nature portfolio

Peer Review File

Temporal heterogeneity shapes diffusion dynamics in complex networks

Corresponding Author: Professor Peng Ji

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Summary and noteworthy results
The manuscript develops a general analytical framework for non-Markovian diffusion on networks by incorporating node-specific waiting-time distributions via renewal processes. A key result is a Laplace-domain formulation that cleanly separates temporal from structural contributions and yields tractable expressions. The empirical application to α-synuclein spreading in mouse brain networks is a useful demonstration of practical relevance and shows improved explanatory agreement compared with memoryless baselines.

Significance and originality
The focus on node-specific temporal heterogeneity, together with the spectral/Laplace treatment and the perturbation perspective, should be of interest to network science and related areas (spreading in neuroscience/biology, temporal networks, transport). The work is well positioned within the broader literature on CTRW/renewal approaches and non-Markovian diffusion, while offering a coherent methodological package and a concrete case study.

Do results support the conclusions?
Overall, the theoretical development supports the claims, and the numerical/empirical section is consistent with the paper's stated goal. The conclusions drawn in the abstract and final discussion are, in my view, supported by the analysis presented.

Methodology and standards
The methodology appears sound and clearly motivated. The Laplace-domain approach is appropriate for the renewal setting, and the numerical experiments are consistent with the theoretical framework.

Main issue requiring revision (minor): notation clarity around the renewal equation
My main suggestion is purely notational but important for readability and to avoid misinterpretation:
• The central renewal equation (Eq. 1) would benefit from being rewritten more explicitly in component form with indices. In its current matrix form, it is easy to misread the "no-jump/persistence" contribution and the implied initial condition.
• Please consider writing the equation using a node-specific waiting-time density with a single node index (e.g., "waiting-time distribution at node i"), and making explicit which index controls the kernel in each term.
• Also, please state the initial condition for the propagator explicitly, and clarify the index convention for the transition matrix (row/column stochastic), so that the order of multiplication is unambiguous.
This change would not affect the results, but would make the key equation immediately clear to a broader readership.

Recommendation
I recommend publication after minor revisions, mainly to improve clarity of notation.

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)
The main focus of this paper is methodological: to introduce the mathematical formulation needed to extend studies of diffusion on networks beyond the Markovian case. Specifically, the paper uses renewal equations to model the situation where continuous-time random walkers have inter-event times that are determined by node-specific waiting time distributions. Analytical results are derived for bounds on mixing times and sensitivities to perturbations. Numerical experiments provide evidence that the theoretical approaches (and the approximations needed to derive them) are valid, and the paper concludes with a nice application of the approach to the study of pathology spreading in mice brains.

Extending existing approaches beyond the Markovian assumption is an important – and very challenging – frontier in network dynamics. This paper makes strong progress towards a more complete understanding of the complex interactions between heterogenous waiting times and network connectivities. Although the main topic is necessarily somewhat abstracted, the use of examples, and particularly the application to the mouse brain case, should make the material accessible to a wide range of interested readers.

