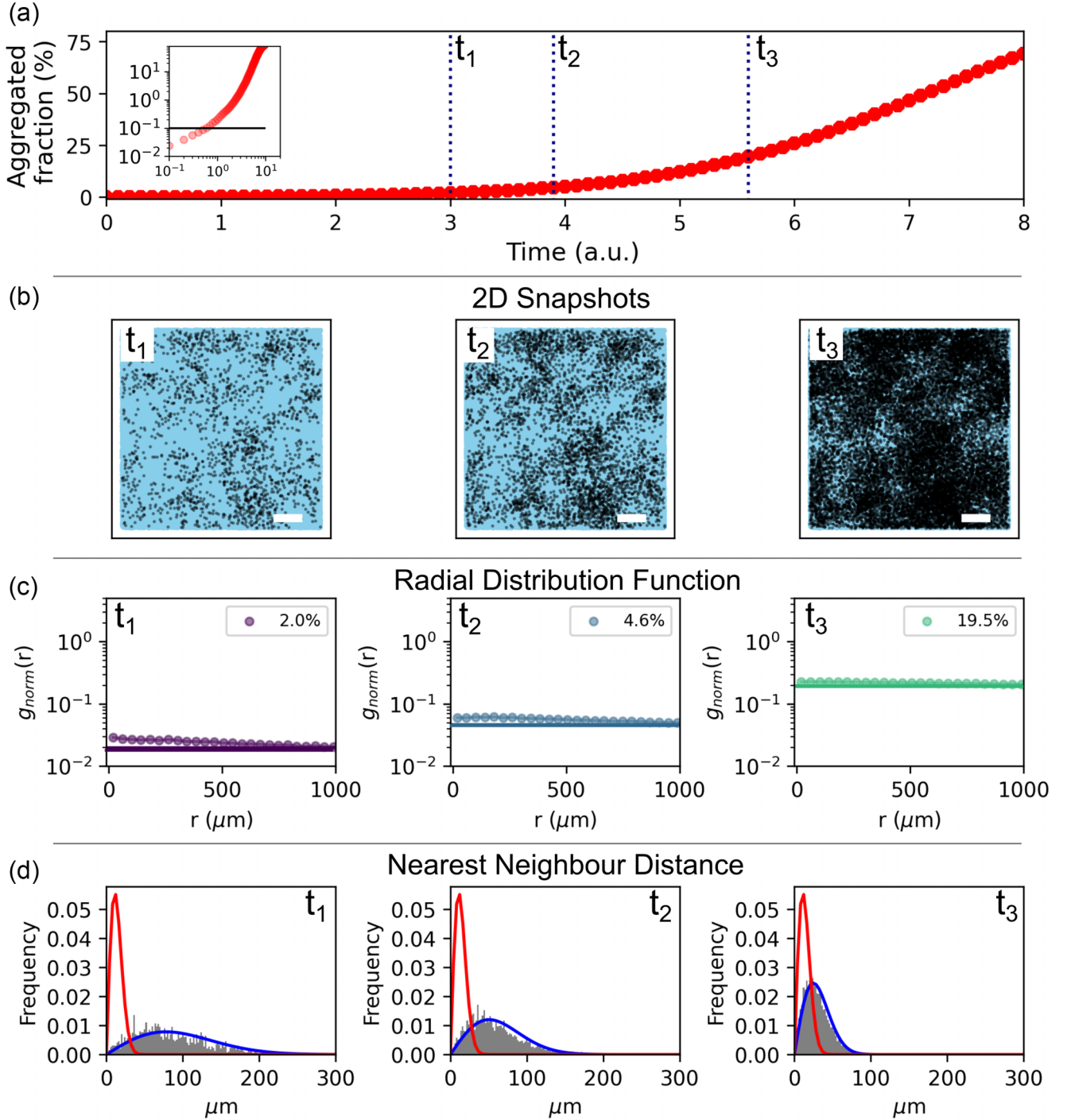


FIG. 7. Intermediate regime–long range coupling. (a) Temporal evolution of total aggregated fraction. The red dots are simulated points. The inset shows the same data plotted on a double logarithmic scale. The solid black line indicates the predicted value of the switch fraction (n_c). (b) Snapshots of simulations of weak spatial coupling case at fraction aggregated = 2%, 5%, 20%. (c) RDF of (b). The flat solid lines correspond to a random arrangement at the average density. (d) Corresponding NND distribution of (b). The gray bars are the histogram of the simulation data. The red curve shows the analytical theory for dense clusters [Eq. (3)], while the blue curve shows the theory for a random Poisson process [Eq. (2)] for comparison. Scale bar on (b): 900 μm . Simulation conditions: total cell number = 100 000, $k_a = 0.001$ a.u. $^{-1}$, $k_s = 1.0$ a.u. $^{-1}$, $\sigma = 300$ μm , coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0.

