



Simulasi Dinamis Penyebaran Penyakit

Parkinson dan ALS di Otak:

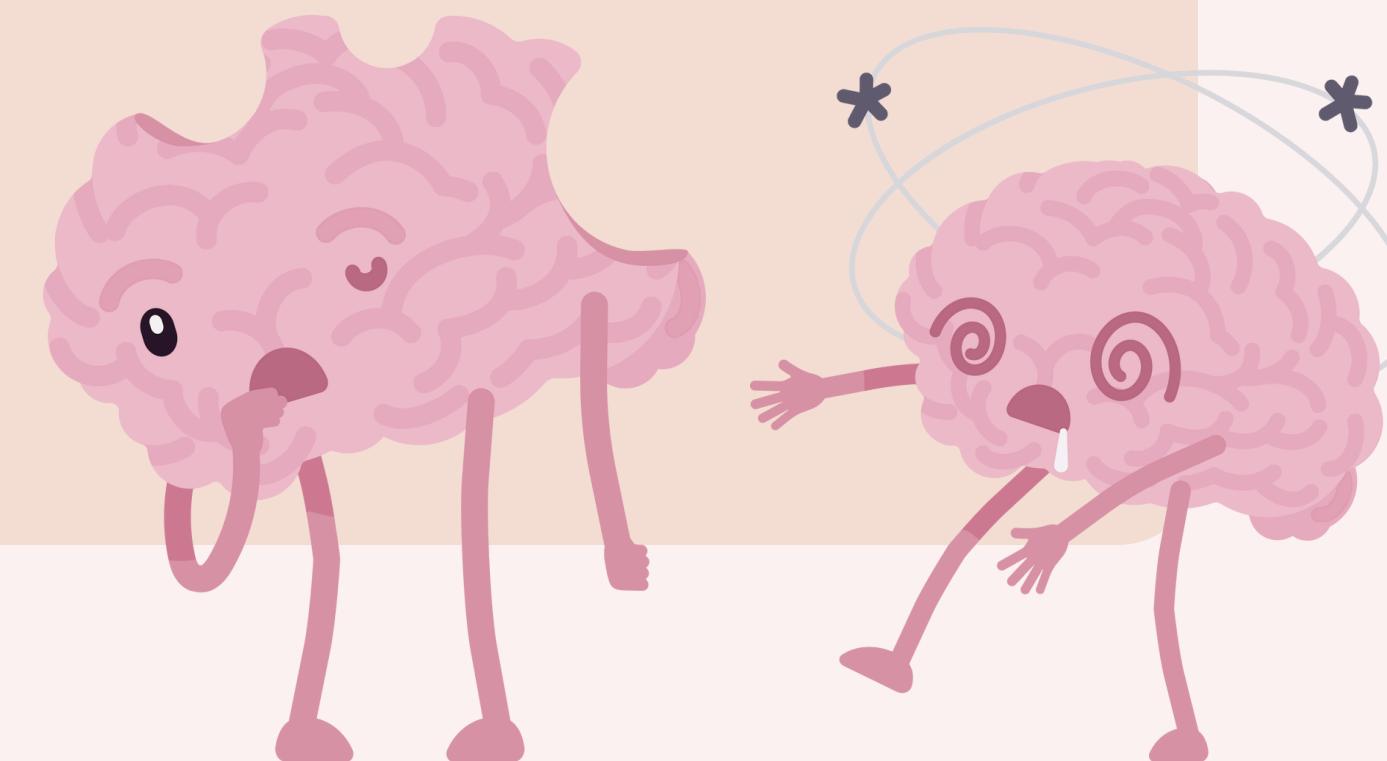
Pendekatan Reaksi-Difusi pada

Jaringan Otak

MA3271 - Pemodelan Matematika

Kelompok : PSP01

Pembimbing: Prama Setia Putra, D.Phil (Oxon)





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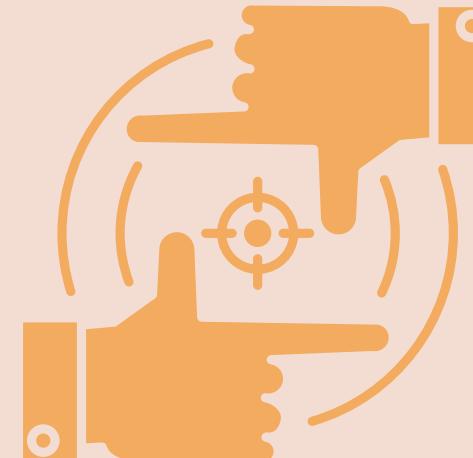


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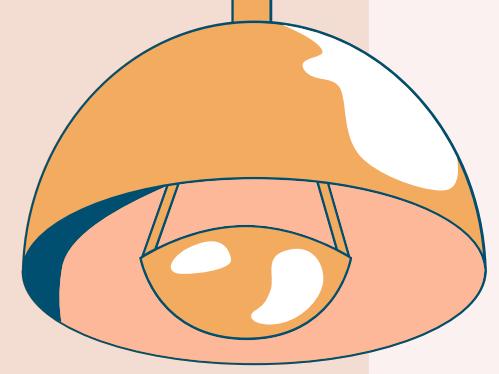
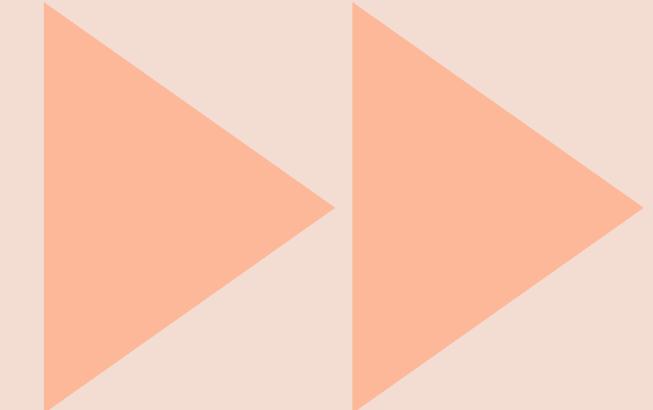


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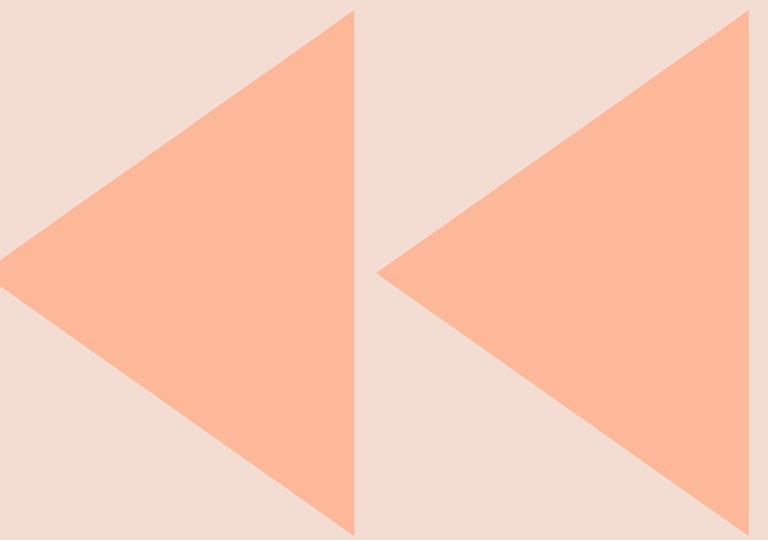
Pokok Bahasan



1. Pendahuluan
2. Kajian Literatur
3. Formulasi Model
4. Hasil dan Pembahasan
5. Kesimpulan



1 Pendahuluan



Latar Belakang

DAN MOTIVASI

NEURODEGENERASI

Kehilangan progresif struktur atau fungsi neuron, termasuk kematian neuron.

ALZHEIMER

amyloid-beta & tau protein

PARKINSON'S

alpha-synuclein

AMYOTROPHIC LATERAL SCLEROSIS

TDP-43

Mengapa?

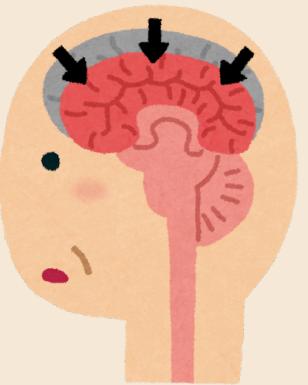
ALASAN UNTUK MEMPELAJARI
PENYAKIT NEURODEGENERATIF



MENYERANG
SEGALA
USIA



BELUM
DITEMUKAN
OBATNYA



PENURUNAN
FUNGSI
KOGNITIF



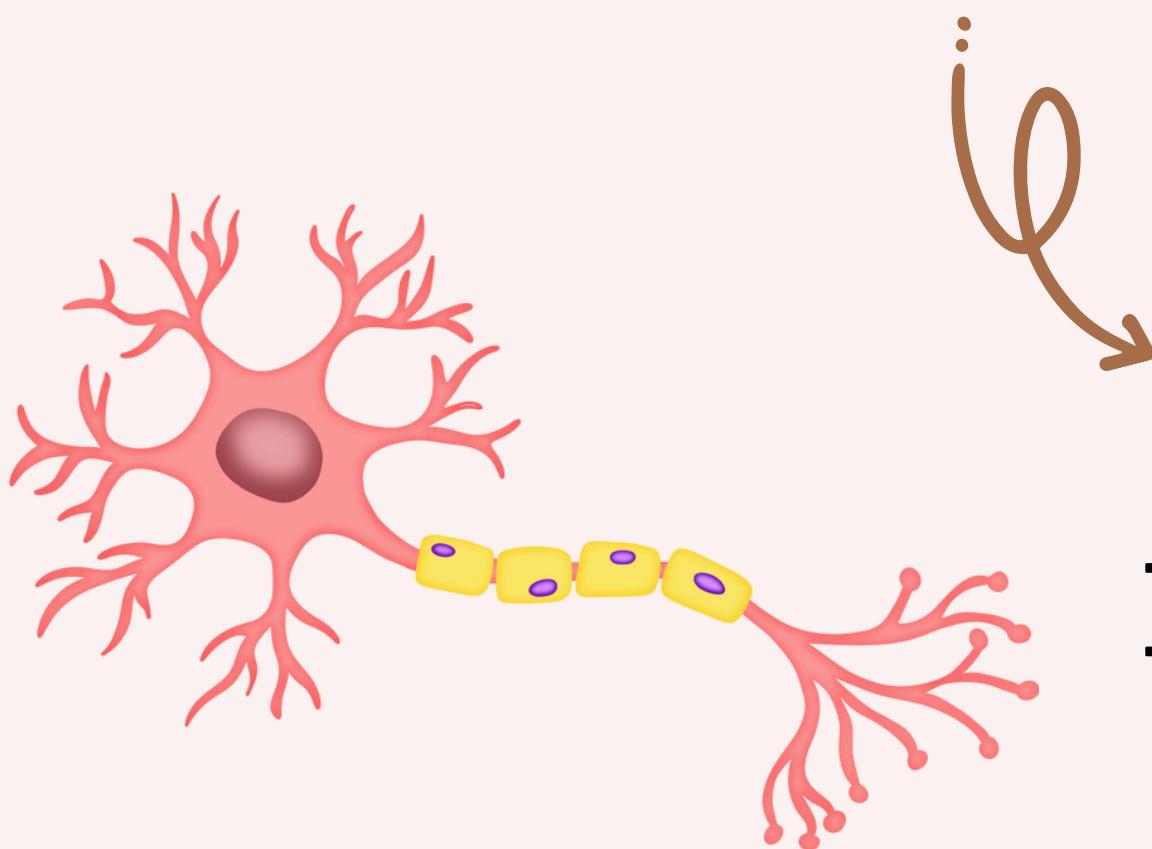
MEMBANTU
DIAGNOSIS
DINI

Batasan Masalah

1. Hanya mengamati penyebaran endapan protein yang menjadi penyebab utama penyakit Parkinson's dan ALS.
2. Tidak memperhatikan penyebab terjadinya awal kerusakan dan penumpukan protein.
3. Tidak mengamati akibat penumpukan protein dan kerusakan bagian otak terhadap kemampuan kognitif maupun motorik.
4. Tidak mengamati pencegahan ataupun penyembuhan dari penyakit.

