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Balancing practicality and complexity in neuroimaging models of Parkinson's disease progression

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Reliable progression models are essential for clinical decision-making and trial design in Parkinson's disease. We discuss linear, exponential, and sigmoidal patterns in PET and SPECT data, emphasizing the mismatch between biomarker and clinical trajectories. We propose more adaptable modeling strategies to improve patient stratification, support trial outcomes, and align imaging biomarkers with real-world disease complexity.

Disease modeling in Parkinson's disease (PD) plays a crucial role in understanding pathophysiology, predicting clinical outcomes, and optimizing clinical trial design[1–3]. Models serve multiple functions: they facilitate patient stratification, enable estimation of disease onset, disease state (staging), and progression rates, and provide a framework for assessing potential disease-modifying treatments. Hitherto, models have often assumed fixed and linear progression trajectories to reduce complexity, yet PD shows substantial variability across individuals and disease stages. In the field of neuroimaging, this modeling typically involves tracking changes in biomarkers such as dopamine transporter (DAT) binding or [^{18}F]fluoro-L-dopa (FDOPA) uptake over time using PET or SPECT.

Yet a fundamental conceptual distinction is often blurred: what exactly are we modeling when we speak of "progression"? In PD, progression may refer to the advancement of the underlying pathological processes (e.g., dopaminergic neurodegeneration or alpha-synuclein spread), or to the evolution of clinical symptomatology (motor or non-motor). While these two types of progression are related, they are not necessarily tightly coupled. Biomarker changes may precede clinical symptoms by years, and compensatory mechanisms, such as motor reserve, may delay symptom onset or mask deterioration.

This misalignment is further compounded by two key issues. First, "de novo" PD patients can look strikingly different at diagnosis depending on when they first present to clinical attention, making any fixed staging assumptions problematic. Second, the clinical severity scores used in trials and observational cohorts, such as the MDS-UPDRS part III, are inherently noisy, with day-to-day variability and susceptibility to medication effects, rater variability, and fluctuations unrelated to underlying pathology.

Thus, while PET and SPECT imaging offer valuable objective indices of disease biology, interpreting their temporal trajectories as proxies for clinical progression remains challenging. A linear decline in dopaminergic signal, for example, does not necessarily imply a linear trajectory in motor symptoms. Recognizing and addressing this complexity is crucial for the next generation of progression models.

In this Comment, we revisit the use of linear, exponential, and sigmoidal frameworks in interpreting longitudinal neuroimaging studies in PD, in the context of recent propositions for biomarker-based definitions and staging of PD[4,5]. We argue for more flexible, individualized models that account for variability in progression patterns, clinical-biomarker misalignment, and the limitation of current measures.

Linear Progression Model: A Simplified but Practical Framework

The linear model assumes that neurodegeneration occurs at a relatively constant rate over time, a concept rooted in the idea that physiological decline in aging may follow approximately linear trajectories (Fig. 1A, the constant-rate model)[6,7]. While this assumption is a simplification, some support comes from studies in non-human primates showing cellular mechanisms that overlap between aging and PD[8]. One variant of this concept is the event-driven linear model (Fig. 1B), in which the onset of degeneration is triggered by a specific external or internal insult, such as an environmental exposure, after which neurodegeneration progresses at a steady rate. This contrasts with the long-latency model (Fig. 1A), where the disease reflects a lifelong predisposition or gradual deviation from normal aging without a clear trigger. Nonetheless, true clinical PD progression is unlikely to follow a strict linear path in most cases over the disease course.

Despite this, a subset of PET and SPECT studies focusing on presynaptic dopaminergic function, such as striatal DAT and aromatic amino acid decarboxylase (AADC, e.g. FDOPA) binding, have reported relatively steady, near-linear reductions over time (Table 1), particularly during the early stages of disease. Similarly, longitudinal studies in Alzheimer's disease (AD) have shown that some biomarkers, including CSF Aβ, FDG-PET and hippocampal volume, may follow approximately linear trajectories across the disease course[9]. These findings suggest that for certain biological systems or disease phases, a linear progression model may provide a reasonable approximation.

Clinically, the linear model continues to be widely used due to its simplicity and interpretability. It remains a standard framework for therapeutic planning and clinical trial simulations, especially in early PD, where symptom progression may appear gradual and relatively uniform. For instance, a recent study by Dzialas et al. demonstrated a significant interaction between time and DAT loss, showing that the rate of DAT decline was indicative of increasing motor symptom severity[10], supporting the model's practical utility in correlating biomarker dynamics with clinical outcomes.