To quantify the competition between cell-autonomous and cell-to-cell triggers, we compare their respective contribution to the rates. The rate of the cell-autonomous process, r_a , is determined by the rate constant k_a and the fraction of healthy cells available to be converted,

$$(1 - n):$$

$$r_a = (1 - n)k_a. \quad (12)$$

We define the transition point, or “switch,” as the moment when the rate at which healthy cells are triggered by

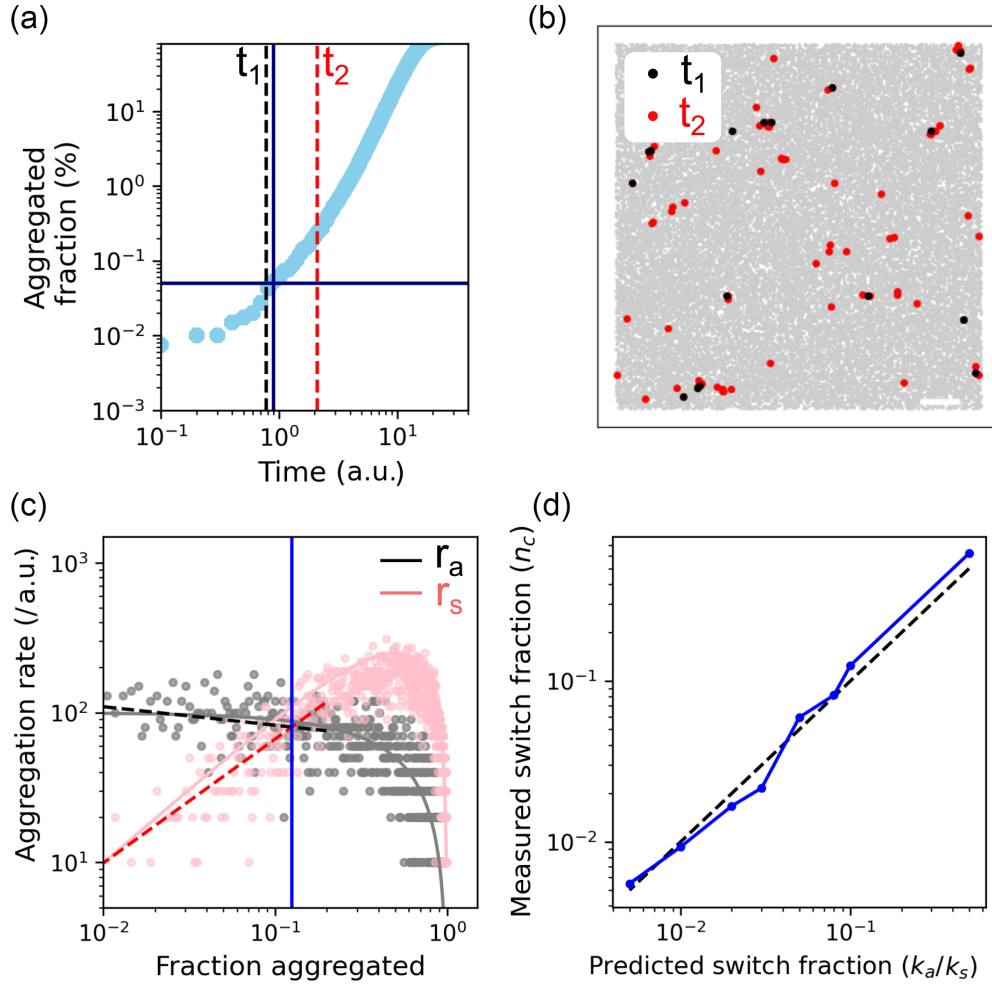


FIG. 8. Switch fraction of different conditions. (a) Selected time points before (t_1 , black dashed line) and after (t_2 , red dashed line) the switch fraction is reached (navy solid lines: switch fraction and switch time). (b) Distribution of aggregated cells before (black dots) and after (red dots) the switch fraction is reached. Two time points corresponded to t_1 and t_2 in Fig. 8(a). (c) Instantaneous rates of cell-autonomous process (r_a) and spatial coupling (r_s) from simulation, vs total fraction aggregated at different rate constants (points). Black and pink curves represent Eqs. (12) and (13), respectively, given simulation conditions. Phenomenological fits (see Appendix B) of the simulation rates of the two processes to estimate the crossover point are also shown (black dashed line: cell-autonomous process; red dashed line: spatial coupling process). The blue solid line highlights the point at which the fits of simulation rates cross over. (d) Comparisons of the switch fraction predicted by our analytical formula ($n_c = k_a/k_s$, black dashed line) with the value measured from the crossover of the rates in our simulations (blue solid line) across a range of different parameters. Simulation conditions: (a), (b) total cell number = 39 999, $k_a = 0.0005$ a.u.⁻¹, $k_s = 1.0$ a.u.⁻¹, $\sigma = 40$ μ m, coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0. (c) total cell number = 10 002, $k_a = 0.01$ a.u.⁻¹, $k_s = 0.1$ a.u.⁻¹, $\sigma = 40$ μ m, coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0. (d) total cell number = 10 002, $k_a = [0.05, 0.01, 0.008, 0.005, 0.003, 0.002, 0.001, 0.0005]$ a.u.⁻¹, $k_s = 0.1$ a.u.⁻¹, $\sigma = 40$ μ m, coupling kernel: Gaussian, $\Delta t = 0.1$ a.u., $\rho = 1341.76/\text{mm}^2$, initial aggregated cell number = 0.