RUMUSAN MASALAH

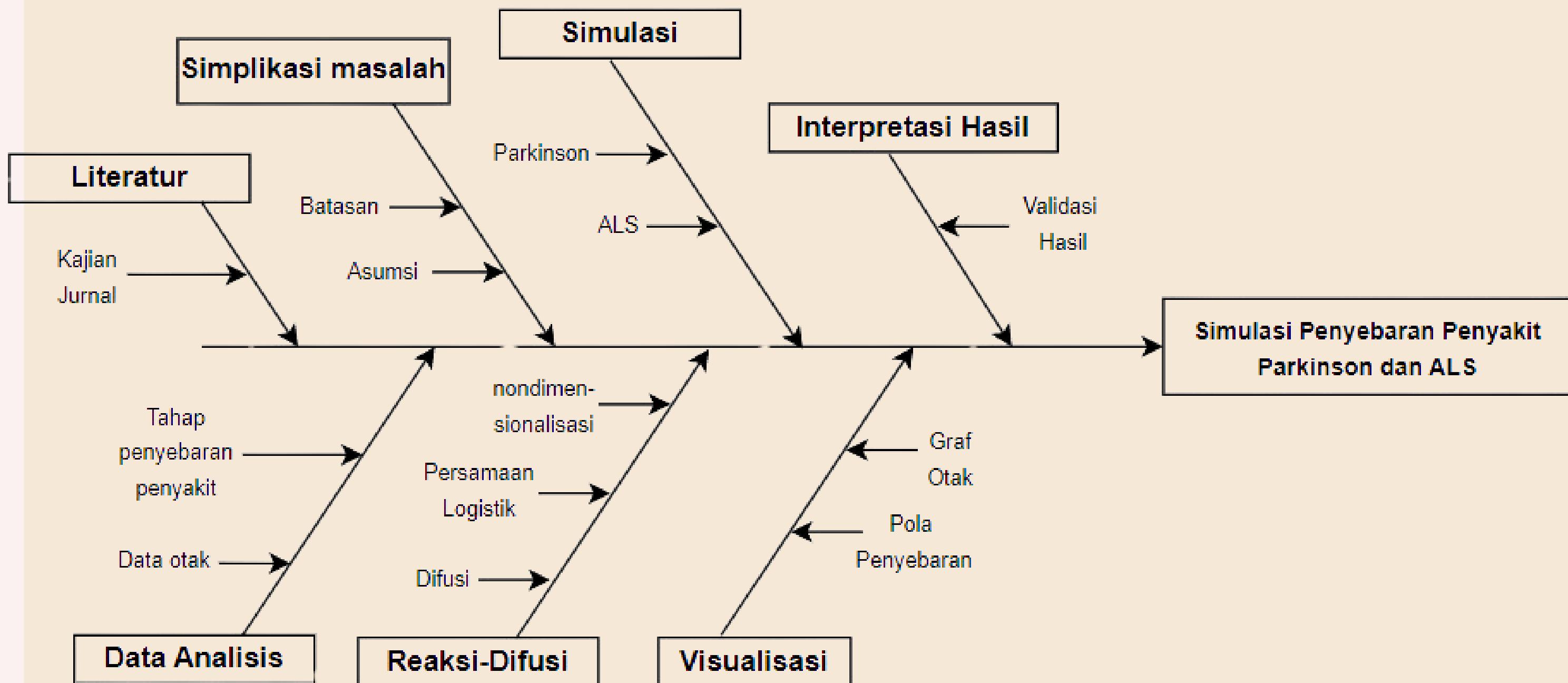
Bagaimana pola penyebaran Parkinson's dan Amyotrophic Lateral Sclerosis (ALS) pada otak terjadi?



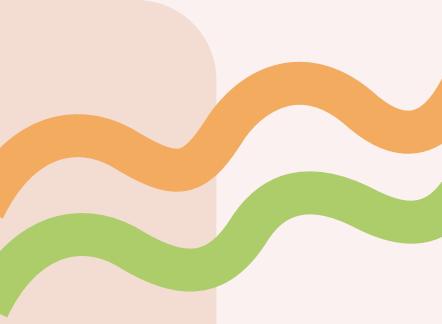
TUJUAN

Mereplikasi pola penyebaran Parkinson's dan Amyotrophic Lateral Sclerosis (ALS) pada otak melalui pemodelan matematika

Diagram Alir



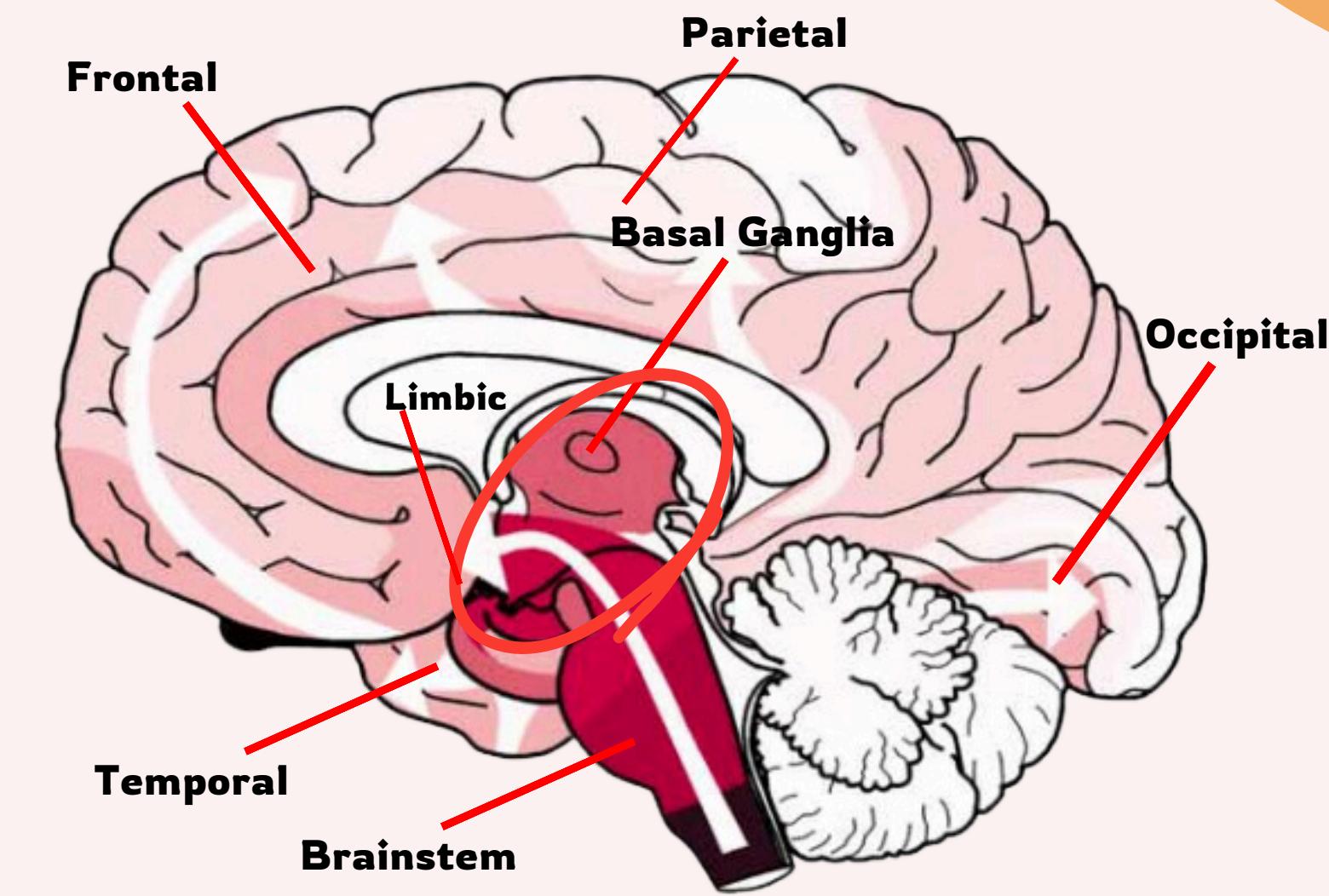
2 Kajian Literatur



Tahapan Penyebaran Parkinson dan ALS

Tahapan penyakit Parkinson

- 01** **Brainstem**
medula oblongata
- 02** **Brainstem**
Pontine Tegmentum
- 03** **Basal Ganglia**
midbrain
- 04** **Temporal**
Basal prosencephalon & mesocortex
- 05** **Frontal & Limbic**
Orbitofrontal, frontal pole
- 06** **Parietal & Occipital**
neocortex, primary sensory areas and motor field



Tahapan Penyebaran Parkinson dan ALS

Tahapan penyakit ALS

01 **Frontal**

Agranular Motor Cortex

02 **Brainstem**

motor nuclei of cranial nerves

03 **Frontal**

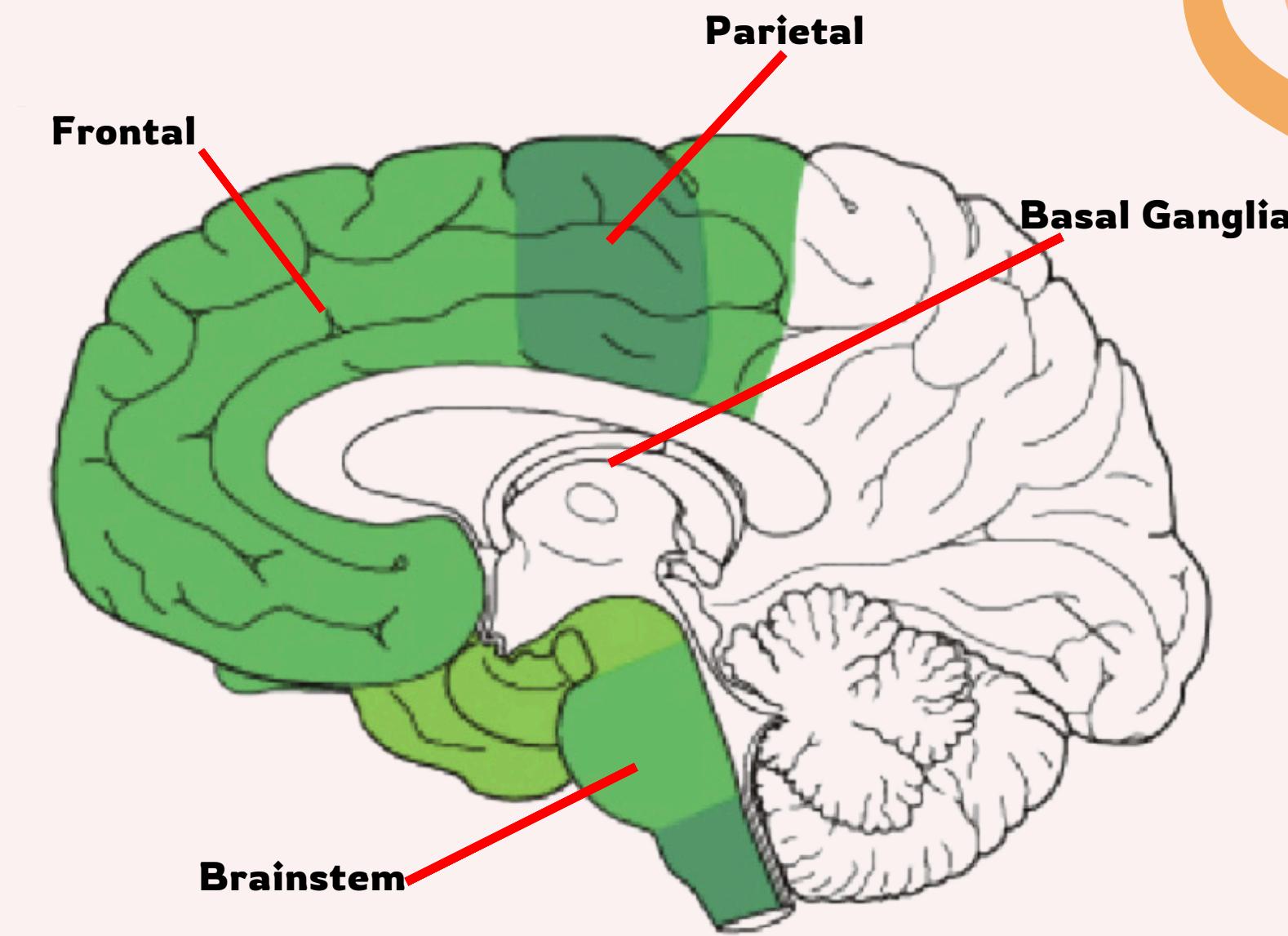
the frontal lobe excluding
the precentral gyrus

04 **Parietal**

postcentral neocortex

05 **Basal Ganglia**

Caudate , Putamen and
accumbens area



Data Jaringan Otak

master_n

Data bobot yang diperoleh dari jumlah banyak neuron antar bagian otak (n), merupakan informasi natural dari otak.

master_w1

Data bobot yang diperoleh dengan membagi banyaknya neuron(n) dengan rataan panjang neuron (L).

