Table S1 General Parkinson's disease calibrations and validations (generally non-power spectrum concepts).

Calibration/Validation	Source
Extensive parameter settings for # of neurons, neuron types, synapses, connections, firing rates, and various other parameters such as variance of parameters. Intended for spiking network models but usable in other types. PD states are represented by degrees of dopamine depletion.	[1]
Simplified parameter settings for neuron types, synapses, connections, and differential parameter sets for healthy vs. PD states. Intended for spiking network models but usable in other model types.	[2]
Loss of ~80% dopaminergic neurons in SNc/VTA required for PD MD symptoms to manifest.	[3]
Qualitative diseased vs. healthy state circuitry: *Weaker* direct pathway *Stronger* indirect pathway Reduced intrapallidal inhibition Lower firing thresholds of GPe and STN Stronger projection from striatum to GPe Weaker cortical interaction with basal ganglia Nigrostriatal degradation correlated with increased theta power and reduced alpha power and peak frequency	[4]
Connectivity from cortex to STN: Most afferents to STN (primarily dorsal): From primary motor cortex, supplementary motor area, and dorsal and ventral premotor cortex Secondary motor cortex afferents to STN (limbic ventromedial): prelimbic-medial orbital areas of prefrontal cortex Somatosensory projections to STN (medial): from cingulate cortex, somatosensory cortex, and insular cortex	[5]
Lesion of STN or pallidal regions ameliorate bradykinesia, akinesia, rigidity, and tremor, and is independent of dopaminergic restoration	[4, 6]
Focal chemical lesion of inhibitory GABA-A neurons in striatum yield 'loss of specificity' and focal muscle twitches	[1]

Stimulation of the cerebellothalamic tract (running from dentate and interposed nuclei of cerebellum through superior cerebellar peduncle to ventral lateral posteroventral thalamic nucleus) hypothesized to control tremor and result in speech side effects.	[7]
Tremor (2-8 Hz) appears in *in vitro* and *in silico* circuit due to weakened GPe-GPi inhibition and strengthened striatal-GPe inhibition, exclusive of cortical effects	[8]
Dopaminergic deficiency in basal ganglia is cause of tremor but not correlated with tremor magnitude	[9]
GPe lesion does not produce PD MDs	[4]
Physical motor thalamus lesion neither worsens Parkinsonian bradykinesia in PD nor regularly causes bradykinesia in patients with essential tremor	[10]
Retrograde APs resulting from stimulation of fibers of passage (corticofugal axons running from motor cortex layer V pyramidal cells through the internal capsule, terminating in the brainstem/spinal cord) are hypothesized to cause DBS PD motor fiber contraction side effects such as in speech.	[11]
Amount of information outflow from cerebellum to cortex correlates with tremor magnitude.	[12]
Symptoms fluctuate dynamically depending on cognitive and motor load and concurrent drug treatment	[13]
Chronic dopamine depletion in rats via 6-OHDA chemical lesion produces decreased GABA and increased glutamate levels in the motor thalamus.	[14]

Table S2 Firing rates in the basal ganglia, thalamus, and motor cortex for calibration of numerical PD models. Data come primarily from healthy and PD-state animal models prepared using chemical lesion of the nigrostriatal dopaminergic neurons. Most sources are primate (monkey).

Nucleus	Rate (Hz)	Comments/Source
Primary motor and somatosensory cortex	Healthy: 5 – 20 PD: Decreased or unchanged	Diseased state: Same firing rate but impaired temporal organization, decreased correlation with striatum activity or reduced firing rate under motor task [15]
Striatal MSN	Healthy: Most: 0.5 – 2	[16]