cell-to-cell coupling (r_s), equals the rate at which they are triggered by cell autonomous processes (r_a). Critically, before this switch point is reached, the autonomous process dominates, creating an approximately spatially uniform distribution of aggregated cells. In this regime, the spatial term ($\nabla^2 n$) in Eq. (7) can be neglected. Hence, the rate at which healthy cells are triggered by cell-to-cell coupling, r_s , can therefore be approximated by the local term:

$$r_s \approx k_s(1 - n)n. \quad (13)$$

This functional form is the hallmark of logistic growth. At the onset of the coupling-dominated phase when n is small, this process is exponential-like, which naturally accounts for the

rapid acceleration of disease seen clinically. The growth then slows as the pool of healthy cells is depleted, leading to the characteristic sigmoidal progression curves [2].

Equating the two rates ($r_a = r_s$) at the switch point allows us to define the critical switch fraction n_c :

$$n_c = \frac{k_a}{k_s}.$$

Before this switch fraction n_c is reached ($n < n_c$), the cell-autonomous process dominates. In this regime, $r_a > r_s$, and the system's dynamics are primarily driven by the creation of new clusters of cells with aggregates. As the system evolves and n approaches n_c , the rates become comparable. Beyond

the switch fraction ($n > n_c$), the cell-to-cell mechanism overtakes the cell-autonomous process as the dominant process ($r_s > r_a$), and the growth is largely driven by the expansion of existing clusters rather than the creation of new ones. In this way, the switch fraction n_c provides a quantitative framework for linking the two mechanisms and understanding the behavior of the system as it transitions from a cell-autonomous phase to a cell-to-cell coupling-dominated phase. Interestingly, a mathematically similar transition occurs in the aggregation of proteins within a single homogeneous system, where early on new aggregates are predominantly formed by primary nucleation processes, but once a sufficient concentration of aggregates has accumulated, aggregate self-replication, via secondary nucleation or fragmentation, instead dominates the formation of new aggregates [6,34].

Our simulations provide definitive validation for this theoretical prediction of a mechanistic switch, as shown in Fig. 8. The plots of the instantaneous rates versus the fraction aggregated [Fig. 8(c)] clearly demonstrate the crossover at the predicted value of n_c for different kinetic parameters [Fig. 8(d)]. This crossover visibly marks the transition from a cell-autonomous ($r_a > r_s$) to a cell-to-cell coupling-dominated ($r_s > r_a$) regime. Furthermore, Fig. 8(b) offers a visual illustration of this switch, contrasting the sparse, randomly seeded pattern of aggregates present before the switch (t_1) with the denser, cluster-driven pattern that emerges after the switch (t_2). Taken together, the results in Fig. 8 provide a robust validation of our analytical framework, establishing a clear and quantitative link between the microscopic kinetic parameters and the emergent macroscopic dynamics of the system.

IV. DISCUSSION

Our multiscale model provides a direct bridge between the microscopic drivers of protein aggregation and the macroscopic patterns of neurodegenerative disease. We show that this type of model exhibits a critical “switch fraction” (n_c), which serves as a quantitative metric that predicts when the behavior transitions from a cell-autonomous to a cell-to-cell coupling-dominated phase. This finding has clear implications for clinical strategy, as it provides a physical basis for stratifying diseases once early biomarkers become more established: conditions dominated by cell-autonomous processes ($k_a \gg k_s$) would be prime candidates for therapies stabilizing the native proteome [35,36], whereas those dominated by cell-to-cell propagation ($k_s \gg k_a$) may also be susceptible to immunotherapies targeting seeds [37–39].

A key insight from our model is that it naturally recapitulates the characteristic temporal progression of diseases such as Progressive Supranuclear Palsy [2,24]. The initial, slow accumulation of pathology corresponds to the cell-autonomous regime ($n < n_c$), where the rate of disease progression is limited by the slow, stochastic formation of new, independent seeds. However, once the density of aggregated cells surpasses the switch fraction, the system transitions to the cell-to-cell coupling-dominated regime. In this phase, a positive feedback loop emerges, leading to a rapid increase in the number of affected cells as pathology spreads efficiently between cells. This mechanistic switch provides a direct physical explanation for the long prodromal period followed by an aggressive

acceleration of pathology that is a hallmark of the clinical presentation of many neurodegenerative disorders.