Merepresentasikan proses propagasi.

$$\left(\frac{n}{L}\right)$$

master_w2

Data bobot yang diperoleh dengan membagi banyaknya neuron(n) dengan rataan kuadrat.

Merepresentasikan proses difusi.

$$\left(\frac{n}{L^2}\right)$$



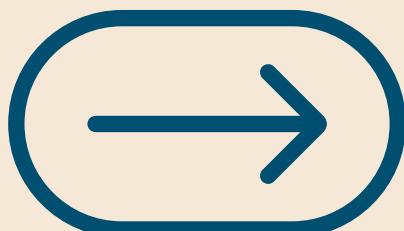
3 Formulasi Model

Cara berpikir untuk memperoleh model yang tepat



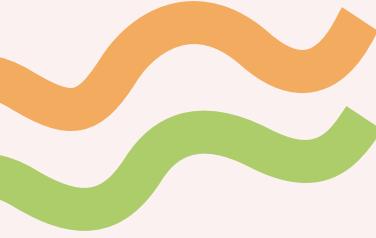
Asumsi

- Protein yang sudah terinfeksi tidak bisa kembali berfungsi normal.
- Semua protein normal pada otak bisa terinfeksi oleh protein rusak yang sejenis.
- Tidak mengamati pencegahan ataupun penyembuhan dari penyakit.
- Jenis protein dianggap homogen dan tidak mempertimbangkan ukuran protein.



Asumsi

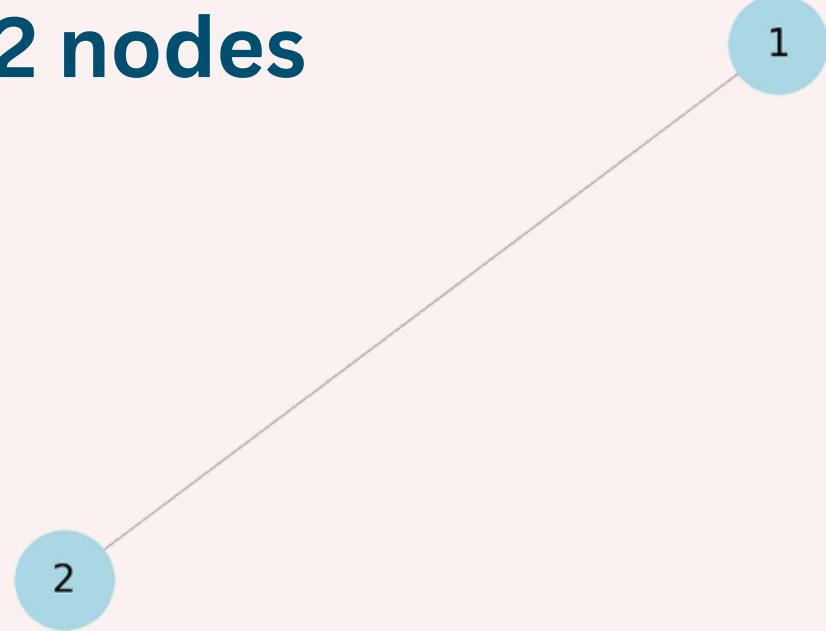
- Titik awal pengendapan protein ditentukan dari literatur, di titik itu konsentrasi protein pada awalnya dibuat tidak nol.
- Dalam penentuan tahapan penyebaran penyakit diasumsikan kemunculan protein pertama kali menentukan urutan penyebaran.
- Mekanisme penyebaran protein rusak menyerupai reaksi-difusi.



Difusi

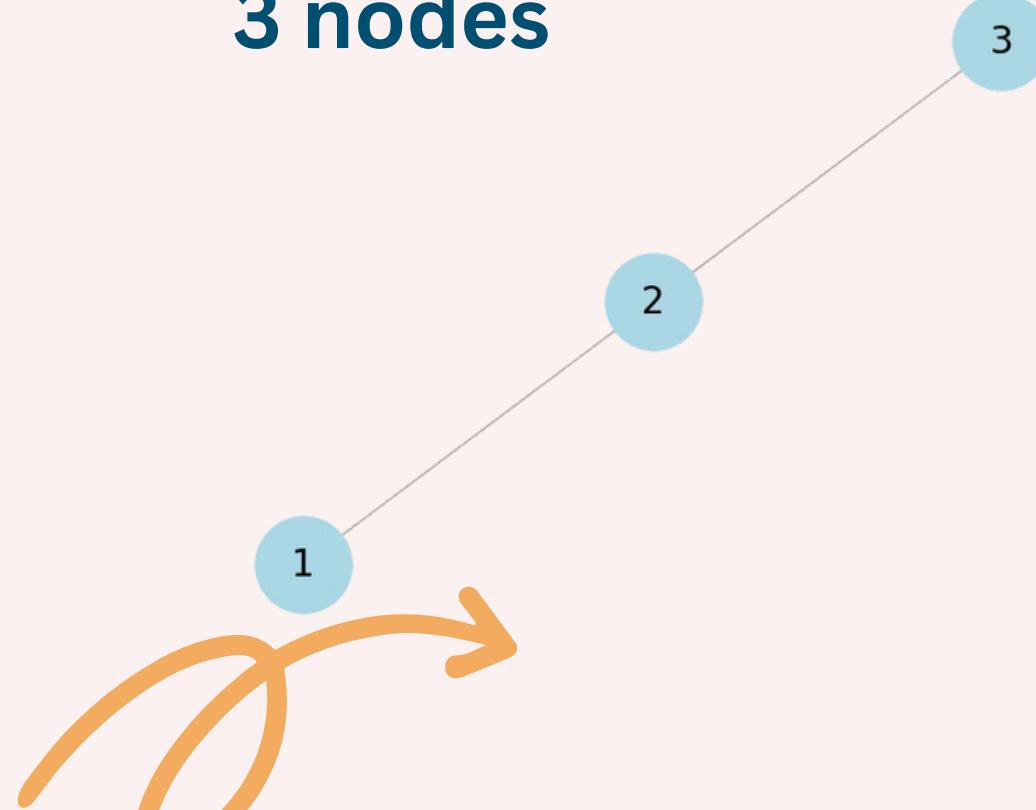


2 nodes



$$A = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$$

3 nodes



$$A = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix}$$

$$\frac{dC_1}{dt} = -C_1 + C_2$$

$$\frac{dC_2}{dt} = C_1 - C_2$$

$$\frac{dC_1}{dt} = -C_1 + C_2$$

$$\frac{dC_2}{dt} = C_1 - 2C_2 + C_3$$

$$\frac{dC_3}{dt} = C_2 - C_3$$



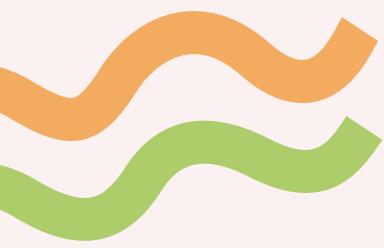
Persamaan Difusi untuk konsentrasi pada node ke-i

$$\frac{dC_i}{dt} = - \sum_{j=1}^n (A_{ij}C_i - A_{ij}C_j)$$

Keterangan

C_i : Konsentrasi di titik ke-i

A : Matriks ketetanggaan ($n \times n$)



Persamaan Logistik



Persamaan logistik yang digunakan dalam formulasi model ini adalah :

$$\frac{dC_i}{dt} = \alpha C_i(1 - C_i)$$

Keterangan

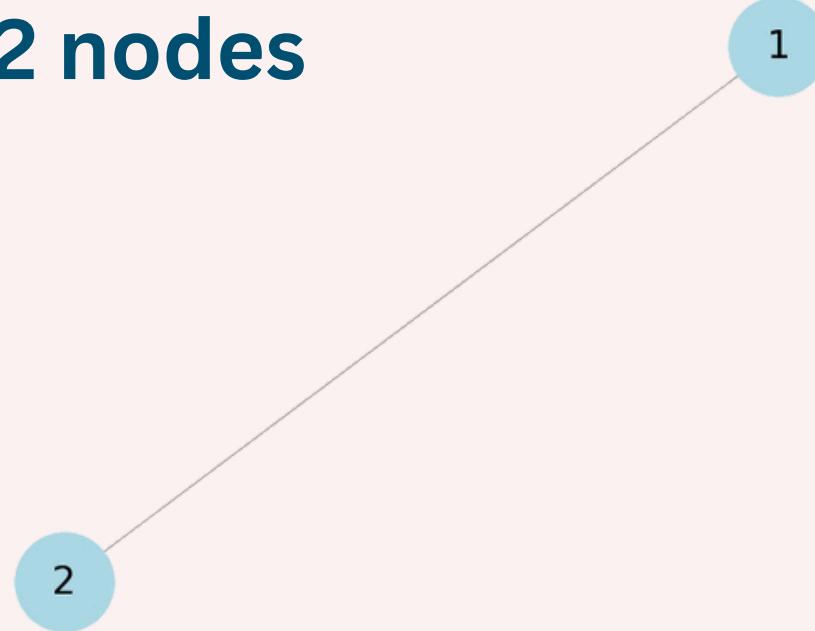
C_i : Konsentrasi di titik ke- i ,
(molekul/Volume)

α : koefisien pertumbuhan



Persamaan Reaksi-Difusi

2 nodes

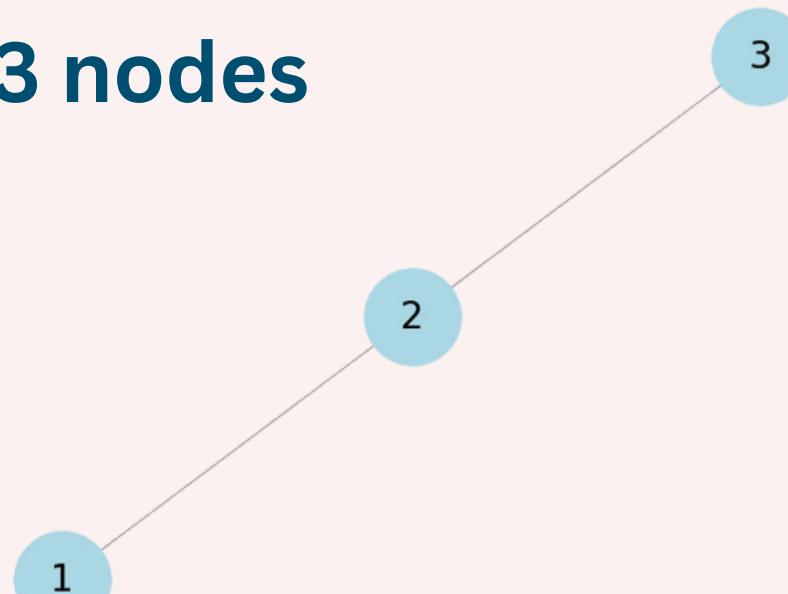


$$A = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}$$

$$\frac{dC_1}{dt} = \alpha C_1(1 - C_1) - \rho(C_1 - C_2)$$

$$\frac{dC_2}{dt} = \alpha C_2(1 - C_2) - \rho(C_2 - C_1)$$

3 nodes

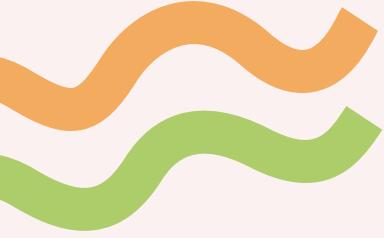


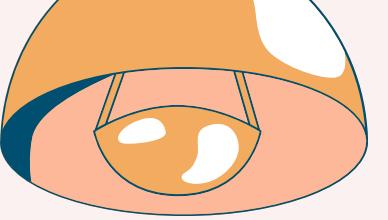
$$A = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \end{pmatrix}$$

