Quantifying Harmony between Direct and Indirect Pathways in A Spiking Neural Network of The Basal Ganglia; Healthy and Parkinsonian States

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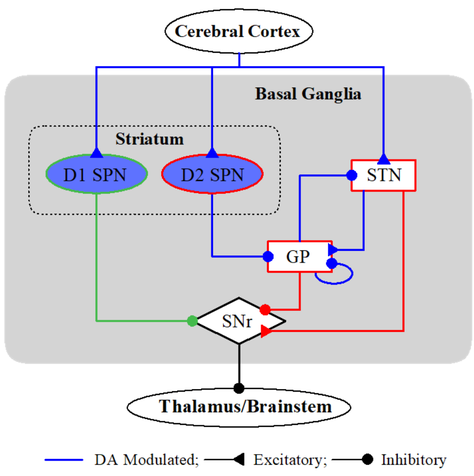
Introduction

- **Basal Ganglia (BG)**
  - A group of subcortical deep-lying nuclei ("dark basement" of the brain)
  - A variety of functions for motor and cognition
    Control of voluntary movement and important roles in cognitive processes
    (e.g., action selection, motor planning)
- **Parkinson's Disease (PD)**
  - Dysfunction of BG (neurodegenerative disease):
    Motor deficits such as slowed movement (bradykinesia), rigidity, and tremor
    Cognitive deficit: dementia
- **Purpose of Our Study**
  Quantitative analysis of competitive harmony between direct and indirect pathways by using competition degree for the healthy and Parkinsonian states

Spiking Neural Network (SNN) of The BG

BG: a collection of subcortical nuclei
[DA (dopamine) modulated: green color]

- **Input Nuclei**
  - **Striatum** (principal input to the BG) spiny projection neurons (**SPNs**) with D1/D2 receptors for the DA
  - **STN** (subthalamic nucleus) only excitatory nucleus in the BG
- **Output Nuclei**
  - **SNr** (substantia nigra pars reticulate)
- **Intermediate Control Nucleus**
  - **GP** (globus pallidus external segment)



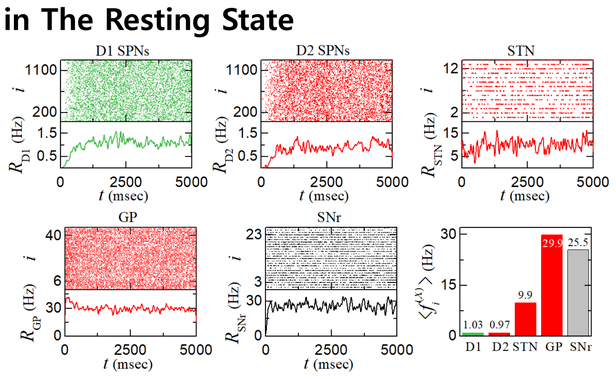
D1 SPNs project inhibition directly to the output nuclei SNr via the **direct ("GO") pathway (DP)**. On the other hand, D2 SPNs are connected to the SNr via the **indirect ("No-GO") pathway (IP)** crossing the GP and the STN.

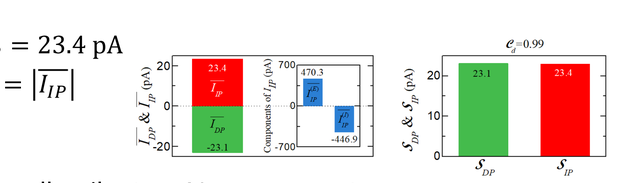
BG: modulating and gating action selection via balance between the Go and No-Go pathways
→ action selection device (gearbox in an auto)

Default State for The Tonic Cortical Input in The Resting State

- **Population and Individual Behaviors of BG Cells for Tonic Cortical Input**
  - Tonic cortical input: $f_{\mathrm{Ctx}} = 3$ Hz → Resting state
  - Normal DA level: $\phi = 0.3$

  D1 & D2 SPNs: nearly silent
  Output SNr cells: very active
  → Leading to no movement





- **Strengths of DP and IP Currents**
  - DP current: $I_{DP} = -I_{syn}^{(\mathrm{SNr,D1})} = -23.1$ pA
  - IP current: $I_{IP} = I_{IP}^{(E)} + I_{IP}^{(I)}$;
    $I_{IP}^{(E)} = -I_{syn}^{(\mathrm{SNr,STN})}$ & $I_{IP}^{(I)} = -I_{syn}^{(\mathrm{SNr,GP})}$ $I_{IP} = 23.4$ pA
  - Strengths of DP & IP Currents: $\mathcal{S}_{DP} = |\overline{I_{DP}}|$ & $\mathcal{S}_{IP} = |\overline{I_{IP}}|$