There are, however, some weaknesses in the presentation that I believe could be improved:
1. The Supplementary Material is extensive and constitutes an important part of the paper. Unfortunately, the referencing in the main text of the relevant supplementary material is inaccurate: the references to Appendices B, C and D do not match the section numbering in the Supplementary Material.
2. A (1,1) Pade approximant is invoked to justify a number of the theoretical results. I think the approximation that is involved here needs to be better explained, as it currently has no critical analysis and the uninformed reader could be misled as to what is actually being assumed. As I understand it, equation (31) in the Supplementary Material defines an assumed form for the (Laplace transform of the) waiting time distribution. This is what is called “the Pade approximation” throughout the paper: it is a (1,1) Pade approximant of a more complicated functon(i.e. a rational function that has both numerator and denominator being linear in s). What isn’t mentioned is that equation (31) can be directly inverse-Laplace-transformed, so the so-called “Pade approximation” just amounts to assuming that the waiting time distribution can be approximated by a sum of an exponential distribution and a delta-function distribution. I think more clarity is needed on this point, along with an analysis of how it affects the validity of the theoretical results, e.g., comment on the applicability to heavy-tailed distributions when the Pade approximation has an exponential tail.
3. On page 10 of the main text, a “heterogeneous mean field approximation” is invoked to gain some insights on the impact of degree heterogeneity in a network. Although not mentioned until later in the main text (and the relevant section 4.4 of the Supp Mat is not cited), it is a configuration model network structure that is assumed. Neither the main text nor the Supplementary Material make any attempt to explain what is mean by “configuration model” and I would imagine that most readers of Nat Comms would not necessarily know this. Also on page 10, the estimate for \lambda_1 has a typo, with d_i appearing instead of d_k in the final equation. Finally, in equation (11), the sum of degrees might usefully be replaced by the number of edges 2m, as was introduced in the previous sentence.
4. The configuration-model results are tested against simulations on ER and BA networks. Agreement of configuration model approximations with ER and BA results is not usually surprising, as both types of networks have low levels of clustering in the large-network limit. However, in this case, there are only 100 nodes in the sample networks, so the clustering coefficient is potentially relatively high for these examples – I think the authors would be better served by explaining this aspect.
5. The mouse brain example is an important component of the paper, but I found the presentation rather compressed. The description of the experiment that is called Synu-M is particularly opaque, and unlike Opti-M and Gamma-M, it isn’t even described in the Supp Mat. As the baseline case, it should be clearly explained before introducing the improved methods that give better results. Also in this section of the main text, the number of brain regions (I found n=116 in the Supp Mat) should be mentioned: this is needed for the reader to understand how many extra parameters are introduced in Gamma-M, as each node has two parameters that are optimised in order to maximise the observed correlation with experimental results. More details of this calibration should also be given (I may be misinterpreting the concise description in the text), and in particular some details of the optimisation process used to determine the fitted parameters in what is a high-dimensional parameter space.

(Remarks on code availability)
I did not see any reference to code availability.
The data on the mouse brain example is made available via Ref [22].

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have followed my recommendations

(Remarks on code availability)

Reviewer #2

(Remarks to the Author)
The authors have addressed all my points in a satisfactory manner and I am happy to recommend publication.

(Remarks on code availability)

Response to referees

Summary of main changes:

- **Notation clarity for the central renewal equation (Eq. (1)):** we rewrote Eq. (1) explicitly in component form with indices, made the persistence term and the implied initial condition unambiguous, used a node-specific waiting-time density with a single node index, and clarified the index convention for the transition matrix (row-stochastic).
- **Corrected and standardized main-text references to the Supplementary Information:** we fixed all mismatched Appendix references and adopted consistent "Appendix X.Y" numbering throughout.
- **Clarified the (1,1) Padé approximation:** we added a dedicated explanation in the main text (including the equivalent time-domain interpretation as a mixture of an exponential distribution and a Dirac delta component, and its limitations for heavy-tailed cases), and added a new modular Supplementary subsection (Appendix 3.2) providing derivations and critical discussion.
- **Made the configuration-model assumption explicit and corrected minor issues:** we added a short explanation of the configuration model and it enters the heterogeneous mean-field approximation; corrected the typo in the estimate of λ_1 ($d_i \to d_k$), and replaced the degree sum by $2m$ in Eq. (11).
- **Expanded discussion and validation on clustering effects:** we expanded discussion of the limitation that degree-based / configuration-model approximations are most accurate in low-clustering regimes, and included systematic numerical validation in the Supplementary (Appendix 4.6).
- **Expanded the mouse-brain example description and calibration details:** we clarified Synu-M (baseline) before introducing Opti-M/Gamma-M, explicitly stated $n = 116$, and added detailed optimization/calibration description in the Supplementary (Appendix 5.2 and Appendix 5.4).
- **Added explicit data and code availability:** we added a dedicated *Data Availability* section (before the References) specifying where the mouse-brain dataset and all experimental network datasets can be accessed, followed by a *Code Availability* section with the public repository link.

Changes in the main text are marked in blue.

Point-by-point Response to Referee 1

Referee 1: *Summary and noteworthy results*
The manuscript develops a general analytical framework for non-Markovian diffusion on networks by incorporating node-specific waiting-time distributions via renewal processes. A key result is a Laplace-domain formulation that cleanly separates temporal from structural contributions and yields tractable expressions. The empirical application to α-synuclein spreading in mouse brain networks is a useful demonstration of practical relevance and shows improved explanatory agreement compared with memoryless baselines.