However, the linear model has certain limitations. It may obscure the biological and clinical heterogeneity of PD, particularly in later stages where compensatory mechanisms begin to fail. External modifiers such as comorbidities, medication changes, or acute stressors can further influence the dynamics of biological and clinical progression. Moreover, the relative

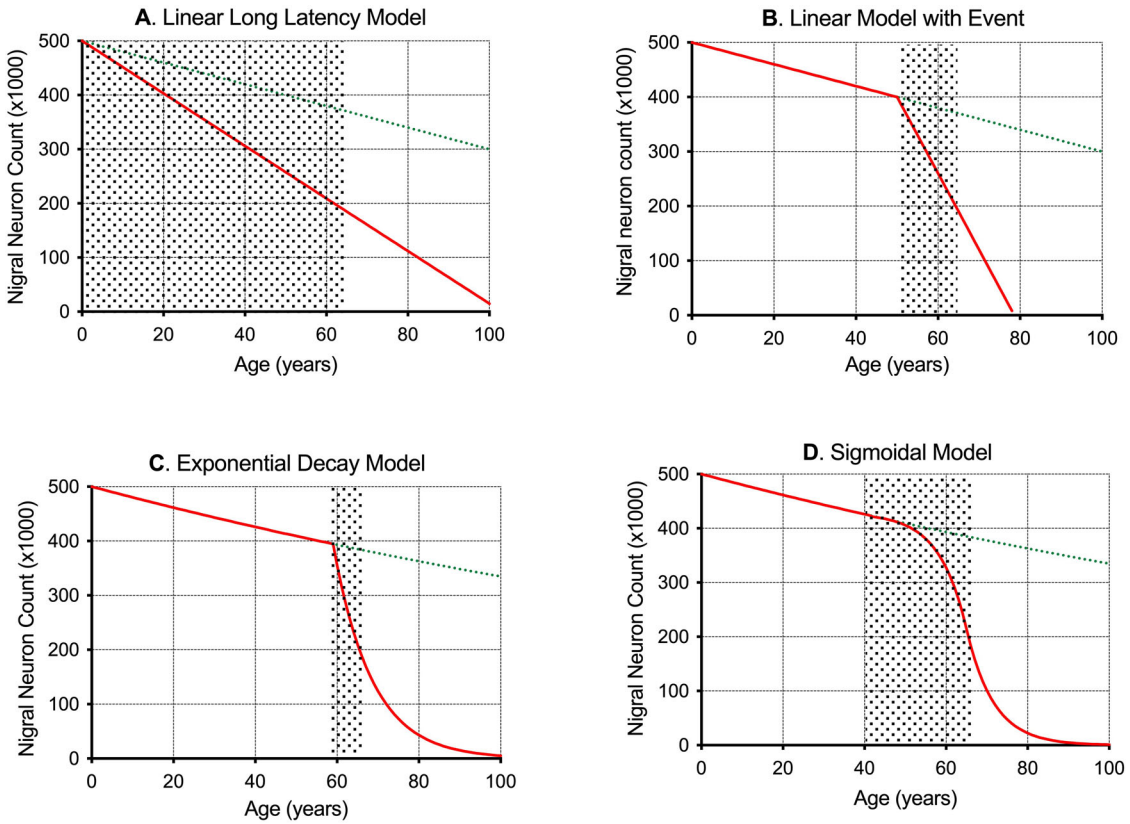

Fig. 1 | Prototypical Models of Neuronal Loss Patterns in PD. Illustrative models of dopaminergic neuron loss in the substantia nigra pars compacta, representing possible progression patterns in PD. For modeling, an initial count of 500,000 dopaminergic neurons at birth was assumed, decreasing to approximately 300,000–400,000 neurons by the seventh decade due to normal aging[44]. Motor symptoms in PD were set to emerge when dopaminergic neuron loss reaches 50% relative to age-matched healthy individuals[13]. The shaded region in each panel represents the premotor phase, the interval between the onset of neuronal pathology and the onset of motor symptoms. Green dotted line denotes age-related neuronal loss. **A** Linear Long Latency Model: This model assumes a congenital predisposition, with neuronal loss following a pattern of accelerated aging over a prolonged premotor phase. **B** Linear Model with Event: This model suggests an event at age 50 disrupts normal aging, leading to a linear decline in neuron count. The premotor period is estimated at 15 years. **C** Exponential Decay Model: Here, an acute event causes a sudden 10% reduction in neurons, followed by a rapid, exponential annual loss of 10%. The premotor period is approximately 5 years. **D** Sigmoidal Model: This model proposes a gradual initiation of pathology starting at age 40, with an accelerating decline that later decelerates, approaching a non-zero asymptote. The premotor phase spans roughly 25 years.

