Visualization and simulated animations of pathology and symptoms of Parkinson’s disease

Prof. Yifan HAN
Email: bctycan@ust.hk
1. Introduction
2. Biochemistry of Parkinson’s disease
3. Course Design
4. Student’s need and the Visualization and simulations of the life cycle of Parkinson’s disease
5. Conclusion
Introduction

Several diseases, including Parkinson’s disease, have been selected as examples in the syllabus of BISC 395. To enhance student learning, we have developed a Simulated Learning Aid (SLA) using Parkinson’s disease as the first selected example.
Outline

• Introduction
• Clinical signs (TRABP)
• Progression changes (I → IV)
  Familiar (≤5%)
• Etiology
  Idiopathic (majority)
• Biochemical hypothesis
  ➢ MPTP
  ➢ Free radicals
  ➢ DA-Neuronal death in SN
Visualization and simulated animations of pathology and symptoms of Parkinson’s disease

- 2D animated simulation of biochemical pathway
- Video of movement
- Label of importance parts
- Reference
- Glossary
- Short test
Introduction

- Parkinson’s disease was first described by Dr. James Parkinson in 1817 as “shaking palsy.”

- Parkinson’s disease is a slowly progressive degenerative neurologic disease characterized by: (TRABP)
  1. tremor,
  2. rigidity,
  3. akinesia (difficult in initiation movements)
  4. bradykinesia (sluggish neuromuscular responsiveness), and
  5. postural instability.

- It is one of the most common hypokinetic disorders occurred after age 50 (with an incidence of 100~150/100,000 population). Onset generally occurs between ages 50 and 65;
Signs and symptoms

1. Tremor
   a) Tremor may be the initial complaint in some patients. It is most evident at rest (resting tremor) and with low-frequency movement. When the thumb and forefinger are involved, it is known as the pill-rolling tremor. Before polls were made by machine, pharmacists made tablets (pills) by hand, which is how this action was named.
   b) Some patients experience action tremor (most evident during activity), which can exist with or prior to the development of resting tremor.

2. Limb Rigidity is present in almost all patients. It is detected clinically when the arm responds with a ratchet-like (i.e. cogwheeling) movement when the limb is moved passively. This is due to a tremor that is superimposed on the rigidity.
3. Akinesia and bradykinesia. Akinesia is characterized by difficulty in initiating movements, and bradykinesia is a slowness in performing common voluntary movements, including standing, walking, eating, writing, and talking. The lines of the patient’s face are smooth, and the expression is fixed (masked face) with little evidence of spontaneous emotional responses.

4. Gait and postural difficulties. Characteristically, patients walk with a stooped, flexed posture; a small shuffling stride; and a diminished arm swing in rhythm with the legs. There may be a tendency to accelerate or festinate.

5. Changes in mental status. Mental status changes, including depression (50%), dementia (25%), and psychosis, are associated with the disease and may be precipitated or worsened by drugs.
Characteristic walk of patients with Parkinson’s disease

- Resting tremors
- Masked face
  - Stare
  - Decrease mobility
Symptoms

with permission © Prof Yi-Fan HAN
The changing brain in Parkinson’s disease
Neuronal circuit disrupted in Parkinson’s disease

NEURONAL CIRCUIT disrupted in Parkinson’s disease is shown schematically. When dopamine-producing neurons die, loss of dopamine release in the striatum causes the acetylcholine producers there to overstimulate their target neurons, thereby triggering a chain reaction of abnormal signaling leading to impaired mobility. The pars compacta region of the substantia nigra in the normal brain appears dark (left photograph) because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson’s disease, the color fades (right photograph).
Extrapyramidal system involved in Parkinson’s disease
In the former, the inhibitory dopaminergic pathway from the substantia nigra to the striatum is impaired, increasing the activity of GABAergic cells in the stratum, which in turn inhibit GABAergic cells in the substantia nigra, thus reducing the restraint on the thalamus and cortex, causing rigidity.

The dopaminergic inhibition of the striatal cells is opposed by excitatory cholinergic interneurons, the defect can be counteracted by dopamine agonists or by ACh (muscarinic) antagonists.