Significance and originality
The focus on node-specific temporal heterogeneity, together with the spectral/Laplace treatment and the perturbation perspective, should be of interest to network science and related areas (spreading in neuroscience/biology, temporal networks, transport). The work is well positioned within the broader literature on CTRW/renewal approaches and non-Markovian diffusion, while offering a coherent methodological package and a concrete case study.

Do results support the conclusions?
Overall, the theoretical development supports the claims, and the numerical/empirical section is consistent with the paper's stated goal. The conclusions drawn in the abstract and final discussion are, in my view, supported by the analysis presented.

Methodology and standards
The methodology appears sound and clearly motivated. The Laplace-domain approach is appropriate for the renewal setting, and the numerical experiments are consistent with the theoretical framework.

Response: We thank the referee for the positive evaluation of our work.

Referee 1: *Main issue requiring revision (minor): notation clarity around the renewal equation*
My main suggestion is purely notational but important for readability and to avoid misinterpretation:

Response: We appreciate this insightful and valuable suggestion and fully agree that clarifying the notation around the renewal equation is necessary to improve readability and prevent misinterpretation. Accordingly, in the revised version, we have rewritten the central renewal equation and its accompanying explanation to enhance overall clarity. These improvements are intended to make the subsequent Laplace-domain derivations easier to follow.

Referee 1: *The central renewal equation (Eq. 1) would benefit from being rewritten more explicitly in component form with indices. In its current matrix form, it is easy to misread the "no-jump/persistence" contribution and the implied initial condition.*

Response: We completely agree. In the revision, we have rewritten Eq. (1) explicitly in component form with indices. This revision makes the "no-jump/persistence" term and the implicit initial condition unambiguous, both within the equation and the surrounding text.

Referee 1: *Please consider writing the equation using a node-specific waiting-time density with a single node index (e.g., "waiting-time distribution at node i"), and making explicit which index controls the kernel in each term.*

Response: We thank the referee for this important point. In the revision, we have introduced a node-specific waiting-time density $\rho_i(\tau)$ for node i and have made the index-dependence of each kernel term explicit in the equation, clarifying which node index controls the waiting-time distribution in each term.

Referee 1: *Also, please state the initial condition for the propagator explicitly, and clarify the index convention for the transition matrix (row/column stochastic), so that the order of multiplication is unambiguous.*

Response: We thank the referee for this valuable suggestion. In the revision, we have explicitly stated the initial condition as $X_{ij}(0) = \delta_{ij}$ and clarified that the transition matrix $\mathbf{P}$ is row-stochastic, with each row summing to 1. This ensures the order of multiplication in the renewal equation is unambiguous.

Referee 1: *This change would not affect the results, but would make the key equation immediately clear to a broader readership.*

Response: We fully agree and thank the referee for emphasizing this point. The revision, incorporating all of the suggested clarifications, substantially improves the accessibility of the key equation for a broader readership while leaving all results unchanged.

Changes made to the manuscript:
Location: Main text, in the paragraph beginning

> "We analyze a continuous-time random walk on networks, "

where Eq. (1) is presented, and the immediately following sentences starting with

> "The initial condition for the process is $X_{ij}(0) = \delta_{ij}$, "

and

> "...by construction, $\boldsymbol{X}(t)$ is a row-stochastic matrix for all t."

What changed: Rewrote Eq. (1) explicitly in indexed component form $X_{ij}(t)$; made the no-jump (persistence) contribution explicit as $\delta_{ij} \int_t^\infty \rho_i(\tau)\, d\tau$; stated the initial condition $X_{ij}(0) = \delta_{ij}$ immediately after the equation; used a single node index in the waiting-time density $\rho_i(\tau)$; and clarified the row-stochastic convention for the transition matrix and propagator (so that index/multiplication conventions are unambiguous).
Revised text:
We now write the renewal equation in component form and state the conventions explicitly, e.g.,

$$X_{ij}(t) = \delta_{ij} \int_t^\infty \rho_i(\tau)\, d\tau + \int_0^t \sum_{k \neq i} \rho_i(\tau) P_{ik} X_{kj}(t-\tau)\, d\tau,$$

together with $X_{ij}(0) = \delta_{ij}$ and the statement that $\boldsymbol{X}(t)$ (and $\mathbf{P}$) is row-stochastic.