$$\frac{dC_1}{dt} = \alpha C_1(1 - C_1) - \rho(C_1 - C_2)$$

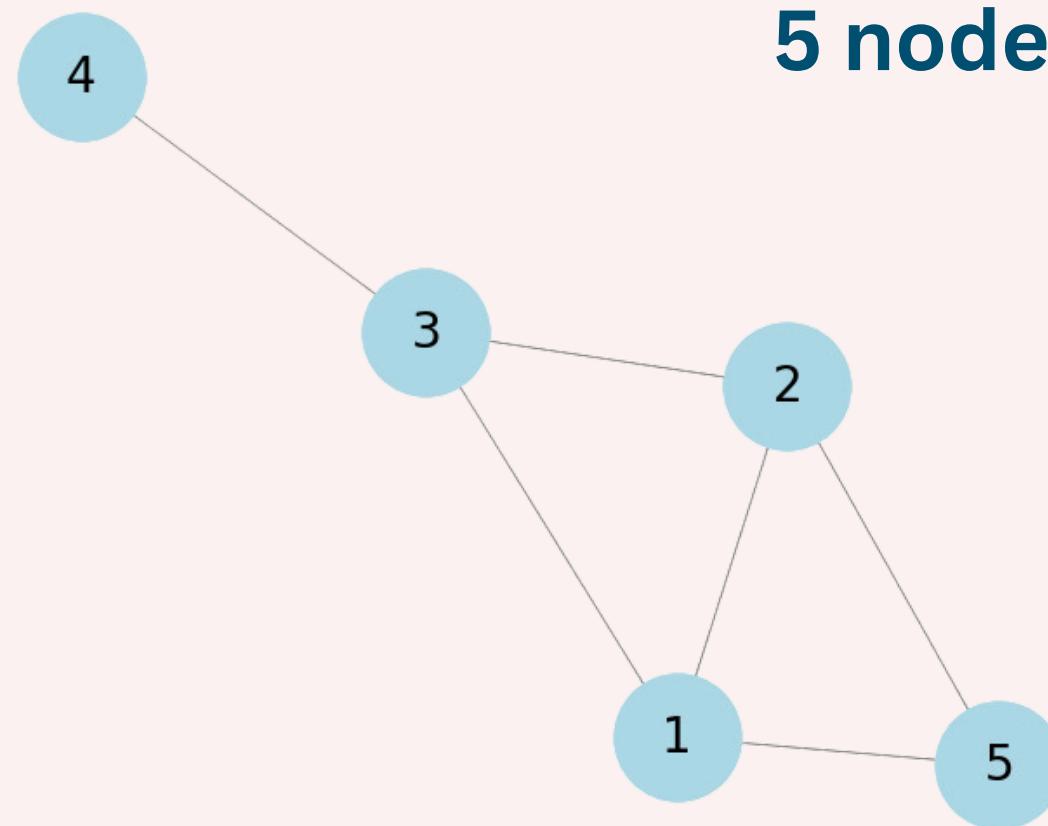
$$\frac{dC_2}{dt} = \alpha C_2(1 - C_2) - \rho(2C_2 - C_1 - C_3)$$

$$\frac{dC_3}{dt} = \alpha C_3(1 - C_3) - \rho(C_3 - C_2)$$





5 nodes



 $A = \begin{pmatrix} 0 & 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \end{pmatrix}$

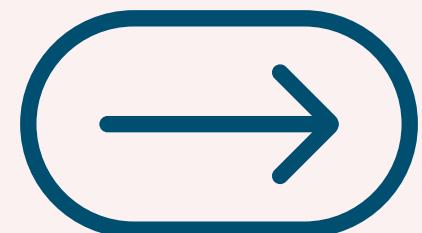
$$\frac{dC_1}{dt} = \alpha C_1(1 - C_1) - \rho(3C_1 - C_2 - C_3 - C_5)$$

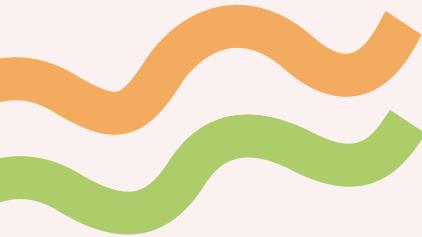
$$\frac{dC_2}{dt} = \alpha C_2(1 - C_2) - \rho(3C_2 - C_1 - C_3 - C_5)$$

$$\frac{dC_3}{dt} = \alpha C_3(1 - C_3) - \rho(3C_3 - C_1 - C_2 - C_4)$$

$$\frac{dC_4}{dt} = \alpha C_4(1 - C_4) - \rho(C_4 - C_3)$$

$$\frac{dC_5}{dt} = \alpha C_5(1 - C_5) - \rho(2C_5 - C_1 - C_2)$$





Persamaan Reaksi-Difusi Konsentrasi Protein



$$\frac{dC_i}{dt} = \alpha C_i(1 - C_i) - \rho \sum_{j=1}^n (A_{ij}C_i - A_{ij}C_j)$$

Keterangan

C_i : Konsentrasi di titik ke-i, (molekul/Volume)

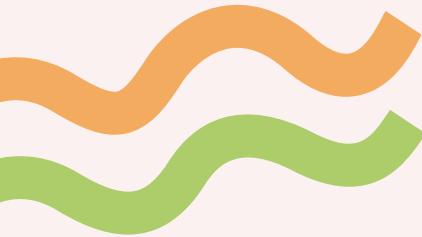
A : Matriks ketetanggaan ($n \times n$)

α : koefisien pertumbuhan

ρ : koefisien penyebaran

n : jumlah node





Persamaan Reaksi-Difusi Konsentrasi Protein (nondimensional)



$$\frac{dC_i}{d\tau} = -k \sum_{j=1}^n (A_{ij}C_i - A_{ij}C_j) + C_i(1 - C_i)$$

Keterangan

C_i : Konsentrasi di titik ke-i, [0,1]

A : Matriks ketetanggaan ($n \times n$)

α : koefisien pertumbuhan

ρ : koefisien penyebaran

k : ρ/α

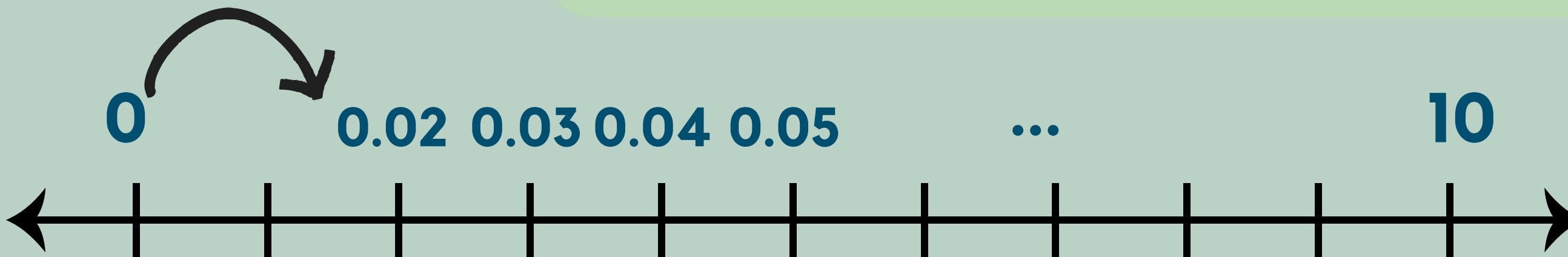
n : jumlah node

Mencari nilai parameter terbaik (α and ρ)

Beberapa penelitian menemukan nilai α dan ρ berkisar antara
 $\text{range}(\alpha) = 0.01-0.1$
 $\text{range}(\rho) = 0.001-0.1$

Dengan menggunakan parameter
 $k = \rho / \alpha$, maka rentang nilai k
akan berkisar antara
 $\text{range}(k) = 0.01-10$

