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Temporal-Spatial Graphs for Lesions in Serial Scans with Neural Imaging*

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Abstract

The phrase *neural dynamics* has diverse interpretations across various research fields, spanning artificial and biological networks, from deterministic to statistical models, and dynamic graphs to differential equations. This report provides a practical interpretation of neural dynamics appropriate for analyzing neural imaging scans from the EPSMS Clinical Trial on entire-body PET scans for multiple sclerosis (MS) patients. This approach involves observing the changing function of the brain and nervous system over time and space to monitor demyelination and remyelination events in MS. For medical imaging scans, abnormalities called lesions appear as hyper- or hypo-intensities that can change in size, shape, location, and activity over a series of scans. The analysis proposes a formal definition of temporal-spatial graphs to model these lesions in serial scans. This graph-based approach tracks lesions across time-ordered scans, linking neuroanatomically adjacent lesions across different time points to better understand the progression of MS.

Keyphrases

Neural dynamics, neural imaging, serial-scan lesions, temporal-spatial graphs.

Neural Dynamics

The phrase *neural dynamics* has been used with diverse interpretations by various research communities. From artificial to biological neural networks, from dynamic graphs to differential equations, using approaches with either mathematical deterministic or statistical probabilistic paradigms, there exist a panoply of network models for neural dynamics with varying scales in time and space. Biological neural networks must consider several hierachical levels from cell-to-cell communication, local neural pathways in the brain for cognition emotion communication and language comprehension, and nervous system connections from the brain to the rest of the body for both sensory perception and motor control. A practical interpretation of the phrase *neural dynamics* is presented here intended for use in the analysis of neural imaging scans from the EPSMS Clinical Trial (Taswell 2020; Taswell 2023) as it applies to the changing function of the brain and nervous system in time and space (ie, anatomic location) for multiple sclerosis (MS) patients who experience demyelination and remyelination of neural pathways in the brain and nervous system. *Immunal dynamics* and interactions between the immune and nervous systems (Klose and Veiga-Fernandes 2021; Shouman and Benarroch 2021; Klein Wolterink et al. 2022; Kim et al. 2024) must also be addressed and will provide earlier outcome measures that precede the appearance of those associated with myelin lesions (Wei et al. 2020; Lauri et al. 2023).

Neural Imaging

In neural imaging with CT, MR, PET, PET-CT, or PET-MR scans, abnormalities measured relative to normal activity levels are commonly termed *lesions* in clinical practice. These lesions may have increased or decreased activity, which are termed respectively *hyper-intensities* (aka 'hot spots') or *hypo-intensities* (aka 'cold spots'). When studied with serial scans to track the presence or absence of myelin lesions in the central and peripheral nervous system of MS patients, these lesions may appear and disappear sequentially over time. Various aspects characterizing these lesions may change over time. The lesion size may increase or decrease and can be measured with an orientation-dependent maximum length and also approximated with spherical, cylindrical, or ellipsoid dimensions. The lesion morphology may change for which a simple list of descriptive categories can be used to characterize the form and shape of the lesions. The lesion location may move for which anatomically labeled regions of interest (ROI) can be used with centers of anatomic xyz spatial coordinates for each ROI. The lesion intensity (aka activity) may increase or decrease for which a variety of metrics can be used including the min-max range, the median and interquartile range, and summed activity measures of the voxels in each ROI. The lesion duration over time may start and stop, cycle on and off, or be present continuously on all imaging scans in the time-ordered sequence of scans. Cortese et al. (2019); Filippi et al. (2019); Hemond and Bakshi (2018) review medical imaging in multiple sclerosis. Ramesh et al. (2021); Salpea et al. (2023) review image segmentation algorithms in medical imaging to differentiate anatomic regions corresponding to lesions from surrounding healthy tissue.

Mathematical Models

A growing body of literature can be found on time-dependent and temporal graphs (Yan and D. Wang 2015; Y. Wang et al. 2019; Longa et al. 2023). However, various approaches described in the literature do not address interpretations of the time dependence in a manner that also imposes a requirement for tracking the spatial dependence consistent with the anatomic requirements of the relevant problem for nervous

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system lesion monitoring in neural imaging. Therefore, for practical application to analysis of the EPSMS PET-CT and PET-MR scans, a formal definition of temporal-spatial graphs for lesions in serial scans with neural imaging is defined here: For the graph $G(V, E)$, temporal graphs may assume a fixed number of vertices in V with varying number and/or weights of edges in E. Associate the scan s-indexed graph G^s with each PET scan as a snapshot in time for the date-ordered s-indexed sequence of S scans $\{1, ..., s, ..., S\}$. For each graph G^s, associate the lesion l-indexed vertex V_l^s with lesion l in scan s for the APSI-ordered l-indexed V_l^s list of L_s lesions $\{1, ..., l, ..., L_s\}$ (APSI = anterior-posterior within slice, superior-inferior across slices). For graphs G^s and G^t and any neuroanatomically adjacent vertices V_l^s and V_m^t, define edges E_{lm}^{st} as the unordered pairs (V_l^s, V_m^t). Then $G = \{V_l^s, E_{lm}^{st} \mid \forall\, s, t \in 1, ..., s, t, ..., S;\ \forall\, l, m \in 1, ..., l, m, ..., L_s\}$ is the temporal graph G for all lesions in all scans. This definition does not detail the vertex properties or edge weights described as possible for the neural dynamics of the scan lesions.

Discussion

When to use the right tool for the right task? If our goal is explainability, reproducibility, validity, and sustainability, then when should we use which models and methods to answer which questions about immunal dynamics and neural dynamics for multiple sclerosis? For which scenarios do we prioritize, or consider more important, the relative change of a feature activity in time over relative change in space and vice versa? Various approaches based on time-frequency time-space wave-propagation exist, but what about time-scale analyses as studied in the wavelets community? Consider a hybridized approach that fuses temporal-spatial graphs with time-scale wavelet-based multiresolution analyses of dynamics? Will the models and methods be explainable, tractable, and reproducible? *All animals, including humans, are complex systems of complex systems.* No mammalian brain has ever existed without multiple other companion systems: immune, endocrine, respiratory, cardiovascular, musculoskeletal, gastrointestinal, urinary, dermatological, etc. Slowing progression of the neurodegenerative disorder multiple sclerosis will require a better understanding most importantly of interactions between the immune and nervous systems, as well as possibly other pairs of interacting systems.

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