From a physical sciences perspective, our work explains how distinct pathological patterns emerge from a single set of underlying microscopic rules. By demonstrating that the balance between cell-autonomous triggers and cell-to-cell propagation governs the outcome, our model reveals three distinct macroscopic regimes: random distributions, the formation of dense clusters with sharp boundaries, and diffuse traveling waves consistent with reaction-diffusion systems described by the Fisher-KPP equation. This work, therefore, provides a unified framework to interpret the diverse tissue pathologies seen in patients.

While we have showcased the model here for a two-dimensional plane with uniform cell density, it can be extended to 3D and populated with patient-specific anatomical maps to make personalized predictions [24,40,41]. Furthermore, by incorporating terms for cell death [42] and aggregate clearance [15,19,20], our model could directly probe the causal links between aggregate load and the rate of neurodegeneration. Finally, extending the description beyond the binary state of cells used here to account for different types of aggregates would enable exploration of how different aggregate morphologies and different cell types contribute to pathology. Our framework thus forms the basis for mechanistic interpretation of patient data, enabling us to distinguish between autonomous and propagating mechanisms *in vivo*. As experimental techniques advance and measurement methods improve, our model will provide a flexible platform for integrating such data to build more comprehensive, patient-specific predictions.

ACKNOWLEDGMENTS

S.-H.H. was supported by a Taiwan Cambridge Scholarship. The work was also supported by the UK Dementia Research Institute (which receives its funding from UK DRI Ltd) and the Royal Society (D.K.) and a UK DRI pilot award (G.M., M.W.C.). We thank Annelies Quaegebeur (Cambridge Brain Bank) for providing an example brain tissue image for Fig. 1.

DATA AVAILABILITY

The data that support the findings of this article are openly available [43].

APPENDIX A: DERIVATION OF CELL-TO-CELL COUPLING MODEL

To derive the functional form of the cell-to-cell coupling and provide a physical interpretation for the parameters, we start from a number of basic requirements. First, the influence of an aggregated cell on a neighboring healthy cell should decay with increasing distance. We select a Gaussian function ($e^{-d^2/(2\sigma^2)}$) to model this decay, as it is a natural and canonical choice for diffusive or short-range interactions, where σ is the characteristic lengthscale of the interaction. Second, we want the total capacity of a single cell to spread pathology to be independent of the interaction range. The “infectious

potential” of a cell could be concentrated within a small area (producing a high-intensity, local effect when σ is small) or distributed over a larger area (resulting in a weaker but more widespread effect when σ is large), but its integrated total strength should not change with the interaction range, σ . We thus use a normalized distribution with a constant prefactor, i.e.,

$$M = \int_{\text{all space}} \frac{M}{2\pi\sigma^2} e^{-x^2/(2\sigma^2)} d^2\mathbf{x}, \quad (\text{A1})$$

where M would, e.g., be the total amount of infectious seeds produced by the cell, and $\frac{1}{2\pi\sigma^2} e^{-x^2/(2\sigma^2)}$ can be thought of as the field of pathology produced by one aggregated cell at the origin. We make this choice, rather than using a non-normalized distribution, as a quantity such as the amount of seeds or inflammation inducing molecules may be experimentally accessible, allowing M to be measured. Now to determine the effect on a single healthy cell, we simply integrate this field over the area (or volume in 3D) of the cell in question,

$$M_{i \rightarrow j} = \int_{\text{cell } j} \frac{M}{2\pi\sigma^2} e^{-x^2/(2\sigma^2)} d^2\mathbf{x} \approx \frac{Ma_0}{2\pi\sigma^2} e^{-d_{ij}^2/(2\sigma^2)}, \quad (\text{A2})$$

where d_{ij} is the distance between the centers of the healthy cell (j) and the “infectious source” cell (i), a_0 is the area (volume) of cell j , and we approximate the field as constant throughout cell j . To now turn this into a rate of triggering a cell to transition from a healthy to a diseased state, we need to link the pathological effect to a rate. We assume that this is a first-order process, i.e.,

$$\text{Rate}_{i \rightarrow j} = k_t M_{i \rightarrow j}, \quad (\text{A3})$$

where k_t is the rate at which a cell exposed to a unit amount of seeds is triggered to switch to an aggregated state. Again, this is a quantity which could be accessible through cell culture experiments, by introducing a known amount of seeds or other compound to trigger the switch to an aggregated state.