$$\Delta = 0.01$$



Diskritisasi untuk mencoba berbagai nilai k

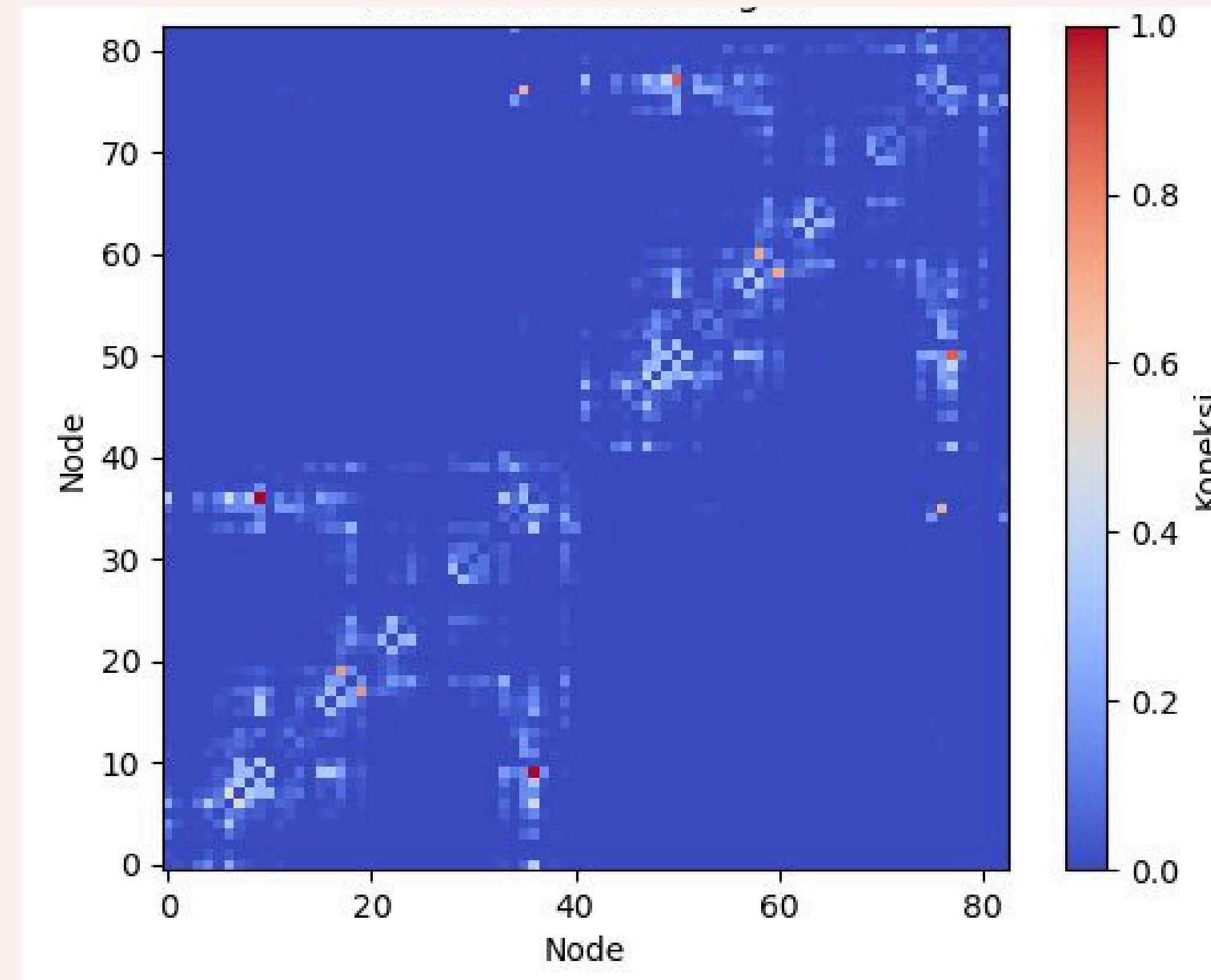




4 Hasil dan Pembahasan

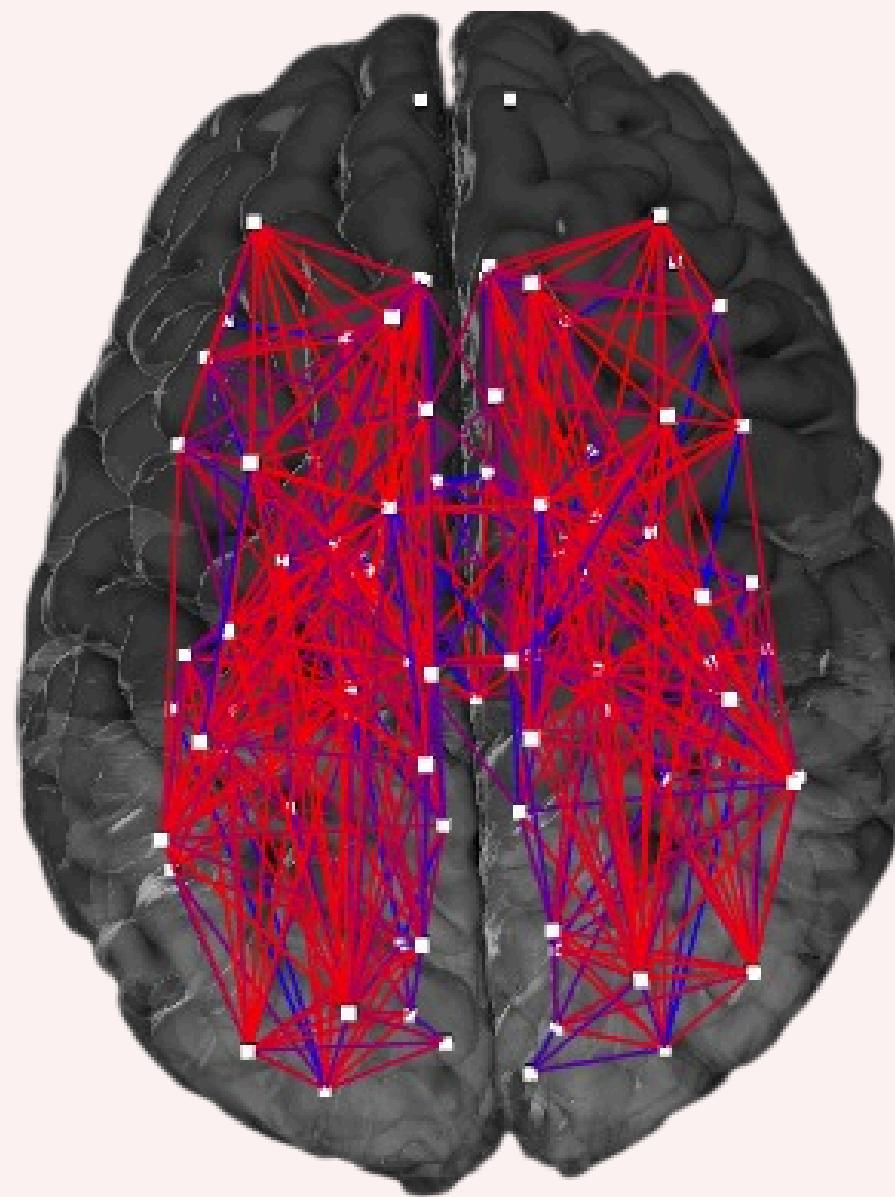


MATRIKS KETERHUBUNGAN

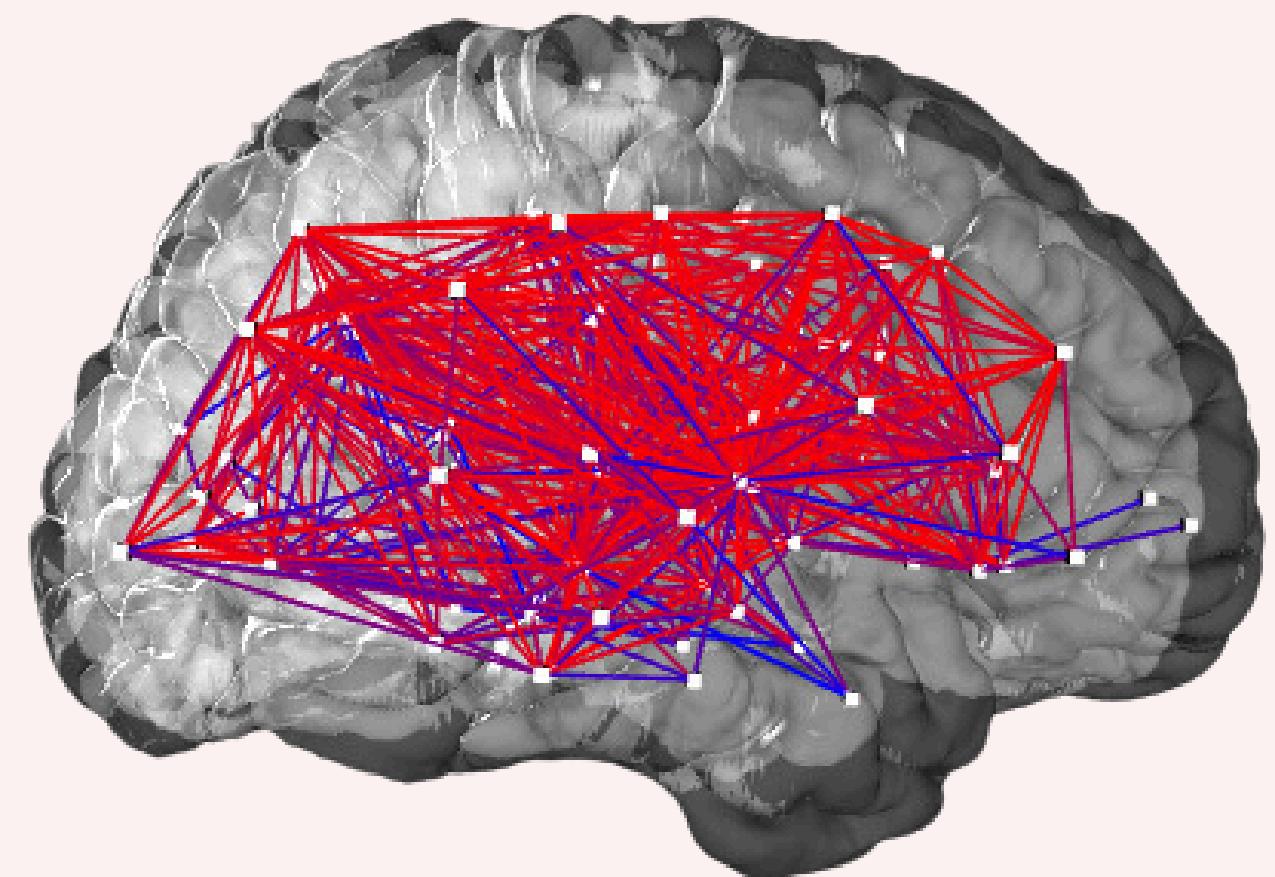


Model Graf Otak