	Small fraction: 6 PD: Elevated	
Substantia nigra pars reticulata	Average firing rate over entire nucleus in healthy rats ~28.6 +/-2.2 Hz (anterior SNpr 24.7 +/-2.5 Hz, posterior SNpr 32.9 +/-2.5 Hz)	[17]
Putamen	PD: Elevated to 10	[16]
Caudate	Healthy: 6 PD: 4	[16]
GPi	Healthy: 60 – 90 PD: Elevated 10 - 20	May affect sensorimotor region only [16]
SNr	Healthy: 50 – 70 PD: ~70 or high end of normal range	May be slightly elevated in diseased state. May be initially elevated and return to normal over time [16]
GPe	Healthy: 85% of neurons: HF bursts separated by seconds of quiescence; mean rate ~55 15%: slowly-discharging at ~10 PD: Decrease of 10 – 20 or no change 40 – 60 in pharmaco-resistant patients	Conflicting reports [16]
STN	Healthy: 20 – 30 in pairs or triplets; PD chemical lesion: Elevated by ~4 - 7 PD human patients: ~37 – 43 43 vs. 53 in healthy vs. PD tremor patients	[16]
STN	Lesion leads to 20% decrease in SN *pars reticulata* firing rate in rat – implies connectivity strength and indicates	[18]

	spontaneous APs in *pars reticulata*	
Relay nuclei	Healthy:10 – 20 PD: Decreased	[16]
Thalamic regions downstream from GPi	Essential tremor or pain, also thought to represent healthy state: 18 - 19 PD: 7 – 8	[16]
BG nuclei targeted by thalamus	PD: Decreased	[16]
BG-Thalamus-Cortex	Acute dopamine depletion in rats via tetradotoxin chemical lesion produces significant reduction in average firing rate but lesser effects on burst rate and thalamo-cortical coupling. MoA in part is motor thalamus GABA enhancement without concomitant change in glutamate levels.	[14]
Cortex to BG	(activation/slow wave) To MSN D1: 448/546 To MSN D2: 592/722 To FSN: 646/787 To STN: 170/250 To GPe TA: 100/200 To GPe TI: 720/1530 To SNr: 1800/1800	Recordings from STN and GPe type A (TA, arkypallidal) and Type I (TI, prototypical) were used to validate the model. [1]

Table S3 Signal latencies. GPe: Globus pallidus external segment. GPi: Globus pallidus internal segment. STN: Sub-thalamic nucleus.

Latencies in GPe response to motor cortex stimulation in healthy, awake monkeys (ms) From motor cortex: • early excitation: 9.2 +/- 3.8 • inhibition: 16.9 +/- 4.4	[19]

• late excitation: 25.8 +/- 2.6 From somatosensory cortex: • early excitation: 10.3 +/-3.04 • inhibition: 18.6 +/- 2.3 • late excitation: 28.2 +/- 3.5 From STN: • excitation: 5.5 +/- 2.3	
Latencies in GPi response to motor cortex stimulation in healthy, awake monkeys (ms): From motor cortex: • early excitation: 7.8 +/- 2.4 • inhibition: 20.9 +/- 5.0 • late excitation: 29.9 +/- 4.5 From somatosensory cortex: • early excitation: 10.3 +/-3.04 • inhibition: 18.6 +/- 2.3 • late excitation: 28.2 +/- 3.5 From STN: • excitation: 4.7 +/- 1.9	[19]
Latencies in STN response to motor cortex stimulation in healthy, awake monkeys (ms): From motor cortex: • early excitation: 5.8 +/- 4.5 • late excitation: 19.8 +/- 5.3 • inhibition: 34.9 +/- 10.4 From somatosensory cortex: • early excitation: 5.8 +/- 2.6 • late excitation: 16.6 +/- 6.9 • inhibition: 32.3 +/- 11.8 •	[19]
Signal latencies: Direct/indirect pathways from STN to motor cortex (orthodromic or antidromic[1], BG-thalamus-cortex): Long latency: ~23 ms[2]; 18-25 ms[3]	1. [20, 21] 2. [22] 3. [21]

Recurrent activation, intermediate latency: 5-15 ms[3] Hyperdirect pathway from STN to GPi/SNr to motor cortex (antidromic): 2-5 ms[2;] 1-3 ms[3]	

Table S4 Power spectra calibrations and validations. Target nucleus of DBS is the subthalamic unless otherwise noted. Equivalence between 1 V in voltage-driven stimulation and 1 mA in current-driven stimulus is based on rule-of-thumb of series resistance of 1 kΩ, which may vary *in vivo*. BG: Basal ganglia. STN: Subthalamic nucleus.