To recover our definition of the rate of triggering due to cell-to-cell interactions, we simply combine the above parameters into an effective constant $k_s = k_t M a_0 \rho$, where ρ is the average density of cells. This can be thought of as the total rate of switching due to a single aggregated cell, taking into account the size and density of the surrounding healthy cells. For simplicity, we call it the spatial coupling strength. The rationale for this choice becomes apparent in the derivation of the continuum limit, Eq. (4) onwards. Note also when cells are densely packed, $a_0 = 1/\rho$ and thus $k_s = k_t M$. For the rate of triggering of cell j due to cell i , we now have

$$k_t M_{i \rightarrow j} = k_t \frac{Ma_0}{2\pi\sigma^2} e^{-d_{ij}^2/(2\sigma^2)} \equiv \frac{k_s}{2\pi\sigma^2\rho} e^{-d_{ij}^2/(2\sigma^2)}. \quad (\text{A4})$$

Finally, the effect from separate cells is assumed to be additive, giving

$$\lambda_i = \frac{k_s}{2\pi\sigma^2\rho} \sum_j \phi_j e^{-d_{ij}^2/(2\sigma^2)}. \quad (\text{A5})$$

We assume instantaneous interaction in Eq. (A5) based on a clear separation of timescales. Biophysical studies indicate that aggregate fronts propagate in minutes or hours [30],

which is negligible compared to the multiyear progression of major neurodegenerative diseases, thereby justifying this quasi-steady-state approximation.

This derivation should be considered an illustrative example, rather than *the* way to arrive at the functional form of the cell-to-cell process. The key ingredients are simply the assumptions that (i) the pathological effect of a single aggregated cell is finite, constant over time and not affected by other cells, and (ii) the effect from multiple aggregated cells is additive. The definition of k_s , in particular the choice of not subsuming the normalization constant into it, is a question of preference and was motivated here by our desire to obtain parameters closely related to ones that may be experimentally determined, e.g., in cell culture.

APPENDIX B: NUMERICAL DETERMINATION OF THE SWITCH FRACTION

To validate our analytical expression for the switch fraction (n_c), we determined its value directly from the simulation data. The switch fraction is defined as the point where the rate of the cell-autonomous process (r_a) equals the rate of cell-to-cell propagation (r_s). The instantaneous value of both of these rates at each time step can be recorded directly during simulation. In the early time, $\log(r_a)$ and $\log(r_s)$ scale linearly with the aggregated fraction, n . We therefore performed a linear regression on the log-transformed data [$\log(r_s)$ and $\log(r_a)$ versus] to determine the point at which the two rates are equal, i.e., estimate n_c . To capture the initial power-law behavior, the fit was restricted to data points where the aggregated fraction was less than twice the theoretical switch fraction. The intersection of the two fitted lines provides a numerical estimate of the switch fraction from the simulation.

APPENDIX C: TOTAL FRACTION OF AGGREGATED CELLS IN THE WEAK SPATIAL COUPLING CASE

Here, we assume that there is no coupling between cells, i.e., $k_s \rightarrow 0$. Suppose that the probability of one cell to be triggered by the cell-autonomous process in the time step Δt is p_{ca} . Since p_{ca} is independent of space, we can write down a Markov-like representation of average triggered cell numbers. $R_m = R_{m-1}(1 - p_{ca})$, where R_m is the number of nucleated cells within the m th time step (each time step is Δt).

Suppose at time step $m = 1$, the number of nucleated cells $R_1 = N p_{ca}$, where N is the total number of cells. Then, we can calculate the total triggered cells up to time step $m = k$ as

$$\sum_{m=1}^k R_m = N[1 - (1 - p_{ca})^k].$$

Taking the limit of $\Delta t \rightarrow 0$ for a step and writing $k = \frac{t}{\Delta t}$ gives $\lim_{\Delta t \rightarrow 0} N[1 - (1 - p_{ca})^{\frac{t}{\Delta t}}] = N(1 - e^{-k_a t})$, where k_a is the rate of cell-autonomous process. We can also work out the relation between the bulk rate of the cell-autonomous process and the probability of the cell-autonomous process in the discrete simulation case: $k_a = -\frac{1}{\Delta t} \log(1 - p_{ca})$.

Hence, the percentage of triggered cells up to time t is

$$\frac{N(1 - e^{-k_a t})}{N} = 1 - e^{-k_a t} \equiv n(t).$$

APPENDIX D: DERIVATION OF THE RDF IN THE SPATIALLY UNCORRELATED LIMIT

In the limiting case of purely cell-autonomous aggregation ($k_s \rightarrow 0$), the conversion of any given cell is an independent event, resulting in a spatially random distribution of aggregated cells. The normalized Radial Distribution Function is defined as the ratio $g_{\text{norm}} = g_{\text{agg}}(r)/g_{\text{nuc}}(r)$, where $g_{\text{agg}}(r)$ and $g_{\text{nuc}}(r)$ are the RDFs of the aggregated and total cell populations, respectively.