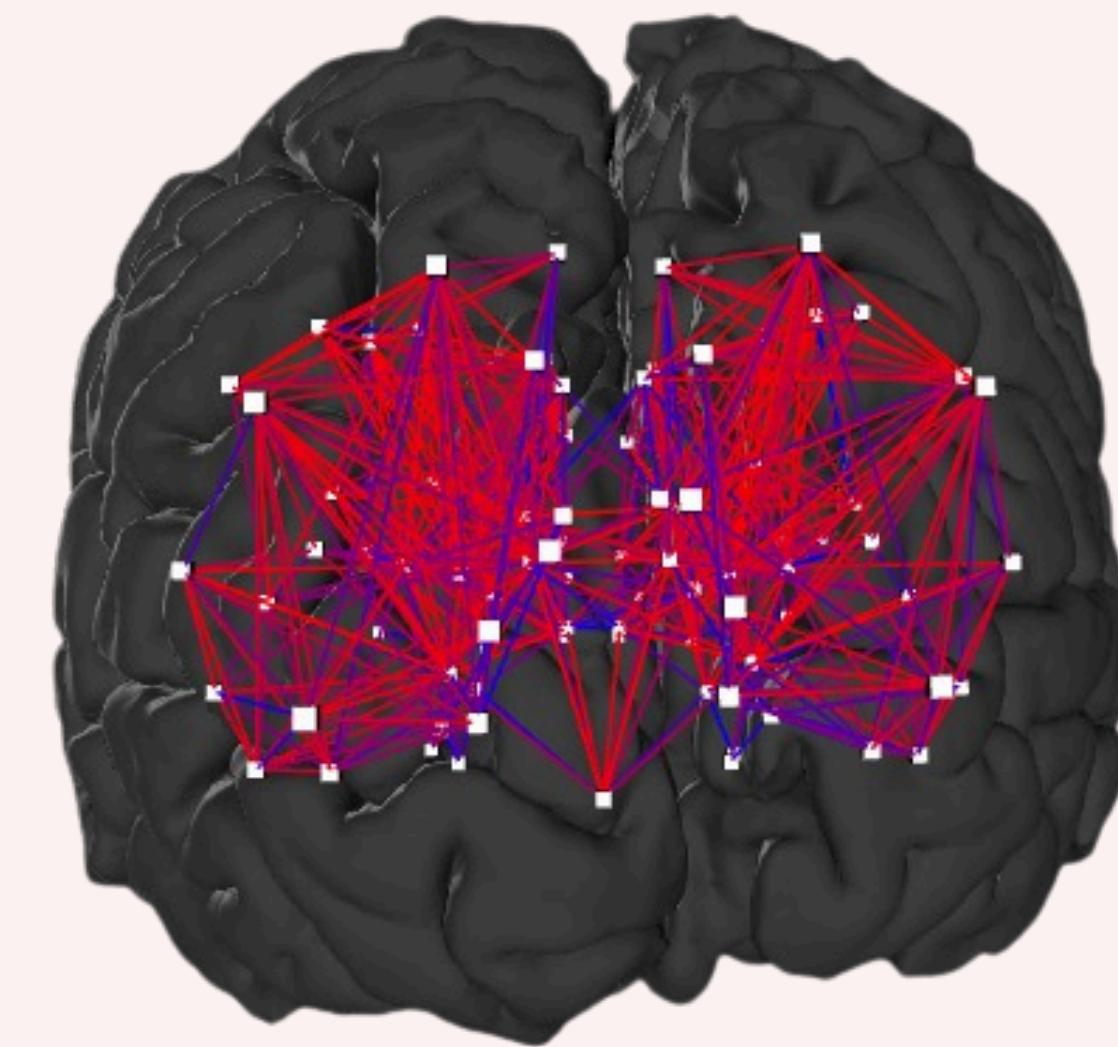
weighted graph



horizontal

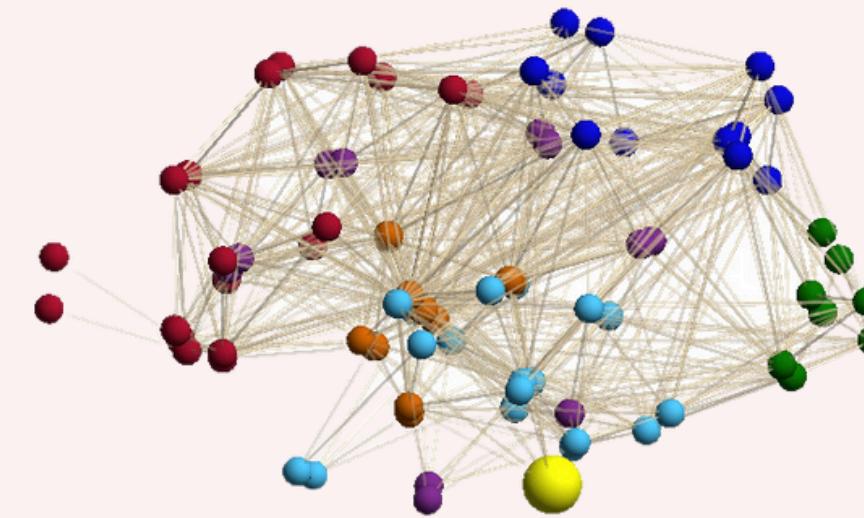


saggital

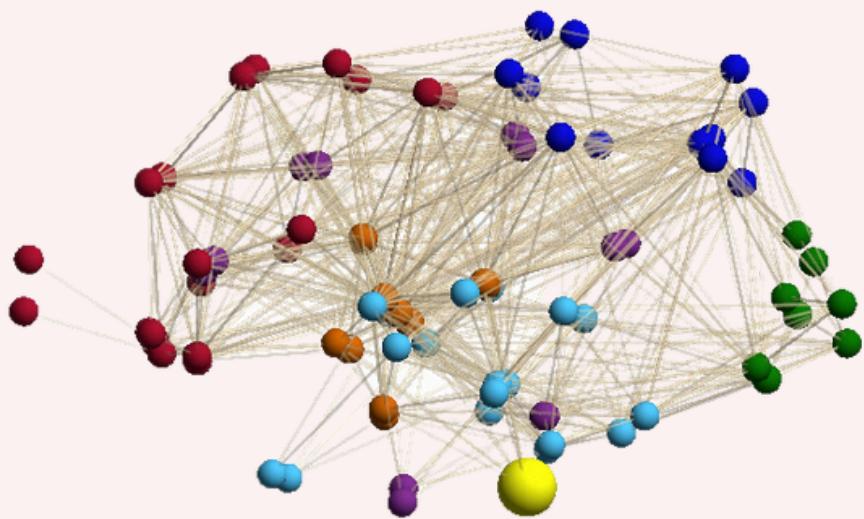
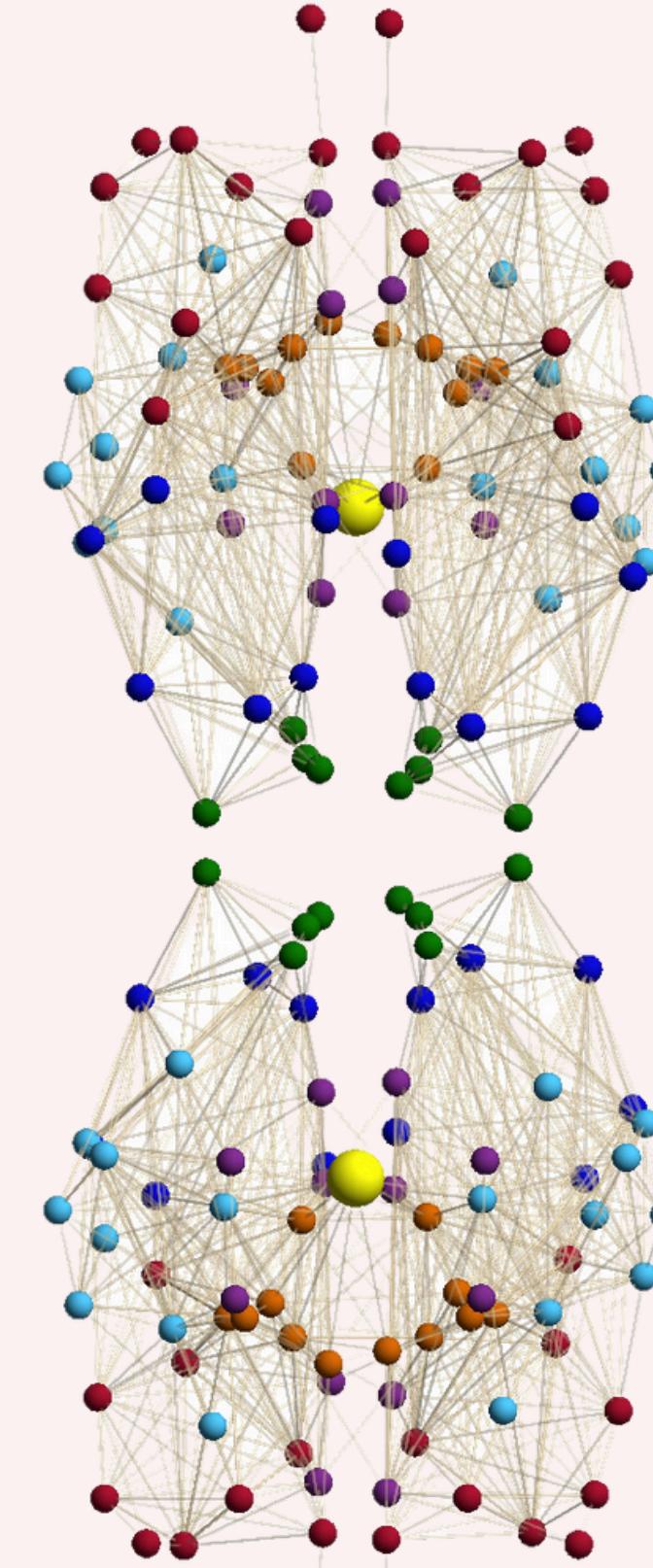
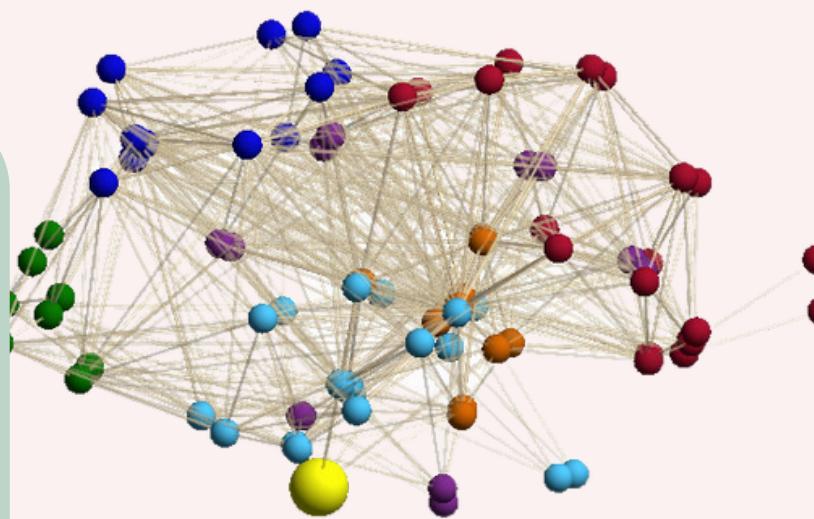
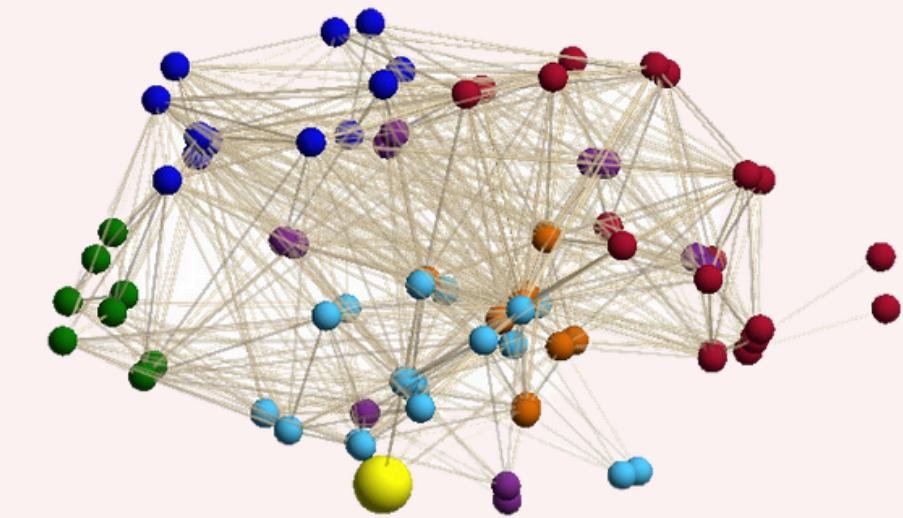