Referee 1: *Recommendation*
I recommend publication after minor revisions, mainly to improve clarity of notation.

Response: We sincerely thank the referee for recommending publication and for their valuable suggestions, which have significantly improved the clarity of our notation.

Point-by-point Response to Referee 2

Referee 2: *The main focus of this paper is methodological: to introduce the mathematical formulation needed to extend studies of diffusion on networks beyond the Markovian case. Specifically, the paper uses renewal equations to model the situation where continuous-time random walkers have inter-event times that are determined by node-specific waiting time distributions. Analytical results are derived for bounds on mixing times and sensitivities to perturbations. Numerical experiments provide evidence that the theoretical approaches (and the approximations needed to derive them) are valid, and the paper concludes with a nice application of the approach to the study of pathology spreading in mice brains.*
Extending existing approaches beyond the Markovian assumption is an important – and very challenging – frontier in network dynamics. This paper makes strong progress towards a more complete understanding of the complex interactions between heterogenous waiting times and network connectivities. Although the main topic is necessarily somewhat abstracted, the use of examples, and particularly the application to the mouse brain case, should make the material accessible to a wide range of interested readers.

Response: We sincerely thank the referee for this thorough and insightful summary of our manuscript. We are especially grateful for their positive assessment of the methodological contribution and the challenging frontier this work addresses. In direct response to their later comments, we have clarified the key approximation steps used to obtain tractable analytical expressions, particularly the use of Padé approximants. We have also added more details regarding the mouse-brain application and its calibration procedure to enhance transparency. To further strengthen the presentation, we revised the manuscript to explicitly state our underlying assumptions and conventions, such as the configuration-model approximation and the row-stochastic nature of the transition matrix $\mathbf{P}$. We also reorganized the Supplementary Information into clearer, modular sections to improve accessibility.

Referee 2: *There are, however, some weaknesses in the presentation that I believe could be improved:*

1. The Supplementary Material is extensive and constitutes an important part of the paper. Unfortunately, the referencing in the main text of the relevant supplementary material is inaccurate: the references to Appendices B, C and D do not match the section numbering in the Supplementary Material.

Response: We thank the referee for pointing out this important oversight regarding the Supplementary Information. We fully agree that clear and accurate cross-referencing is essential, especially given its extensive nature. In the revision, we have corrected all mismatched Appendix references and have standardized the section numbering throughout the Supplementary Information. Every citation in the revision now correctly points to the corresponding supplementary section.

Changes made to the manuscript:
Location: Main text throughout (Supplementary cross-references); Supplementary Information section numbering.
What changed: Corrected inaccurate Appendix references and adopted consistent "Appendix X.Y" numbering.

Referee 2: *2. A (1,1) Pade approximant is invoked to justify a number of the theoretical results. I think the approximation that is involved here needs to be better explained, as it currently has no critical analysis and the uninformed reader could be misled as to what is actually being assumed. As I understand it, equation (31) in the Supplementary Material defines an assumed form for the (Laplace transform of the) waiting time distribution. This is what is called "the Pade approximation" throughout the paper: it is a (1,1) Pade approximant of a more complicated function (i.e. a rational function that has both numerator and denominator being linear in s). What isn't mentioned is that equation (31) can be directly inverse-Laplace-transformed, so the so-called "Pade approximation" just amounts to assuming that the waiting time distribution can be approximated by a sum of an exponential distribution and a delta-function distribution. I think more clarity is needed on this point, along with an analysis of how it affects the validity of the theoretical results, e.g., comment on the applicability to heavy-tailed distributions when the Pade approximation has an exponential tail.*

Response: We agree that this step required a clearer and more critical explanation. To address this, we have added an explicit time-domain interpretation of the (1,1) Padé approximant, clarifying that it corresponds to a mixture of an exponential distribution and a Dirac delta function. We also now include a brief discussion of its limitations, particularly regarding its applicability to genuinely heavy-tailed waiting-time distributions. A full derivation and a more detailed critical analysis are provided in the new Appendix 3.2 of the Supplementary Information.