Because the aggregated cells form a random subset of the total cell population, their spatial distribution is statistically identical to that of the total population. Consequently, the functional forms of $g_{\text{agg}}(r)$ and $g_{\text{nuc}}(r)$ are identical, differing only by a scaling factor proportional to their respective average densities (ρ_{agg} and ρ_{nuc}). When the ratio is taken, this functional dependence on distance, r , cancels out, leaving only the ratio of the average densities:

$$g_{\text{norm}} = \frac{\rho_{\text{agg}}}{\rho_{\text{nuc}}},$$

which is exactly the total fraction of aggregated cells.

APPENDIX E: NND DISTRIBUTION IN THE WEAK SPATIAL COUPLING CASE

To calculate the NND distribution of aggregate, we are essentially asking the probability distribution of finding the

nearest-neighbor aggregate at a distance from a reference point. Let us assume that the reference point is at the origin.

To calculate the probability density of having the nearest-neighbor aggregate at a certain distance, we can break this down into two parts. The first part is the probability density not finding an aggregate in the circle with radius r , where mathematically speaking it is $P(X = 0 \text{ in radius } r)$. Since the events of cell aggregation are independent and random in space, the probability of encountering k aggregation events in the circle follows a Poisson distribution. The probability mass function reads $P(X = k) = \frac{\lambda^k e^{-\lambda}}{k!}$, where k is the number of aggregate events, and λ is the expected value of the aggregation events X , which is $\pi r^2 D$ in the current case. Hence, $P(X = 0 \text{ in radius } r) = e^{-\pi r^2 D}$.

The second part is the probability density of finding an aggregate in the ring $r \rightarrow r + dr$, which mathematically speaking is $P(X = 1 \text{ in ring } r \rightarrow r + dr)$, or equivalently $P(X = 1 | \lambda = 2\pi r D dr)$. Again, refer to the definition of Poisson distribution, $P(X = 1 | \lambda = 2\pi r D dr) = (2\pi r D dr) e^{-2\pi r D dr} \approx 2\pi r D dr$. Here we make an assumption of small ring width, i.e., $dr \rightarrow 0$.

Finally, the NND distribution when the aggregates are randomly distributed is

$$\begin{aligned} P(\text{nearest-neighbor distance is } r \rightarrow r + dr) \\ = P(X \leq 1 | \lambda = \pi r^2 D) P(X = 1 | \lambda = 2\pi r D dr) \\ = 2\pi r D e^{-\pi r^2 D} dr. \end{aligned} \quad (\text{E1})$$

-
- [1] F. Chiti and C. M. Dobson, Protein misfolding, amyloid formation, and human disease: A summary of progress over the last decade, *Annu. Rev. Biochem.* **86**, 27 (2017).
 - [2] C. R. Jack, D. S. Knopman, W. J. Jagust, L. M. Shaw, P. S. Aisen, M. W. Weiner, R. C. Petersen, and J. Q. Trojanowski, Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, *Lancet Neurol.* **9**, 119 (2010).
 - [3] G. Meisl, T. P. Knowles, and D. Klenerman, The molecular processes underpinning prion-like spreading and seed amplification in protein aggregation, *Curr. Opin. Neurobiol.* **61**, 58 (2020).
 - [4] T. P. J. Knowles, C. A. Waudby, G. L. Devlin, S. I. A. Cohen, A. Aguzzi, M. Vendruscolo, E. M. Terentjev, M. E. Welland, and C. M. Dobson, An analytical solution to the kinetics of breakable filament assembly, *Science* **326**, 1533 (2009).
 - [5] S. I. A. Cohen, M. Vendruscolo, M. E. Welland, C. M. Dobson, E. M. Terentjev, and T. P. J. Knowles, Nucleated polymerization with secondary pathways. I. Time evolution of the principal moments, *J. Chem. Phys.* **135**, 065105 (2011).
 - [6] G. Meisl, J. B. Kirkegaard, P. Arosio, T. C. T. Michaels, M. Vendruscolo, C. M. Dobson, S. Linse, and T. P. J. Knowles, Molecular mechanisms of protein aggregation from global fitting of kinetic models, *Nat. Protoc.* **11**, 252 (2016).
 - [7] J. W. Vogel, N. Corriveau-Lecavalier, N. Franzmeier, J. B. Pereira, J. A. Brown, A. Maass, H. Botha, W. W. Seeley, D. S. Bassett, D. T. Jones, and M. Ewers, Connectome-based modeling of neurodegenerative diseases: Towards precision medicine and mechanistic insight, *Nat. Rev. Neurosci.* **24**, 620 (2023).
 - [8] S. Fornari, A. Schäfer, E. Kuhl, and A. Goriely, Spatially-extended nucleation-aggregation-fragmentation models for the dynamics of prion-like neurodegenerative protein-spreading in the brain and its connectome, *J. Theor. Biol.* **486**, 110102 (2020).
 - [9] A. Mudher, M. Colin, S. Dujardin, M. Medina, I. Dewachter, S. M. Alavi Naini, E.-M. Mandelkow, E. Mandelkow, L. Buée, M. Goedert, and J.-P. Brion, What is the evidence that tau pathology spreads through prion-like propagation?, *Acta Neuropathol. Commun.* **5**, 99 (2017).
 - [10] F. Clavaguera, T. Bolmont, R. A. Crowther, D. Abramowski, S. Frank, A. Probst, G. Fraser, A. K. Stalder, M. Beibel, M. Staufenbiel, M. Jucker, M. Goedert, and M. Tolnay, Transmission and spreading of tauopathy in transgenic mouse brain, *Nat. Cell Biol.* **11**, 909 (2009).
 - [11] G. Meisl, E. Hidari, K. Allinson, T. Rittman, S. L. DeVos, J. S. Sanchez, C. K. Xu, K. E. Duff, K. A. Johnson, J. B. Rowe, B. T. Hyman, T. P. J. Knowles, and D. Klenerman, In vivo rate-determining steps of tau seed accumulation in Alzheimer's disease, *Sci. Adv.* **7**, eabh1448 (2021).
 - [12] K. Amunts, H. Mohlberg, S. Bludau, S. Caspers, S. B. Eickhoff, and P. Pieperhoff, Whole-brain parcellation of the Julich-Brain cytoarchitectonic atlas (v2.9) [Dataset], *EBRAINS* (2021).
 - [13] S. Brenner, Sequences and consequences, *Philos. Trans. R. Soc. B* **365**, 207 (2010).
 - [14] G. Meisl, The thermodynamics of neurodegenerative disease, *Biophys. Rev.* **5**, 011303 (2024).