coronal

L

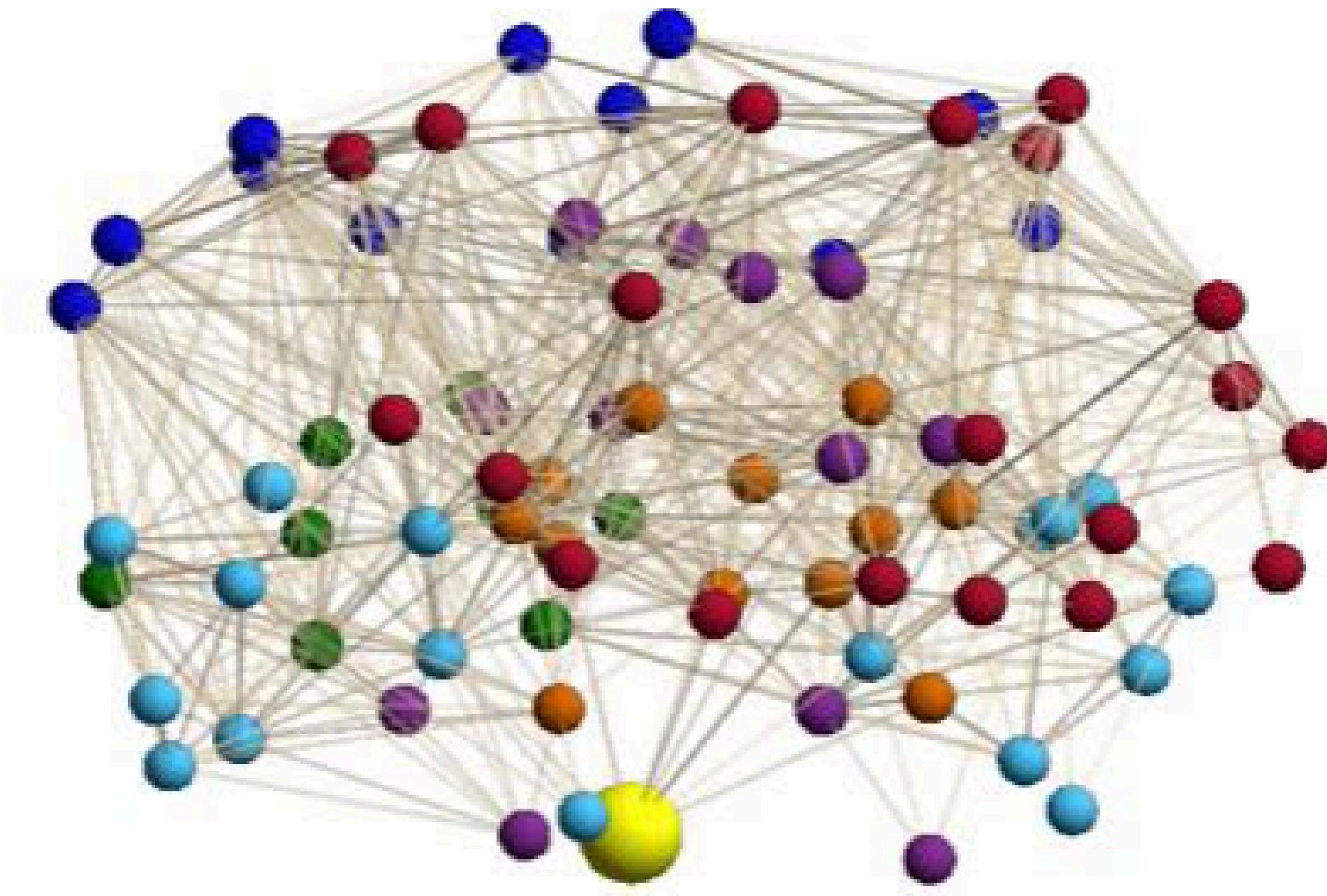


R

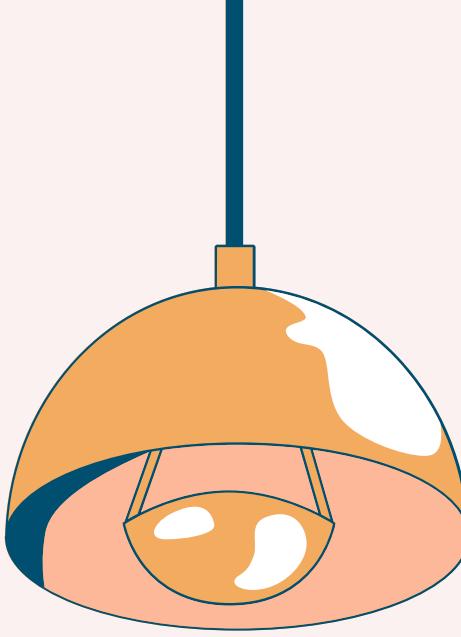


Model Graf Otak

Visualisasi Graf Otak

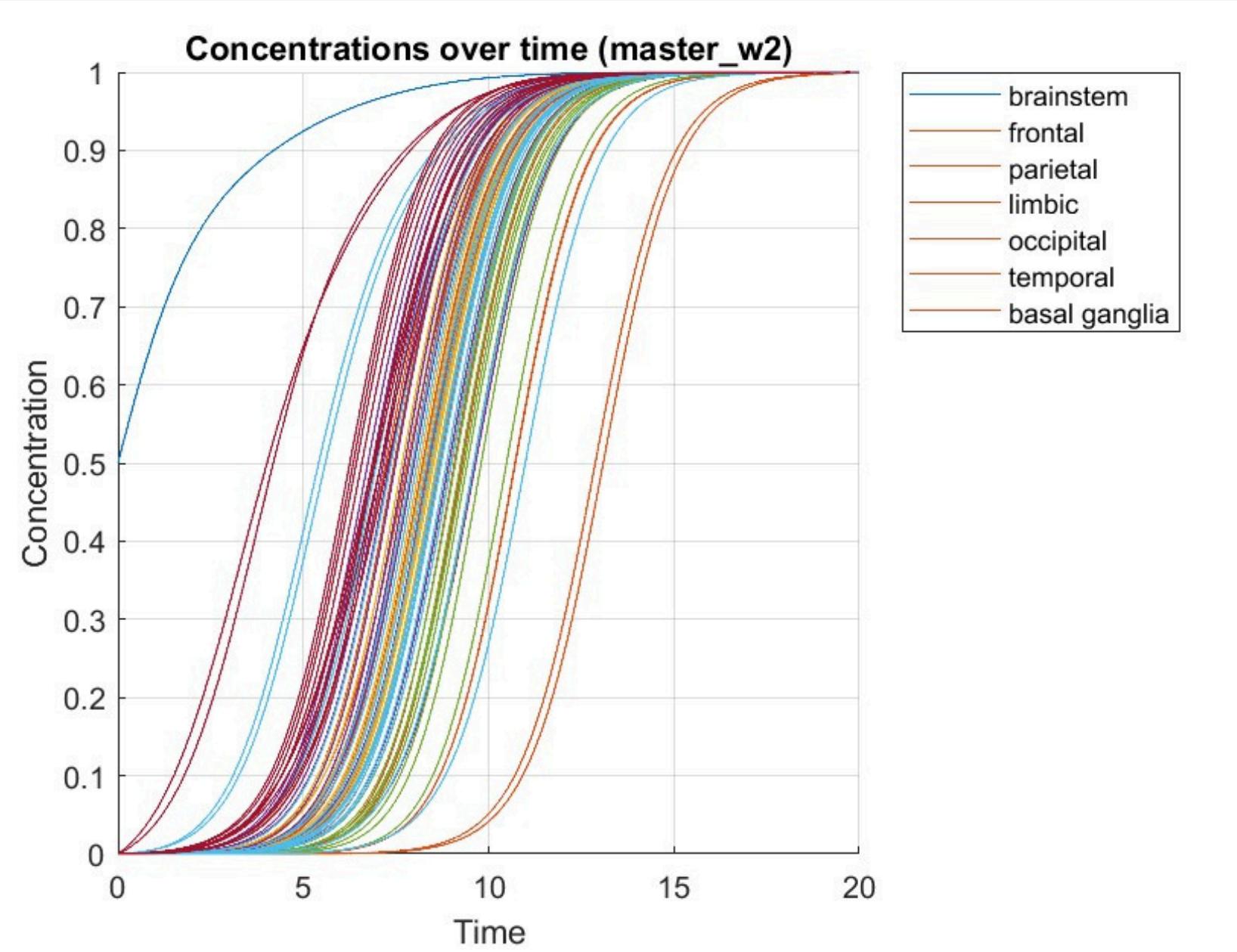


- Frontal
- Parietal
- Occipital
- Temporal
- Basal Ganglia
- Limbic
- Brainstem

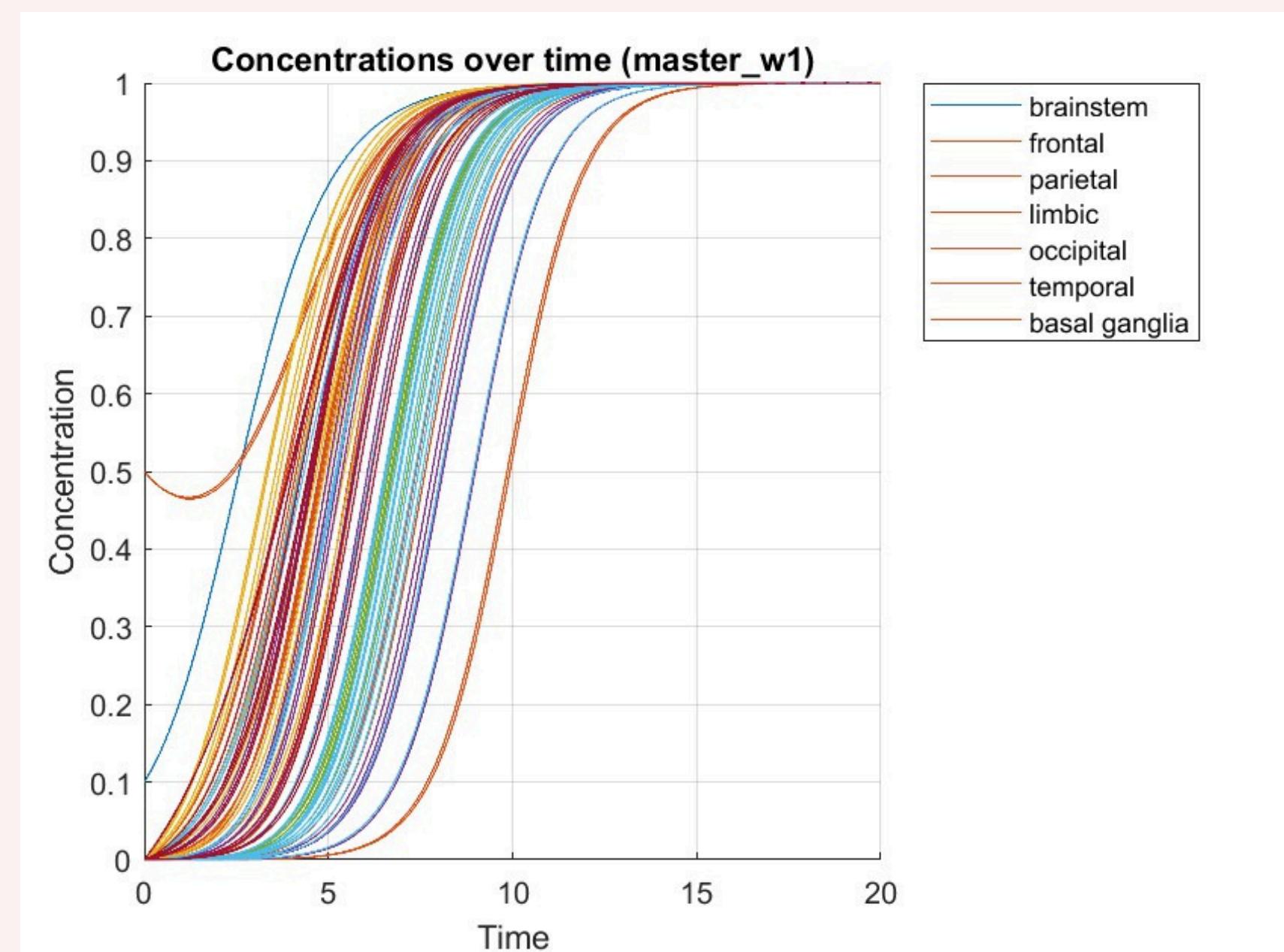


Contoh : Hasil Simulasi

Parkinson

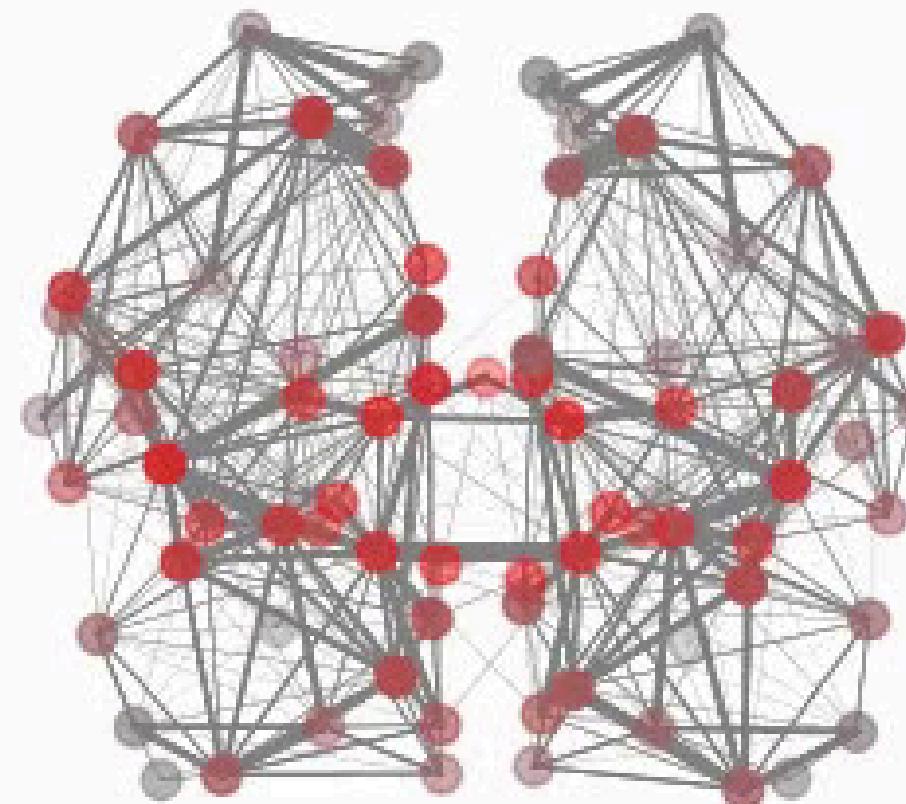


ALS

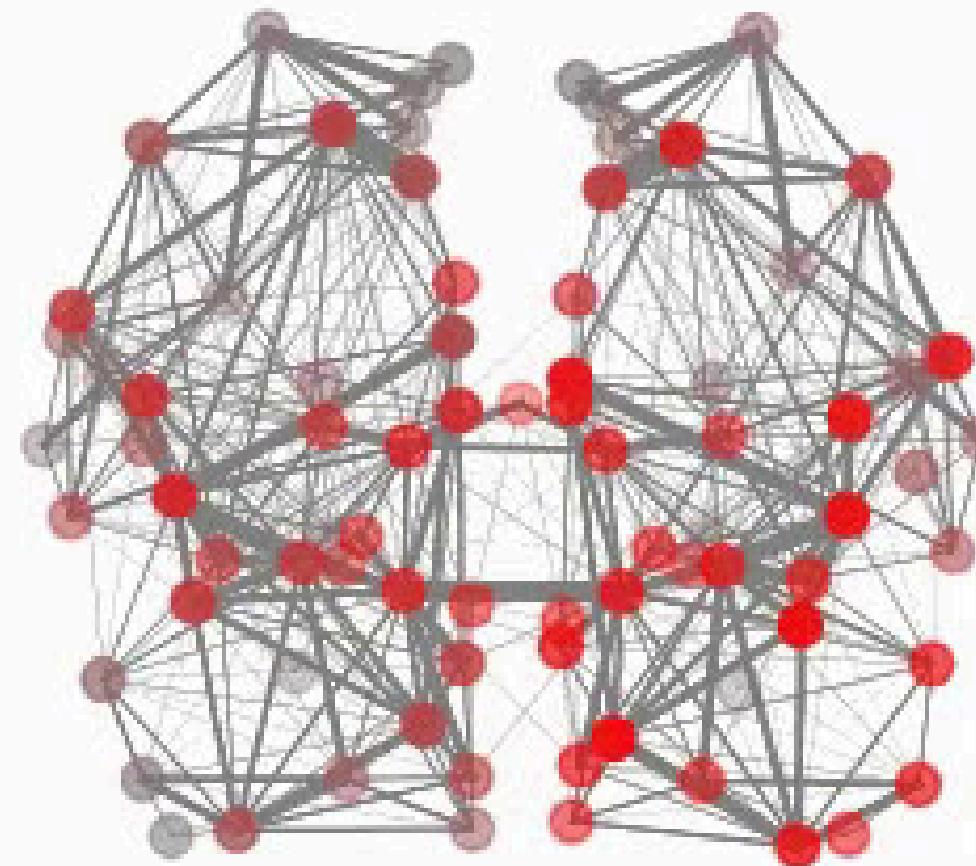


Visualisasi Penyebaran

Parkinson

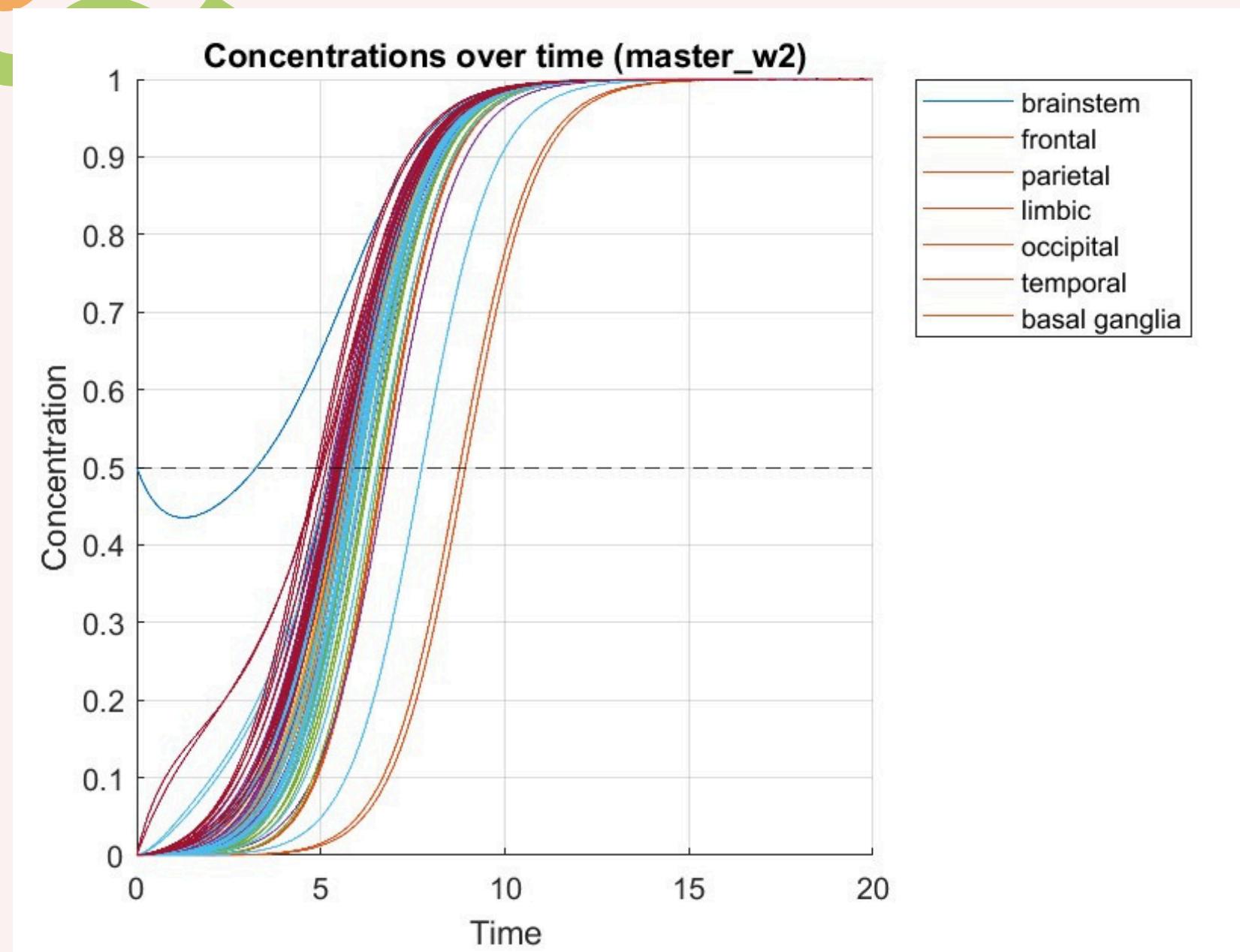


ALS



Menentukan Rank

Parkinson k=1.2



83: 0.001	Brainstem
80: 4.886	Basal Ganglia
39: 4.965	Basal Ganglia
76: 4.987	Basal Ganglia
35: 5.037	Basal Ganglia
79: 5.151	Basal Ganglia
56: 5.246	Limbic
81: 5.278	Temporal
38: 5.302	Basal Ganglia
55: 5.350	Limbic
82: 5.393	Basal Ganglia
15: 5.396	Limbic
40: 5.417	Temporal

Ranked parts based on time
brainstem: 0.001
basal ganglia: 4.886
limbic: 5.246
temporal: 5.278
frontal: 5.479
parietal: 5.488
occipital: 6.052

Rank: [1; 2; 4; 3; 4; 5; 5]

Ket: 1:Brainstem
2:Basal ganglia

3:Temporal
4: Frontal & Limbic

5: Parietal & Occipital

Rentang kesesuaian Parkinson

Rank literatur: 1 - 2 - 3 - 4 - 5

Rank simulasi:

■ : 1 - 2 - 3 - 4 - 5

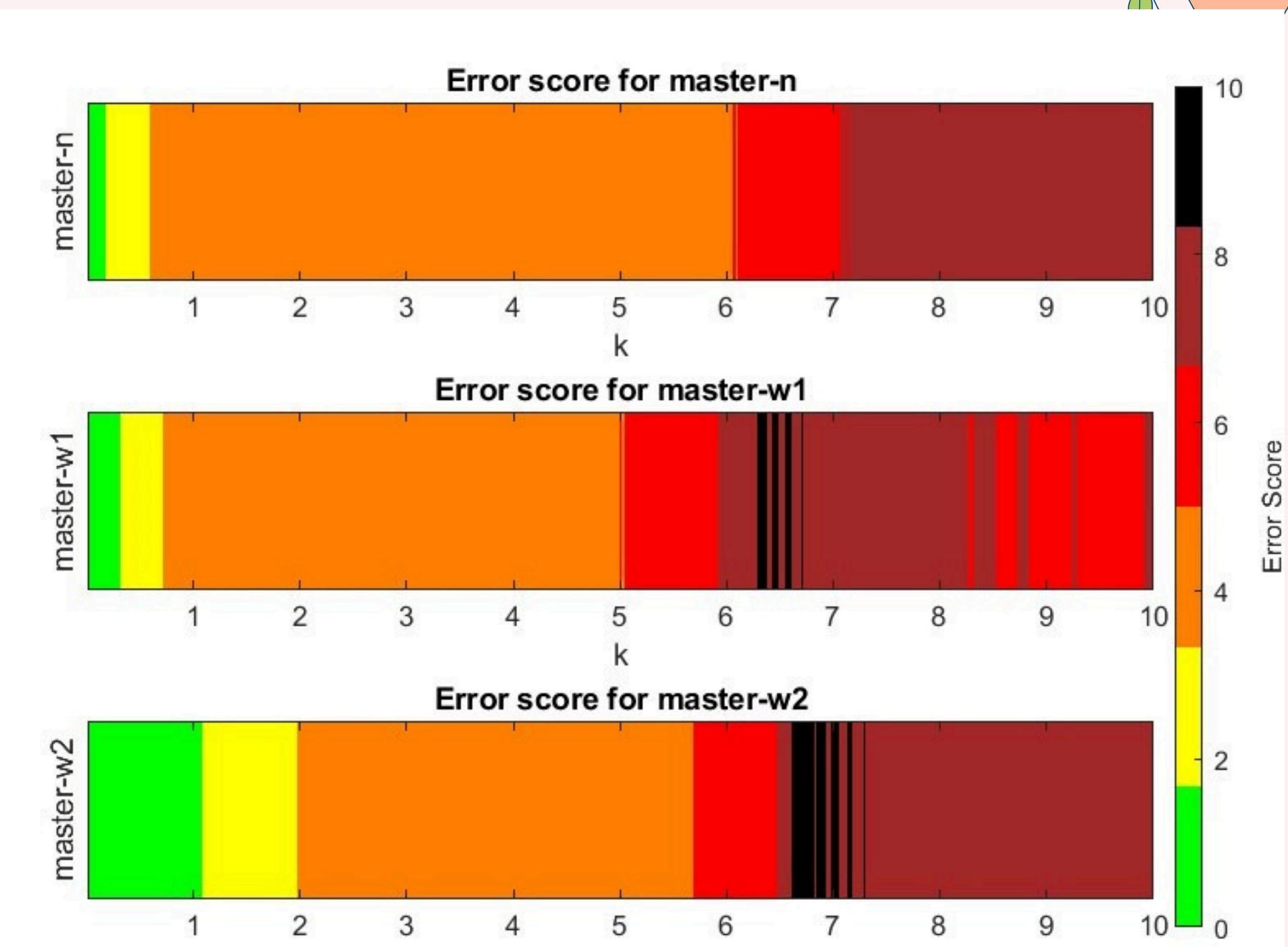
■ : 1 - 2 - 3 - 5 - 4

■ : 1 - 2 - 5 - 3 - 4

■ : 1 - 5 - 2 - 3 - 4

■ : 1 - 5 - 4 - 3 - 2

■ : 1 - 5 - 4 - 2 - 3



Ket: 1:Brainstem
2:Basal ganglia

3:Temporal
4:Frontal atau Limbic

5: Parietal atau Occipital

Rentang kesesuaian ALS

Rank literatur: 1 - 2 - 3 - 4

Rank simulasi:

■ : 1 - 2 - 3 - 4

■ : 1 - 2 - 4 - 3

■ : 1 - 4 - 2 - 3

■ : 1 - 4 - 2 - 3



Ket: 1: Frontal
2: Brainstem

3: Parietal
4: Basal ganglia



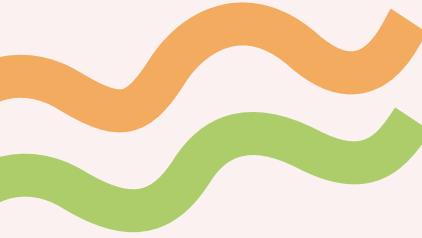
5 Kesimpulan

Kesimpulan

Model matematika reaksi-difusi yang digunakan cukup untuk mereplikasi pola penyebaran ALS dan Parkinson