sparsity of longitudinal neuroimaging data, limited by cost, participant burden, and radiation exposure, constrains the development and validation of more complex models. Biomarkers, particularly those derived from PET and SPECT neuroimaging studies conducted in early to mid-stage PD patients, may not fully cover the final plateau phase, potentially creating the impression of linearity[11]. Furthermore, it is possible that the aggregate of individual exponential or sigmoidal decline patterns within a heterogeneous population could collectively appear as a linear trajectory. This effect may arise from variability in disease dynamics, including differences in onset timing, progression rates, and underlying pathological mechanisms across the observed cohort. Thus, while useful, the linear model should be applied cautiously, particularly when forecasting long-term clinical outcomes and modeling advanced disease.

Exponential Progression Model: The Concept of Accelerated Degeneration

Exponential decay is a well-characterized principle in the natural sciences, observed across diverse processes, such as radioactive decay and the physiological clearance of substances. It can be understood within a risk-based stochastic framework, where neurodegeneration occurs probabilistically, with each neuron facing a time-invariant risk of death. In such cases, the number of surviving neurons decreases exponentially over time, forming the basis of a constant-risk model[7].

Applied to neurodegeneration, an exponential model suggests an early rapid loss of neurons following a short-term trigger, after which the rate of degeneration slows most likely due to reaching a biological "floor" (Fig. 1C). The landmark neuropathological study by Fearnley and Lees supported the non-linear model, proposing that the bulk loss of dopaminergic cells in PD happens within a relatively brief time period[12]. By fitting an exponential decay curve to the observed nigral neuronal loss, the authors estimated the presymptomatic phase to be around 5 years—considerably shorter than previous estimates. More recent findings, including evidence of a rapid decline in dopaminergic function within the putamen during the first 1-4 years post-diagnosis, followed by a plateau, further support a negative exponential non-linear trajectory[13].

Table 1 | Longitudinal PET or SPECT studies (n ≥ 10) investigating the progression pattern of dopamine transporter (DAT) or aromatic amino acid decarboxylase (AADC) binding loss in PD

Study	Tracer	n	Mean disease duration at baseline (years)	Number of time-points	Mean scan interval (years)	Pattern of decline in studies with >2 time points	Hemispheric differences
PPMI Dzialas et al.[10]	[^{123}I]FP-CIT	274	1.0	5	1.0	Linear	More pronounced decline on the ipsilateral side
PPMI Simuni et al.[30]	[^{123}I]FP-CIT	235	0.6	4	1.0	Exponential[A]	More pronounced decline on the ipsilateral side
CALM-PD Parkinson Study Group[31]	[^{123}I]beta-CIT	65	1.3-1.6	4	1.8, 1.0 and 1.0	Linear	No differences
Marek et al.[32]	[^{123}I]beta-CIT	32	2.5	2[B]	2.3	Linear	n/r
Morrish et al.[33]	[^{18}F]FDOPA	32	3.3	2	1.5	Exponential[C]	n/r
Hilker et al. 2005a[34]	[^{18}F]FDOPA	31	2.9	2	5.4	Exponential[C]	n/r
Jakobson Mo et al.[35]	[^{123}I]FP-CIT	22	1.5	3	1.0 and 2.0	Exponential[D]	More pronounced decline on the ipsilateral side
Pirker et al.[36]	[^{123}I]beta-CIT	21	2.4	3	2.2 and 3.2	Linear	No differences
Nurmi et al.[37]	[^{18}F]FDOPA	21	5.3	2	5.3	Linear[E]	n/r
Nandhagopal et al.[38]	[^{11}C]MP [^{18}F]FDOPA	19	7.6	3	4.0	Exponential	More pronounced decline on the ipsilateral side
Morrish et al.[39]	[^{18}F]FDOPA	17	1.5/5.9	2	1.3/1.5	Linear[E]	n/r
Vingerhoets et al.[40]	[^{18}F]FDOPA	16	4.5	2[B]	7.4	Linear	n/r
Brück et al.[41]	[^{18}F]FDOPA	16	1.2	3	2.0 and 3.5	Exponential	More pronounced decline on the ipsilateral side[F]
Staffen et al.[42]	[^{123}I]FP-CIT	15	n/r	2	1.3	Exponential[G]	n/r
Huang et al.[43]	[^{18}F]FP-CIT	10	<2.0	3	2.0	Linear	n/r