- [15] M. W. Cotton, A. Goriely, D. Klenerman, and G. Meisl, A universal phase-plane model for in vivo protein aggregation, [arXiv:2511.18893](https://arxiv.org/abs/2511.18893).
- [16] T. P. J. Knowles, D. A. White, A. R. Abate, J. J. Agresti, S. I. A. Cohen, R. A. Sperling, E. J. D. Genst, C. M. Dobson, and D. A. Weitz, Observation of spatial propagation of amyloid assembly from single nuclei, *Proc. Natl. Acad. Sci. USA* **108**, 14746 (2011).
- [17] T. Sinnige, G. Meisl, T. C. T. Michaels, M. Vendruscolo, T. P. J. Knowles, and R. I. Morimoto, Kinetic analysis reveals that independent nucleation events determine the progression of polyglutamine aggregation in *C. elegans*, *Proc. Natl. Acad. Sci. USA* **118**, e2021888118 (2021).
- [18] T. Bae, L. Fasching, Y. Wang, J. H. Shin, M. Suvakov, Y. Jang, S. Norton, C. Dias, J. Mariani, A. Jourdon, F. Wu, A. Panda, R. Pattni, Y. Chahine, R. Yeh, R. C. Roberts, A. Huttner, J. E. Kleinman, T. M. Hyde, R. E. Straub, *et al.*, Analysis of somatic mutations in 131 human brains reveals aging-associated hypermutability, *Science* **377**, 511 (2022).
- [19] J. Hardy, V. Escott-Price, The genetics of neurodegenerative diseases is the genetics of age-related damage clearance failure, *Molecular Psychiatry* **30**, 2748 (2025).
- [20] T. B. Thompson, G. Meisl, T. P. J. Knowles, and A. Goriely, The role of clearance mechanisms in the kinetics of pathological protein aggregation involved in neurodegenerative diseases, *J. Chem. Phys.* **154**, 125101 (2021).
- [21] J. Weickenmeier, E. Kuhl, and A. Goriely, Multiphysics of prionlike diseases: Progression and atrophy, *Phys. Rev. Lett.* **121**, 158101 (2018).
- [22] B. Frost, R. L. Jacks, and M. I. Diamond, Propagation of tau misfolding from the outside to the inside of a cell, *J. Biol. Chem.* **284**, 12845 (2009).
- [23] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/PhysRevX.10.110309> for additional simulation results.
- [24] S.-H. Huang, A. Quaegebeur, T. Pansuwan, T. Rittman, R. Wang, T. P. Knowles, J. B. Rowe, D. Klenerman, and G. Meisl, A mathematical model of cellular aggregation predicts patterns of tau accumulation in neurodegenerative disease, *Adv. Sci.* **13**, e11297 (2026).
- [25] D. Böken, D. Cox, M. Burke, J. Y. L. Lam, T. Katsinelos, J. S. H. Danial, E. Fertan, W. A. McEwan, J. B. Rowe, and D. Klenerman, Single-molecule characterization and super-resolution imaging of Alzheimer's disease-relevant tau aggregates in human samples, *Angew. Chem. Int. Ed.* **63**, e202317756 (2024).
- [26] R. A. Fisher, The wave of advance of advantageous genes, *Ann. Eugenics* **7**, 355 (1937).
- [27] M. S. Bartlett, Measles periodicity and community size, *J. R. Stat. Soc. A* **120**, 48 (1957).
- [28] D. G. Kendall, Mathematical models of the spread of infection, *Math. Comput. Sci. Biol. Med.*, H.M. Stationary Off, London 213 (1965).
- [29] J. Medlock and M. Kot, Spreading disease: Integro-differential equations old and new, *Math. Biosci.* **184**, 201 (2003).