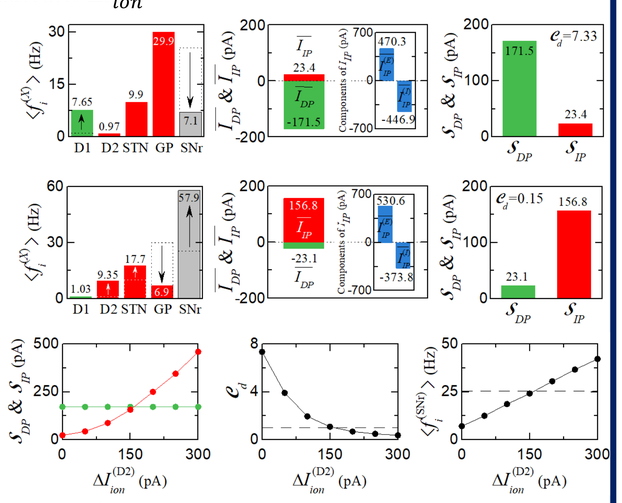
- **Competition Degree**
  $\mathcal{C}_d = \mathcal{S}_{DP}/\mathcal{S}_{IP}$=0.99
  DP & IP: balanced → SNr: fire actively → Thalamic cells: silent → No movement

Activation of Direct and Indirect Pathways

- **Activation and Deactivation of Target Cells Using Optogenetic Technique**
  - Fusion of the opsins (light-sensitive proteins) into the target cells & Activation of opsins by specific wavelengths of light → Variation of intrinsic ionic current $\Delta I_{ion}^{(X)}$

- **Activation of DP:** $\Delta I_{ion}^{(\mathrm{D1})} = 120$ pA
  - Increase in activity of D1 SPNs
    → Suppressing of SNr activity
    → Increase in $\mathcal{C}_d$ & Facilitating movement

- **Activation of IP:** $\Delta I_{ion}^{(\mathrm{D2})} = 150$ pA
  - Increase in activity of D2 SPNs
    → Suppressing of GP activity & Enhancing of STN
    → More activity of SNr
    → Decrease in $\mathcal{C}_d$ & Suppressing movement



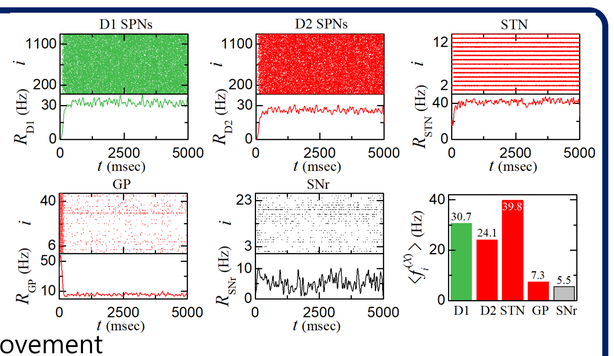
- **Competition between DP & IP**
  With increasing $\Delta I_{ion}^{(\mathrm{D2})}$ for $\Delta I_{ion}^{(\mathrm{D1})} = 120$
  → Increasing strength of IP → Decrease in $\mathcal{C}_d$
  → Increase in SNr activity

  $\Delta I_{ion}^{(\mathrm{D2})} < \Delta I_{ion}^{(\mathrm{D2})*}$: $\mathcal{C}_d > 1$ → DP>IP → Facilitating movement
  $\Delta I_{ion}^{(\mathrm{D2})} > \Delta I_{ion}^{(\mathrm{D2})*}$: $\mathcal{C}_d < 1$ → DP<IP → Suppressing movement

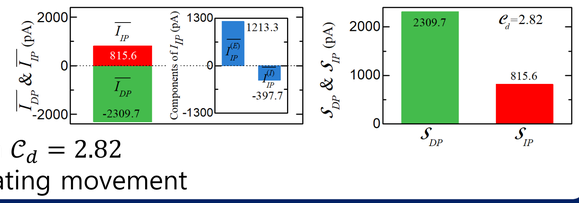
Healthy State for The Phasic Cortical Input

- **Population and Individual Behaviors of BG Cells for Phasic Cortical Input**
  - Cortical input: $f_{\mathrm{Ctx}} = 10$ Hz
  - Normal DA level: $\phi = 0.3$
    → Healthy Phasically-active state

  D1 & D2 SPNs: Active
  → Increase in activity of STN
  & decrease in activity of GP
  Output SNr cells: Decreased activity → Facilitating movement