Note: Several studies in this table report linear patterns of biomarker decline. However, due to limited information about the timing and triggers of disease onset in these cohorts, it is generally not possible to distinguish whether the observed trajectories align more closely with the "long latency" linear model (Fig. 1A) or the "event-driven" linear model (Fig. 1B).
[^{11}C]MP = [^{11}C]d-*threo*-methylphenidate, n/r = not reported, n = number of PD patients at last time-point.
[A]Most rapid decline observed during the early phase of follow-up, [B]More than two scans conducted in some patients, [C]Greater decline observed in patients with shorter disease duration, [D]Greater decline observed during the early phase of the follow-up,[E]No differences in decline between de novo and advanced patients with PD, [F]According to reported mean values, no statistical comparisons, [G]Greater decline observed in patients with less severe motor symptoms.

Much like the linear model, there is PET and SPECT dopaminergic neuroimaging evidence supporting an exponential model of PD progression (Table 1). One notable observation comes from hemispheric asymmetry: the ipsilateral hemisphere (relative to the initial side of motor symptom onset) often shows a delayed but steep decline in dopaminergic function compared to the contralateral side[14]. While this asymmetric pattern may reflect a non-linear trajectory of neuronal degeneration, it could also be influenced by compensatory mechanisms. For instance, early upregulation of DAT expression in the less affected hemisphere might temporarily mask underlying neurodegeneration. Once these compensatory processes are exhausted, a marked drop in DAT signal becomes detectable. Thus, the observed asymmetry may not solely reflect differences in neurodegeneration timing or rate, but also in the failure dynamics of compensatory responses, adding another layer of complexity to the interpretation of progression patterns captured by imaging.

Sigmoidal Progression Model: A Framework for Pathological and Clinical Complexity

Compared to the exponential decay model, sigmoidal biomarker progression may better reflect the heterogeneous and non-linear nature of PD. This model accounts for an initial resilience, followed by acceleration of degeneration and eventual plateauing (Fig. 1D). The sigmoidal model aligns with a prion-like spread of alpha-synuclein pathology, which follows non-linear propagation dynamics across brain regions[1]. This model also reflects the long premotor phase of PD, during which pathology may spread silently before the relatively rapid progression of motor symptoms. The pattern is mirrored in clinical observations where patients experience a rapid loss of motor function after a stable period[15], and sigmoidal models may align more accurately with longitudinal UPDRS data, potentially capturing the initial slow progression, rapid middle-phase worsening, and later plateau[3].

Sigmoidal patterns have been documented in AD, where repeated PET imaging suggests that PiB-PET binding follows a sigmoidal trajectory[16], with similar patterns observed for tau and p-tau biomarkers[9]. In PD, the exponential decline observed in PET and SPECT studies could represent the tail-end of a longer sigmoidal trajectory, where initial progression is slow, followed by acceleration and then stabilization. However, limited sensitivity of neuroimaging at extreme stages of neurodegeneration can introduce both floor (detection limit) and ceiling (saturation) effects, potentially creating a sigmoid appearance, as observed in amyloid imaging studies[17]. While a sigmoidal trajectory is one possible interpretation of PD progression patterns, no published longitudinal dopaminergic neuroimaging studies to date have explicitly modelled progression using a sigmoidal function.

Although sigmoidal models are conceptually well-aligned with the prion-like spread of alpha-synuclein, a major limitation in current biomarker research is the absence of validated α-synuclein PET tracers for routine human use. As such, no longitudinal neuroimaging studies in PD

Table 2 | Conceptual and practical comparison of linear, exponential and sigmoidal progression models in PD

Feature	Linear Model	Exponential Model	Sigmoidal Model
Assumed rate of change	Constant over time	Rapid early loss, then deceleration	Slow onset, acceleration, then plateau
Pathophysiological plausibility	Moderate: Oversimplifies complex processes	Good: Reflects probabilistic neuron loss	High: Consistent with prion-like alpha-synuclein spread
Simplicity and interpretability	High: Easy to communicate	Moderate	Moderate to low
Data requirements	Low: Few timepoints sufficient	Moderate: Multiple timepoints including early and late	High: Requires data across all disease stages
Applicability to clinical imaging trials	Widely used	Occasionally used; limited examples	Emerging use
Sensitivity to floor/ceiling effects	Low	Moderate	High
Captures early compensation mechanisms	No: Assumes immediate decline without buffering	No: Rapid initial decline leaves little room for compensation	Yes: Initial plateau/slow decline reflects preserved function despite pathology

have yet applied α-synuclein imaging to assess disease progression. The eventual availability of specific and reliable α-synuclein PET tracers could provide crucial data to directly test sigmoidal propagation hypotheses in vivo and help bridge the gap between pathology-based models and longitudinal biomarker trajectories.