Changes made to the manuscript:
Location:

- **Main text:** immediately after the paragraph ending with "The competition between these factors determines the dominant timescale of the system." and *before* the paragraph starting "The heterogeneous case with non-uniform waiting time distributions across nodes ...". The new paragraph begins with:

  > "To obtain a closed-form estimate, we approximate $\hat{\rho}(s)$ by its (1,1) Padé form."

- **Supplementary Information:** Appendix 3.2 (new), titled "Critical analysis of the (1,1) Padé approximant".

What changed: Added a time-domain interpretation of the (1,1) Padé approximant (exponential + Dirac-delta mixture), clarified the assumptions behind using it for root-finding in the negative half-plane, and added a critical discussion of validity/limitations, especially for heavy-tailed waiting-time distributions.
Revised text:

> "To obtain a closed-form estimate, we approximate $\hat{\rho}(s)$ by its (1,1) Padé form. This approximation captures both the mean and variance of the waiting-time distribution, while maintaining the algebraic simplicity required for an explicit solution of the root condition. Physically, the inverse Laplace transform of the (1,1) Padé form approximates the waiting-time distribution as a mixture of an exponential decay and a Dirac delta distribution, effectively characterizing both the average waiting time and the impact of temporal heterogeneity (i.e., long-tail effects)."

Referee 2: *3. On page 10 of the main text, a "heterogeneous mean field approximation" is invoked to gain some insights on the impact of degree heterogeneity in a network. Although not mentioned until later in the main text (and the relevant section 4.4 of the Supp Mat is not cited), it is a configuration model network structure that is assumed. Neither the main text nor the Supplementary Material make any attempt to explain what is mean by "configuration model" and I would imagine that most readers of Nat Comms would not necessarily know this. Also on page 10, the estimate for λ_1 has a typo, with d_i appearing instead of d_k in the final equation. Finally, in equation (11), the sum of degrees might usefully be replaced by the number of edges $2m$, as was introduced in the previous sentence.*

Response: We thank the referee for these precise and constructive suggestions regarding clarity and technical accuracy. To improve clarity, we have made the configuration-model assumption explicit at the point where the heterogeneous mean-field approximation is introduced, providing a brief definition and a direct pointer to Appendix 4.4 for the full derivation. Regarding technical accuracy, we have corrected the typo in the estimate for $\lambda_1(\mathbf{M}_{kk})$ by replacing d_i with d_k in the final expression, and have rewritten the degree sum in Eq. (11) as $2m$ for consistency with the preceding definition.

Changes made to the manuscript:
Location:

- **Main text** (Results, page 11; around Eqs. (10)–(11)): the paragraph beginning with *"To obtain a tractable degree-based approximation of the upper bound, we next estimate $\lambda_1(\mathbf{M}_{kk})$ using a heterogeneous mean-field approach within the configuration model."*
- **Main text** (same place, immediately following that paragraph): the displayed leading-order estimate for $\lambda_1(\mathbf{M}_{kk})$ and the subsequent approximation Eq. (11), where $2m$ (number of edges) is explicitly used.
- **Main text** → **Supplementary cross-reference** added in the same paragraph: *"(see Appendix 4.4 for details)"* to point readers to the full derivation.

What changed:

- Added an explicit definition/interpretation of the *configuration model* and stated clearly that the heterogeneous mean-field estimates are derived under this assumption.
- Corrected the typo in the $\lambda_1(\mathbf{M}_{kk})$ estimate by replacing d_i with d_k in the final expression (so the leading correction is $d_k/(2m)$).
- In Eq. (11), replaced the degree sum by the number of edges $2m$ (consistent with the definition introduced in the preceding sentence) to improve readability.
- Added explicit pointers to the relevant Supplementary derivations (Appendix 4.4; and related discussion as appropriate).