Calibration/Validation	Source
A simplified basic PD calibration: Initiate beta-band oscillations in the cortex, adjust cortico-striatal synchrony via synaptic gain adjustment from cortex to STN, between self-inhibitory GPe neurons, and mutually between STN and GPe until beta synchrony manifests in STN and GPe.	[20]
4 – 8 Hz oscillations in motor cortex produce resting tremor	[4, 23]
Enhanced theta (3 – 7 Hz) and beta (7 – 30 Hz) in GPe, GPi, STN, SNr, pallidal and cerebellar targets of thalamus, striatal medium spinal neurons, tonically active interneurons, and sensory and motor cortices	See sources in [4]
Increase in STN beta band (13 – 35 Hz) power and beta peaks correlate with PD bradykinesia	[24]
Reduction of STN beta band (13 – 30 Hz) power spectra and increase in desynchronization in BG-cortical loop is correlated with PD 3 - 7 Hz tremor. Cortical broadband gamma band increase associated with voluntary movement onset is not present with tremor.	[25] [24]
Subthalamic high frequency (>200 Hz) oscillation power is strongly correlated with PD rest tremor	[26]
Magnitude of tremor is not correlated with 1) dopamine level in striatum; 2) beta-band power in STN or pallidum; which differentiates PD MD pathophysiology from that of bradykinesia and rigidity	[12, 23, 27]
Correlation of beta phase in the BG (GPi) to broadband (50 – 200 Hz) gamma power in the motor cortex and hypokinetic MD. γ-power peaks are coupled to, and precede, β-power troughs.	[28, 29]
Beta rhythms in rat PD models using dopamine-depleting drugs:	[30]

Reserpine (effects are acute and long-lasting): high beta peak (27 Hz); no peak in motor cortex, but correlated beta power with STN, SNr 6-hydroxydopamine (6-OHDA) (effects are chronic and progressive over several weeks): low beta peak (17 Hz)	
Magnitude of tremor is not correlated with 1) dopamine level in striatum; 2) beta-band power in STN or pallidum; which differentiates PD MD pathophysiology from that of bradykinesia and rigidity	[12, 23, 27]

Table S5 DBS Calibrations. Target is STN unless otherwise noted.

Calibration	Source
DBS therapeutic electrode amplitudes (STN) Omni-directional probes Therapeutic: 0.8 – 1.8 mA (mean 0.66) Side effects: 1.1 – 4 mA (mean 3.0) Directional probes set to optimal direction Therapeutic: 0.4 – 1.0 mA (mean 1.2) Side effects: 2.0 – 3.5 mA (mean 2.9)	[31]
60 Hz DBS amplified low-beta 11-15 Hz and attenuated high-beta 19-27 Hz power in human PD patients. 140 Hz DBS broadly attenuated beta power 15-30 Hz. No correlation of beta power attenuation and bradykinesia.	[32]
PD DBS to GPi decreases high β coherence (19–29 Hz, peak 25.07) in human patients between GPi and M1/PM by 38% • Not in the primary somatosensory cortex S1 Low beta coherence inconsistent across individuals	[33]
HF DBS 130 – 180 Hz reduces bradykinesia and resting tremor	[25]
HF DBS affects levodopa-responsive symptoms but effects on axial symptoms (e.g. balance, gait, speech, and swallowing) are temporary or detrimental	[34]
HF DBS frequency > 100 Hz (typically 130 Hz) reduces tremor better than LF DBS < 100 Hz (typically 40 – 60 Hz)	[35]
LF DBS (typically 40 – 60 Hz) frequency reduces akinesia, gait, and FOG better than HF DBS	[35]

DBS at 80 - 130 Hz significantly improved upper limb rigidity and tremor compared to 40 Hz. Lower frequencies in the efficacy range outperformed higher ones.	[36]
20 Hz DBS in STN amplifies beta power in GPi at similar frequencies but did not worsen bradykinesia.	[37]
Duration of beta band power bursts in STN correlates with severity of symptoms; adaptive DBS shortens burst duration while conventional DBS does not, but globally decreases beta band power. Beta band synchrony in STN effects synchrony in the ambient BG circuit	[38, 39]
DBS to STN, but not GPi, produces acute antidromic stimulation of motor cortex (M1) that wanes over 4 hours	[40]
DBS to STN at 140 Hz reduces γ-power to β-phase coupling (γ-power in cortex preceding and coinciding with PD-related β-peaks (13 – 30 Hz) in GPi).	[28, 41]
HF DBS (>130 Hz) to STN restores thalamic activity from reduced levels to close to normal (computational model of BG dopamine depletion)	[42]
60 and 140 Hz DBS improved angular velocity and frequency of movement in human PD patients.	[32]
Efficacy stimulus amplitude range is 1 – 4 V or 0.8 – 3.2 mA, depending on patient and pulse width (e.g. 60 – 300 μs)	[43-45]