Beyond Traditional Models: A Case for Multi-Dimensional Approaches

Given the variability in PD progression across patients and symptom domains, a single rigid model is unlikely to fully capture clinical disease complexity (Table 2). This complexity in PD parallels the inter- and intraindividual variability of disease progression in amyotrophic lateral sclerosis (ALS), which presents a wide range of decline patterns. ALS patients exhibit diverse clinical trajectories, including sigmoidal, convex, concave, and linear forms of progression[18]. Moreover, sudden and dramatic declines, or "functional cliffs," can be triggered, possibly by external factors such as infections, vascular events, or medication changes[18]. In PD, similar "last straw" events may act as tipping points[19], where a relatively stable disease state transitions into rapid deterioration due to minor external or internal perturbations. This concept mirrors models from other fields, such as climate science, where systems can remain in equilibrium until a threshold is crossed, leading to significant and dynamic changes. For example, cognitive function in PD patients appears to remain stable for years before reaching a certain inflection point, commonly around 13 years post-diagnosis, at which deterioration accelerates[20]. Data from the Parkinson's Progression Markers Initiative (PPMI) further support this complexity[18,21]. Machine learning analyses of PPMI and Parkinson's Disease Biomarkers Program (PDBP) data have identified eight unique PD states with overlapping trajectories of motor and non-motor impairments, highlighting the non-linear and non-sequential nature of clinical progression[22].

Recent developments in data-driven disease progression modeling have introduced powerful statistical frameworks that complement and extend traditional biomarker trajectory models. Several approaches now estimate individualized disease time and stage while flexibly modeling non-linear biomarker change across the disease course. These include latent time joint mixed-effects models[23], as well as disease course mapping that summarizes the range of possible PD trajectories by positioning the progression of each patient relative to a reference population in several dimensions[24,25]. Event-based generative statistical models offer an alternative formulation by ordering biomarker abnormality without assuming a fixed scale, with recent PD applications incorporating MRI data and subtyping strategies[26–28]. These methods collectively demonstrate the feasibility of reconstructing latent progression time, subtype, and inter-individual variation from cross-sectional and sparse longitudinal data. While many of these approaches are still in the research stage, their incorporation into future imaging studies could enhance the field's capacity to capture the full complexity of PD progression.

Conclusions and Future Directions

Models assuming fixed progression rates for dopaminergic imaging in PD have thus far offered limited utility, largely due to their inability to account for individual variability, stage-dependent dynamics, and clinical-biomarker misalignment. Considering these insights, we advocate for the development and clinical implementation of adaptable, multimodal progression models that reflect the non-linear and heterogeneous nature of PD. Integrating neuroimaging with clinical, genetic, and digital health data into individualized modeling frameworks—validated across diverse longitudinal cohorts—should be a central aim of future research.

Although the assumption of an underlying sigmoidal model aligns with the dynamics of initially localized polynomial spreading of alpha-synuclein pathology, significant disconnects can exist between this pathological trajectory and clinical symptoms. Even the basic assumption of monotonicity (markers progressing consistently from normal to diseases levels) may not be true for all biomarkers[11]. The heterogeneity in PD progression calls for a flexible approach that goes beyond a uniform, rigid model, considering the influence of cerebral co-pathologies[29], recognizing the limitations of relying on any single proteinopathic mechanism or neuroimaging method.

In the clinic, predicting individual disease progression based on a short-term clinical 'snapshot' remains challenging due to the unpredictable nature of PD and the wide range of possible trajectories. For neuroimaging research, developing integrative computational models[11] that incorporate variability in progression rates, PD subtypes, and the impact of co-pathologies and co-morbidities is essential. These models should be validated with diverse longitudinal datasets and used to inform both clinical practice and trial designs.

Data Availability

No datasets were generated or analysed during the current study.

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Author contributions

V.K. conceived and organized the research project, executed the analysis, and wrote the first draft of the manuscript. T.E. contributed to the execution of the research and critically reviewed and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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