Revised text:
To obtain a tractable degree-based approximation of the upper bound, we next estimate $\lambda_1(\mathbf{M}_{kk})$ using a heterogeneous mean-field approach within the configuration model. The configuration model is a widely used random-graph null model that randomizes edges while controlling for degree information. Here we consider the degree-sequence ensemble, where the degree sequence is fixed and edges are otherwise wired uniformly at random; it therefore retains degree heterogeneity but averages out higher-order correlations [26]. Within this framework one obtains a simple leading-order estimate, valid when the leading eigenvalue is close to unity (see Appendix 4.4 for details), $\lambda_1(\mathbf{M}_{kk}) \approx \frac{\sum_i d_i - d_k}{\sum_i d_i} = 1 - \frac{d_k}{2m}$, where d_i denotes the degree of node i and m is the number of edges. In this case, the upper bound (10) can be further approximated as $\Delta\tau_{mix} \approx \mu\left(\frac{2m}{d_k} - 1\right) + \frac{1}{\hat{\rho}^{-1}(1/\lambda_1(\boldsymbol{P}))}$.

Referee 2: *4. The configuration-model results are tested against simulations on ER and BA networks. Agreement of configuration model approximations with ER and BA results is not usually surprising, as both types of networks have low levels of clustering in the large-network limit. However, in this case, there are only 100 nodes in the sample networks, so the clustering coefficient is potentially relatively high for these examples – I think the authors would be better served by explaining this aspect.*

Response: We thank the referee for this important observation regarding network structure and

approximation validity. We fully agree that the agreement with the configuration-model approximation in small ER and BA networks merits explicit discussion. In the revision, we have added an explanation that this approximation is most accurate in low-clustering regimes, which applies to the large-network limit of these models. To provide a more rigorous assessment, we have systematically quantified the approximation error under finite-size and clustering effects. A new supplementary module (Appendix 4.6) presents a comprehensive numerical scan, validating the accuracy of the degree-based estimates as a function of network size N and global clustering coefficient C. This analysis includes new figures and details on how the errors in the estimated eigenvalue $\lambda_1(\mathbf{M}_{kk})$ and the resultant mixing-time bound scale with these parameters.

Changes made to the manuscript:
Location:

- **Main text** (discussion of approximation scope/assumptions near the configuration-model analysis): the paragraph beginning with

  > "The reliability of the configuration-model-based approximations in these simulations is further supported by additional analytical and numerical evidence (see Appendix 4.4–4.6 for details)."

- **Main text** (same section, immediately following the network-size discussion): the paragraph beginning with

  > "We also assessed the sensitivity of these approximations to triangle-induced correlations by varying clustering through degree-preserving rewiring and measuring the errors as a function of the global clustering coefficient (global transitivity) C (see Appendix 4.6 for details)."

- **Supplementary Information** (Appendix 4.6, new subsection titled *"Node-level spectral and dynamical approximations"*): in particular the paragraphs beginning with

  > "A central approximation used in the main text is the node-level eigenvalue estimate $\lambda_1(\mathbf{M}_{kk}) \approx 1 - d_k/(2m)$ ..."

  and

  > "To probe the inffuence of clustering at ffxed degree sequence ..."

What changed:

- Added an explicit discussion in the main text clarifying that configuration-model/degree-based approximations are most accurate in low-clustering regimes, and explaining why ER/BA networks serve as appropriate baselines.
- Added a new Supplementary validation module (Appendix 4.6) that quantifies approximation accuracy as a function of network size N (finite-size effects) and clustering C, using degree-preserving rewiring to vary C while keeping the degree sequence fixed.
- **Added additional experiments and four new Supplementary figures in Appendix 4.6** to make the finite-size and clustering trends visually transparent (network-size scan and clustering-rewiring validation; see the four new figures in Appendix 4.6).
- Reported how errors in $\lambda_1(\mathbf{M}_{kk})$ and the induced errors in $\Delta\tau_{\mathrm{mix}}$ change with increasing clustering and with finite N, thereby making the regime of validity transparent.