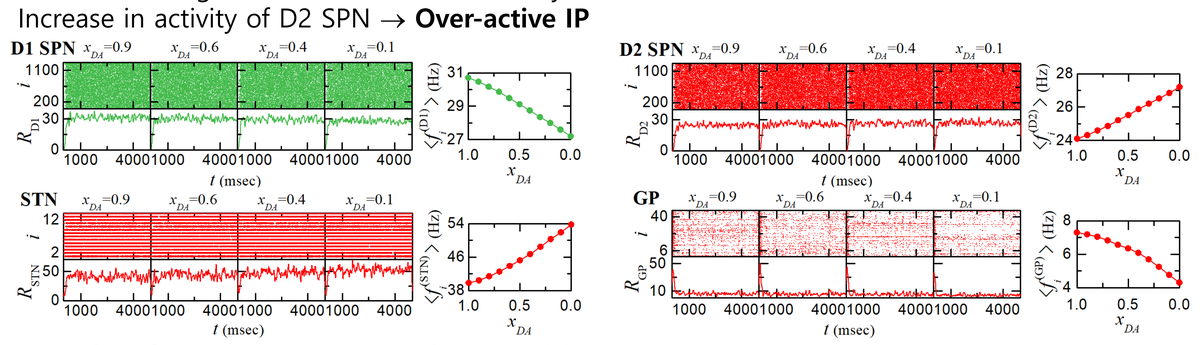


- **Strengths of DP & IP Currents and Competition Degree**
  - Increase in Strengths of DP & IP currents:
    $\mathcal{S}_{DP} = 2309.7$ & $\mathcal{S}_{IP} = 815.6$
    $\mathcal{S}_{DP}$ is much more increased than $\mathcal{S}_{IP}$ → Increase in $\mathcal{C}_d = 2.82$
  - BG gate to the thalamus becomes opened → Facilitating movement

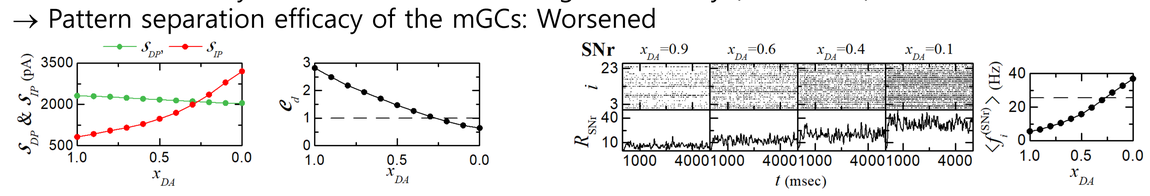


Pathological State for The Phasic Cortical Input

- **Pathological State**
  - Reduced DA level: $\phi = \phi^*(= 0.3)x_{DA}$ with phasic cortical input: $f_{\mathrm{Ctx}} = 10$ Hz
  - With decreasing DA level, Decrease in activity of D1 SPN → **Under-active DP**
    Increase in activity of D2 SPN → **Over-active IP**

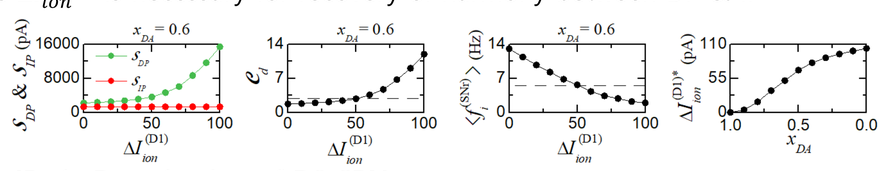


- **Strengths of DP & IP Currents and Competition Degree**
  - With decreasing DA level, little decrease in $\mathcal{S}_{DP}$ & increase in $\mathcal{S}_{IP}$ → Decrease in $\mathcal{C}_d$
  - Increase in activity of SNr; For $x_{DA} < x_{DA}^*$ ($\simeq 0.27$), $\mathcal{C}_d < 1$ → No movement
    Effect of low excitatory innervation > Effect of high excitability ($x > x^* \geq 0$)
    → Pattern separation efficacy of the mGCs: Worsened