P comp, pars compacta;

P ret, pars reticulata;
Schematic representation of the mechanisms involved in toxicity of MPTP

- **MPP⁺** blocks mitochondrial oxidation, ↓ ATP formation ("complex I")
- ↑ The release of superoxide anion radical (O₂⁻)
- ↓ Ion transportation
- ↑ Cytosolic Ca²⁺ to toxic level

**BBB:** blood-brain barrier;

**MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine;

**MPP⁺:** its four electron oxidation product N-methyl-4-phenylpyridinium
Free radical reactions in Parkinson’s disease

DA: dopamine;
DOPAA: 3,4-dihydrophenyl-acetaldehyde;
GP: glutathione peroxidase;
GSH and GSSH: reduced and oxidized glutathione;
ncNOS: neuronal isoform of nitric oxide synthase;
SOD: superoxide dismutase;
SQ: semiquinone

with permission © Prof Yi-Fan HAN
Cascade of Cellular Reactions

Unknown trigger causes microglia to become overactive.

OVERACTIVE MICROGLIAL CELL

Nitric oxide and superoxide free radicals are released.

Nitric oxide levels rise.

Superoxide levels rise.

Unknown substance releases iron from storage molecules.

Iron levels rise.

Iron interacts with dopamine and neurotrophic factors.

OVERACTIVE GLUTAMATE-PRODUCING NEURON

Calcium levels rise.

Free radical levels rise.

Radicals damage many parts of cell.

Cell dies when it can no longer maintain itself and efficiently repair the damage it suffers.

Mutation occurs in an undetermined mitochondrial gene.

Unknown toxin acts on a critical mitochondrial protein.

The "complex I" protein in mitochondria is inhibited.

Nitric oxide participates in reactions that generate more free radicals.

DOPAMINE-MAKING NEURON

with permission © Prof Yi-Fan HAN
Free radical reactions in Parkinson’s disease

- Oxygen free radicals, shown schematically as colored dots, can directly damage cells in many ways.
- They can injure nuclear and mitochondrial DNA, cell membranes and proteins.
Sites of inhibition (-) or excitation (+) in the striatum and substantia nigra

1. **Substantia nigra**: the substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum.

   - Each **dopaminergic** neuron makes **thousands** of **synaptic contacts** within the striatum and therefore modulates the activity of a large number of cells.

   - These dopaminergic projections from the substantia nigra fire tonically, rather than in response to specific muscular movements or sensory input.

   - Thus, the dopaminergic system appears to serve as a **tonic, sustaining influence** on motor activity, rather than participating in specific movements.
**Sites of inhibition (-) or excitation (+) in the striatum and substantia nigra**

2. **Striatum**: normally, the striatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra.

- In turn, cells of the substantia nigra send neurons back to the striatum, secreting the inhibitory transmitter dopamine at their termini.
- This **mutual inhibitory pathway** normally maintains a degree of inhibition of the two separate areas. Nerve fibers from the cerebral cortex and thalamus secrete ACh in the neostriatum, causing excitatory effects that initiate and regulate gross intentional movements of the body.
- In Parkinson’s disease, destruction of cells in the substantia nigra results in the degeneration of neurons responsible for secreting dopamine in the neostriatum.
- Normal aging: 5% degeneration per decade; Parkinson’s Disease: 12% degeneration per year;
- Only 50% cell death ——— BD syndromes;
- Thus the normal modulating inhibitory influence of dopamine on the neostriatum is significantly diminished, resulting in the parkinsonian degeneration of the control of muscle movement.
Treatment of PD

A. Drug treatment and its strategy

- In addition to an abundance of (a) **inhibitory dopaminergic** neurons, the neostriatum is also rich in (b) **excitatory cholinergic** neurons that oppose the action of dopamine; *(causes)*

- Many of the symptoms of parkinsonism reflect an imbalance between the **excitatory cholinergic** neurons and the greatly diminished number of **inhibitory dopaminergic** neurons;

- Therapy is aimed at:
  1. restoring dopamine in the basal ganglia and;
  2. antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance; *(therapy)*
  3. future pharmacological strategies include the use of glutamate or adenosine receptor antagonists.
Treatment of PD

B. Surgical approaches

Surgical approaches involve selective lesions of the globus pallidus pars interna, subthalamus or ventrolateral tralamus, and the transplant of dopaminergic cells, harvested from the midbrain of human fetuses, into the striatum.
Schematic diagram illustrating:

1. the release of dopamine by a neuron is the substantia nigra;

2. the sites of action of drugs that ameliorate or induce parkinsonism.
Conclusion

Using the SLAs, symptoms and pathology of Parkinson’s disease can be simulated in the class. Students are expected to be given a clear impression of the framework and have a better understanding of Parkinson’s disease. Next year, the SLAs programme will be implemented in the class.