Pada Parkinson, master w2 memberikan hasil simulasi terbaik karena memiliki rentang kesesuaian yang paling besar

Pada ALS, master n memberikan hasil simulasi terbaik karena memiliki rentang kesesuaian yang paling besar



Daftar Pustaka

Balázs Szalkai, Csaba Kerepesi, Bálint Varga, Vince Grolmusz, The Budapest Reference Connectome Server v2.0, Neuroscience Letters, Vol. 595 (2015), Pages 60-62, <http://dx.doi.org/10.1016/j.neulet.2015.03.071>. arth: Leipzig).

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Brodmann, K. (1909). Vergleichende lokalisationslehre der grobhirnrinde (Barth: Leipzig).

Smith, L. M., Schiess, M. C., Coffey, M. P., Klaver, A. C., & Loeffler, D. A. (2012). A-synuclein and anti-a-synuclein antibodies in Parkinson's disease, atypical Parkinson syndromes, REM sleep behavior disorder, and healthy controls. *PloS One*, 7(12), e52285. <https://doi.org/10.1371/journal.pone.0052285>

Tian, C., Liu, G., Gao, L., Soltys, D., Pan, C., Stewart, T., Shi, M., Xie, Z., Liu, N., Feng, T., & Zhang, J. (2019). Erythrocytic a-Synuclein as a potential biomarker for Parkinson's disease. *Translational Neurodegeneration*, 8(1). <https://doi.org/10.1186/s40035-019-0155-y>

Weickenmeier, J., Jucker, M., Goriely, A., & Kuhl, E. (2019). A physics-based model explains the prion-like features of neurodegeneration in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. *Journal of the Mechanics and Physics of Solids*, 124, 264-281.

Xia M, Wang J, He Y (2013) BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. *PLoS ONE* 8: e68910

Szalkai, B., Kerepesi, C., Varga, B., & Grolmusz, V. (2017). Parameterizable consensus connectomes from the Human Connectome Project: the Budapest Reference Connectome Server v3.0. *Cognitive Neurodynamics*, 11(1), 113–116. <https://doi.org/10.1007/s11571-016-9407-z>





Thank You!

KALO RAME LANJUT KONFERENSI