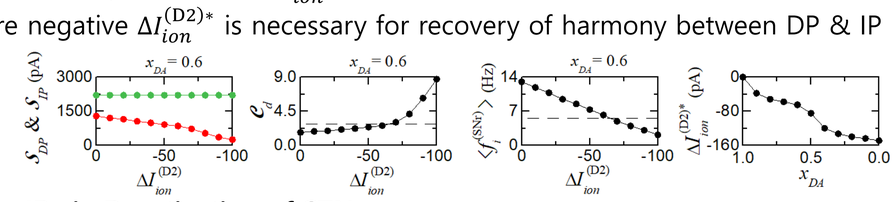


Treatment of Pathological States

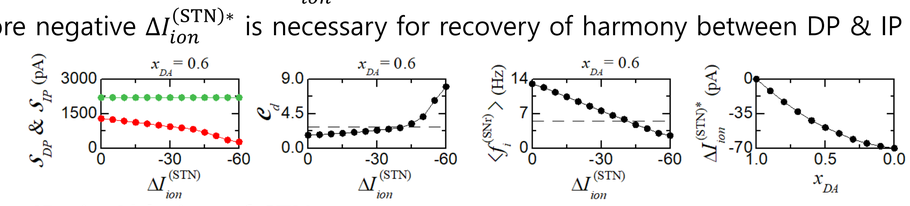
- **Strengthening DP via Activation of D1 SPN**
  For $x_{DA} = 0.6$, Strengthened DP → Increase in $\mathcal{C}_d$
  $\Delta I_{ion}^{(\mathrm{D1})*} = 51$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ (=2.82 for healthy state) → Harmony between DP & IP is recovered
  As x_{DA} is decreased, increase in $\Delta I_{ion}^{(\mathrm{D1})*}$
  → More $\Delta I_{ion}^{(\mathrm{D1})*}$ is necessary for recovery of harmony between DP & IP



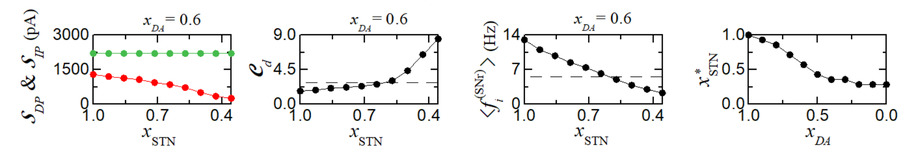
- **Weakening IP via Deactivation of D2 SPN**
  For $x_{DA} = 0.6$, Weakened IP → Increase in $\mathcal{C}_d$
  $\Delta I_{ion}^{(\mathrm{D2})*} = -65$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
  As x_{DA} is decreased, decrease in $\Delta I_{ion}^{(\mathrm{D2})*}$
  → More negative $\Delta I_{ion}^{(\mathrm{D2})*}$ is necessary for recovery of harmony between DP & IP



- **Weakening IP via Deactivation of STN**
  For $x_{DA} = 0.6$, Weakened IP → Increase in $\mathcal{C}_d$
  $\Delta I_{ion}^{(\mathrm{STN})*} = -42$ pA → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
  As x_{DA} is decreased, decrease in $\Delta I_{ion}^{(\mathrm{STN})*}$
  → More negative $\Delta I_{ion}^{(\mathrm{STN})*}$ is necessary for recovery of harmony between DP & IP



- **Weakening IP via Ablation of STN**
  For $x_{DA} = 0.6$, Weakened IP → Increase in $\mathcal{C}_d$
  $x_{\mathrm{STN}}^* \simeq 0.51$ → $\mathcal{C}_d = \mathcal{C}_d^*$ → Harmony between DP & IP is recovered
  As x_{DA} is decreased, decrease in x_{STN}^*
  → More ablation (smaller x_{STN}) is necessary for recovery of harmony between DP & IP



Summary

- **Basal Ganglia (BG)**
  - A group of subcortical nuclei exhibiting a diverse of functions for motor and cognition
  - Parkinson's disease: motor and cognition deficits
- **Quantifying Competitive Harmony between "Go" Direct Pathway (DP) and "No-Go" Indirect Pathway (IP)**
  - Competition degree $\mathcal{C}_d(= \mathcal{S}_{DP}/\mathcal{S}_{IP})$: Ratio of strength of DP ($\mathcal{S}_{DP}$) to strength of IP ($\mathcal{S}_{IP}$)
  - Default BG state: $\mathcal{C}_d \simeq 1$ → DP and IP are nearly balanced
    → Locked state of BG gate to the thalamus → No voluntary movement
  - Phasically-active healthy state: $\mathcal{C}_d = 2.82$ → DP is 2.82 times stronger than IP
    → Opened state of BG gate to the thalamus → Normal movement
- **Pathological State and Treatment**
  - Pathological state: Reduced DA level
    Decrease in activity of D1 SPN → **Under-active DP**
    Increase in activity of D2 SPN → **Over-active IP**
  - Treatment of pathological state
    Strengthening DP via Activation of D1 SPN
    Weakening IP via Deactivation of D2 SPN & STN or Ablation of STN
    → Increase in $\mathcal{C}_d$ → Harmony between DP & IP is recovered

Reference

- S.-Y. Kim and W. Lim, "Quantifying harmony between direct and indirect pathways in the basal ganglia; healthy and Parkinsonian states," Cognitive Neurodynamics 18, 2809-2829 (2024)