Referee 2: *5. The mouse brain example is an important component of the paper, but I found the presentation rather compressed. The description of the experiment that is called Synu-M is particularly opaque, and unlike Opti-M and Gamma-M, it isn't even described in the Supp Mat. As the baseline case, it should be clearly explained before introducing the improved methods that*

give better results. Also in this section of the main text, the number of brain regions (I found $n = 116$ in the Supp Mat) should be mentioned: this is needed for the reader to understand how many extra parameters are introduced in Gamma-M, as each node has two parameters that are optimised in order to maximise the observed correlation with experimental results. More details of this calibration should also be given (I may be misinterpreting the concise description in the text), and in particular some details of the optimisation process used to determine the fitted parameters in what is a high-dimensional parameter space.

Response: We agree and have expanded and reorganized the presentation of the mouse-brain example for better clarity. In the revision, we have explicitly introduced the Synu-M baseline model before presenting the Opti-M and Gamma-M improvements. We have also added the specific number of brain regions ($n = 116$) directly to clarify the parameter scales. Furthermore, we provide comprehensive methodological details in the Supplementary Information, including dedicated subsections that fully describe the Synu-M baseline (Appendix 5.2) and the high-dimensional optimization procedure used for model calibration (Appendix 5.4).

Changes made to the manuscript:
Location:

- **Main text** (mouse-brain application section, at the start of the empirical case study): the paragraph beginning with

  > "To illustrate the potential applications of our findings in an empirical setting, we consider the mapping of spatiotemporal α-synuclein pathology patterns in the brain [22] ..."

- **Main text** (same section, when introducing Gamma-M and the parameter count): the paragraph beginning with

  > "while Gamma-M denotes the corresponding gamma waiting-time model, which assumes gamma-distributed waiting times, and requires 116 parameters ..."

- **Supplementary Information** Appendix 5.2 (new), titled *"Baseline Model: Synu-M"*: the subsection beginning with

  > "The Synu-M model replicates the framework of Henderson et al. [1], serving as our biologically informed baseline."

- **Supplementary Information** Appendix 5.4 (new), titled *"Optimization and Calibration Details"*: the subsection beginning with

  > "To calibrate the parameters in the high-dimensional space of Opti-M (58 independent parameters) and Gamma-M (116 independent parameters), we implement a greedy coordinate-wise optimization (hill-climbing) procedure."

What changed:

- Clarified the definition and interpretation of the **Synu-M baseline** and introduced it *before* Opti-M and Gamma-M to provide a transparent reference point for later improvements.
- Stated the number of brain regions $n = 116$ **explicitly in the main text** to make the parameter count and model complexity immediately clear to readers.
- Expanded the description of the **calibration/optimization procedure** in the main text (objective and parameter count), and provided **algorithmic details** (objective function, step sizes, update rule, stopping criterion) in the Supplementary (Appendix 5.4).

Referee 2: *Remarks on data and code availability*
I did not see any reference to code availability. The data on the mouse brain example is made available via Ref [22].

Response: We thank the referee for highlighting this important omission. In the revision, we have now added explicit "Data Availability" and "Code Availability" sections (before the References), with direct links to the mouse-brain dataset (via Ref. [22]) and to a public repository containing all simulation and analysis code, as well as all synthetic network datasets used in the study.

Changes made to the manuscript:
Location: Main text, new *Data Availability* and *Code Availability* sections (before References).
What changed: Added explicit data and code availability statements with repository links.
Revised text:

> **Data Availability.** The mouse-brain connectome diffusion dataset analyzed in this study is publicly available at: `https://github.com/ejcorn/connectome_diffusion`. The network datasets supporting the other experiments are available at: `https://github.com/naivefrog0817-chengluo/temporal_diffusion`.
> **Code Availability.** All code used in this study to generate the results and graphs is publicly available at: `https://github.com/naivefrog0817-chengluo/temporal_diffusion`.

Dear Editor,

We sincerely thank both reviewers for their valuable and critical comments, which have helped us significantly improve our manuscript. Their thorough evaluation is greatly appreciated.

We have also revised the manuscript in accordance with the editor's suggestions.

Sincerely,
Cheng Luo, Renaud Lambiotte, and Peng Ji*

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have followed my recommendations

Reviewer #2 (Remarks to the Author):

The authors have addressed all my points in a satisfactory manner and I am happy to recommend publication.

Response: We sincerely thank both referees for their insightful suggestions and for recommending publication. Their input has significantly improved the quality of our manuscript.