- [30] S. I. A. Cohen, L. Rajah, C. H. Yoon, A. K. Buell, D. A. White, R. A. Sperling, M. Vendruscolo, E. M. Terentjev, C. M. Dobson, D. A. Weitz, and T. P. J. Knowles, Spatial propagation of protein polymerization, *Phys. Rev. Lett.* **112**, 098101 (2014).
- [31] S. B. Prusiner, Novel proteinaceous infectious particles cause scrapie, *Science* **216**, 136 (1982).
- [32] G. Banerjee, S. F. Farmer, H. Hyare, Z. Jaunmuktane, S. Mead, N. S. Ryan, J. M. Schott, D. J. Werring, P. Rudge, and J. Collinge, Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone, *Nat. Med.* **30**, 394 (2024).
- [33] G. G. Kovacs, M. I. Lutz, G. Ricken, T. Stroebel, R. Hoeffberger, M. Preusser, G. Regelsberger, S. Hoenigschnabl, A. Reiner, P. Fischer, H. Budka, and J. A. Hainfellner, Dura mater is a potential source of $\alpha\beta$ seeds, *Acta Neuropathol.* **131**, 911 (2016).
- [34] P. Arosio, T. P. J. Knowles, and S. Linse, On the lag phase in amyloid fibril formation, *Phys. Chem. Chem. Phys.* **17**, 7606 (2015).
- [35] B. Bulic, M. Pickhardt, E.-M. Mandelkow, and E. Mandelkow, Tau protein and tau aggregation inhibitors, *Neuropharmacology* **59**, 276 (2010).
- [36] M. Bourdenx, A. Martin-Segura, A. Scrivo, J. A. Rodriguez-Navarro, S. Kaushik, I. Tasset, A. Diaz, N. J. Storm, Q. Xin, Y. R. Juste, E. Stevenson, E. Luengo, C. C. Clement, S. J. Choi, N. J. Krogan, E. Mosharov, V. L. Santambrogio, F. Gruening, L. Collin, D. L. Swaney, *et al.*, Chaperone-mediated autophagy prevents collapse of the neuronal metastable proteome, *Cell* **184**, 2696 (2021).
- [37] G. Yadollahikhales and J. C. Rojas, Anti-amyloid immunotherapies for Alzheimer's disease: A 2023 clinical update, *Neurotherapeutics* **20**, 914 (2023).
- [38] J. Cummings, L. Apostolova, G. D. Rabinovici, A. Atri, P. Aisen, S. Greenberg, S. Hendrix, D. Selkoe, M. Weiner, R. C. Petersen, and S. Salloway, Lecanemab: Appropriate use recommendations, *J. Prev. Alzheimers Dis.* **10**, 362 (2023).
- [39] M. Vaz and S. Silvestre, Alzheimer's disease: Recent treatment strategies, *Eur. J. Pharmacol.* **887**, 173554 (2020).
- [40] K. Chung, J. Wallace, S.-Y. Kim, S. Kalyanasundaram, A. S. Andalman, T. J. Davidson, J. J. Mirzabekov, K. A. Zalocusky, J. Mattis, A. K. Denisin, S. Pak, H. Bernstein, C. Ramakrishnan, L. Grosenick, V. Gradinaru, and K. Deisseroth, Structural and molecular interrogation of intact biological systems, *Nature (London)* **497**, 332 (2013).
- [41] N. Renier, Z. Wu, D. J. Simon, J. Yang, P. Ariel, and M. Tessier-Lavigne, idisco: A simple, rapid method to immunolabel large tissue samples for volume imaging, *Cell* **159**, 896 (2014).
- [42] K. Jellinger, Cell death mechanisms in neurodegeneration, *J. Cell. Mol. Med.* **5**, 1 (2001).
- [43] S.-H. Huang, M. W. Cotton, T. P. Knowles, D. Klenerman, and G. Meisl, Dataset for: A cell-level model to predict spatiotemporal dynamics of neurodegenerative disease, Apollo—University of Cambridge Repository, <https://doi.org/10.17863/CAM.120852> (2025).