Table S6 Sample hypotheses for modelers to test.

Hypothesis	Sources
Are network alterations of oscillations that are intrinsic in the basal ganglia necessary and sufficient to produce beta band peaks or is the larger circuit involving the motor cortex, basal ganglia, and thalamus circuits required?	[46, 47]
PD MD is caused by hyperactivity of the inhibitory indirect pathway and hypoactivity of the excitatory direct pathway activity.	[4]
Imbalance of the concurrent activation of direct and indirect pathways causes contraversive MDs.	[48, 49]
Focal dystonia results from increased effect of the direct pathway	[50]
Generalized dystonia results from increased effect of the indirect pathway	[50]
What are the effects of physical lesion on the BG and movement disorder?	[10]
Is one MoA of DBS PD acting as a physical lesion?	[50]

Chronic dopamine depletion in rats via 6-OHDA chemical lesion produces decreased GABA and increased glutamate levels in the motor thalamus via a compensatory mechanism counterbalancing acute dopamine depletion.	[14, 50-52]
Is the cause of synchrony in BG, thalamus, and/or cortex at the circuit-level, or cell-level, or both?	[1]
Are PD-related beta band peaks causal or correlated with PD MD? Why is the efficacious frequency range 130 – 180 Hz? Why is the preferred target the STN?	[25]
Why is the efficacious stimulus amplitude 2 – 5 volts/mA?	[43, 45]
What are different signatures for different types of tremor and why are they correlated with the tremor types? What signatures can be used to improve efficacy? What signatures can be used to avoid deleterious side effects?	[25, 53]
What signatures can be used with machine learning techniques?	[54]

Supplement S7: Signaling Pathways of Parkinson's Disease

Modelers at the cellular level will increasingly need to integrate the underlying genetic causes of PD into models as these become elucidated.

Healthy State

To sketch the normal, healthy state: Tyrosine regulates L-DOPA, producing dopamine that is encapsulated in vesicles transported to, and released into, the synaptic cleft. On the post-synaptic side, dopamine triggers two receptor types, D1 and D2, which cause a signaling cascade, part of which regulates PKA, which regulates a third receptor, AMPAR/NMDAR (Table 1, drawn from (Cell Signaling Technologies Inc., 2015)).

Diseased States

PD can be caused by several known mechanisms, which fall into 3 classes.

1) Microglia activation, the hallmark of brain pathology due to their principal role in the CNS' immune system, regulate cell stress and in pathological overactivated states cause dysfunction leading to cell death, e.g. via the release of cytokines causing inflammatory response, production of reactive oxygen species (ROS), proteinases, and complement proteins (Dheen, Kaur, & Ling, 2007; Yang et al., 2020). The end pathology is cell death either by directly upregulating apoptosis or indirectly by downregulating cell survival signaling.

2) Environmental toxins – pesticides, solvents, metals, and other pollutants – are the key suspect in idiopathic PD (i.e. when another cause is not known) and animal PD models have been used to support hypotheses [55, 56]. Toxins affect mitochondria, causing excess ROS production, which in turn triggers

apoptosis, or the accumulation of 'junk' in the cell directly via production of Lewy bodies, or indirectly via deregulation of the proteasome, leading to cell death.

3) Genetic mutations can a) trigger mitochondrial disfunction, in turn leading to excess ROS and/or inability of the cell to clear degraded proteins as in the toxins' pathways, b) directly upregulate excess ROS production, or c) upregulate α-synuclein, which in turn leads to Lewy body production and/or degraded proteasomes.

While a growing set of environmental and genetic causes of PD has been identified, more remain to be uncovered.

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