

Numerical modelling and simulation as a tool to study the Parkinsonian disease

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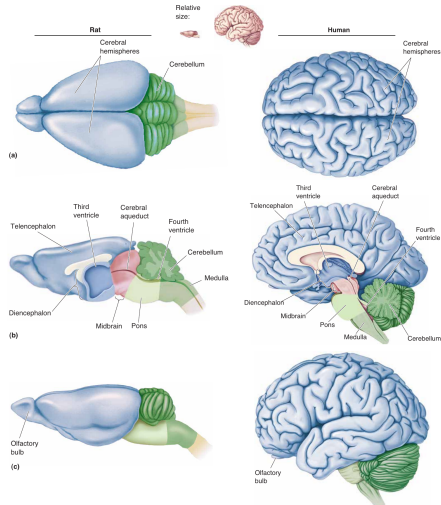


Parkinsonism, Models, Neurons and Brains

Parkinson disease

- ▶ $\sim 2\%$ of ≥ 60 years old
- ▶ Degeneration of dopaminergic and other structures
- ▶ Debilitating motor and psychological symptoms
- ▶ No cure
- ▶ Some treatments (Levodopa, deep brain stimulation) with heavy side effects

Animal models

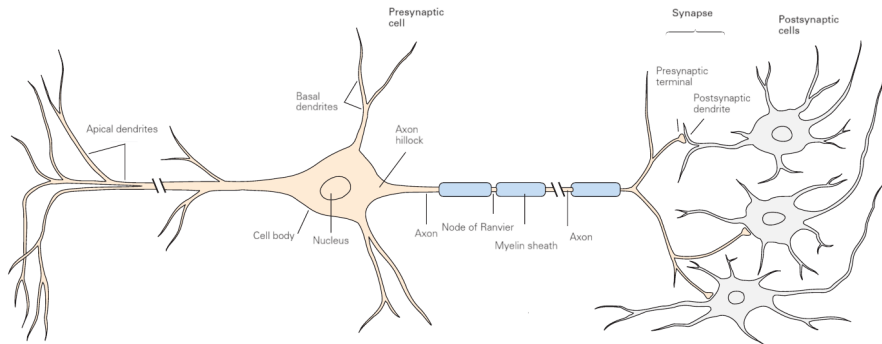


- ▶ Similarity with human depending on species
- ▶ Requires understanding of which aspects translate to human
- ▶ Ethical challenges
- ▶ Measurement challenges

Computational models

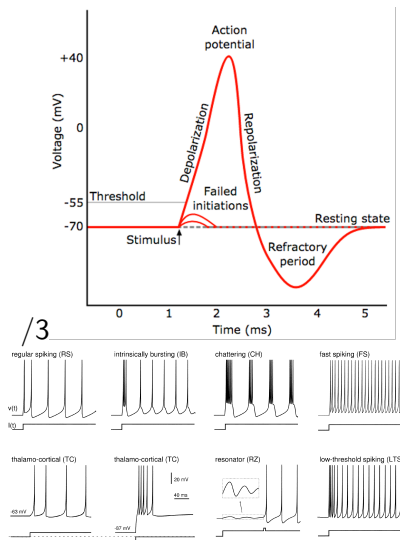
- ▶ Limited data
- ▶ Noisy data
- ▶ Computational complexity
- ▶ Need validation of predictions
- ▶ Guide experimental studies
- ▶ Individualized treatments!

Neurons and the brain



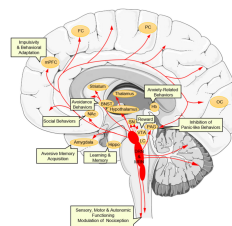
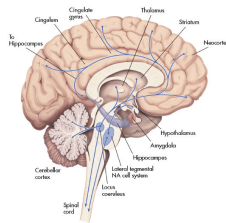
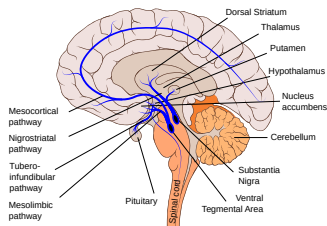
- ▶ 85 billions neurons
- ▶ 85 billions non-neuronal cells
- ▶ 100s of different neuron types
- ▶ 10 000 dendrites each
- ▶ 100 000 synapses each
- ▶ 100s of different synapse types

Electrical/chemical behaviour: bottom up approach



- Integrate and fire models
- Spiking neurons models
- Electrical, chemical, physical simulation
- Blue brain project (EPFL)

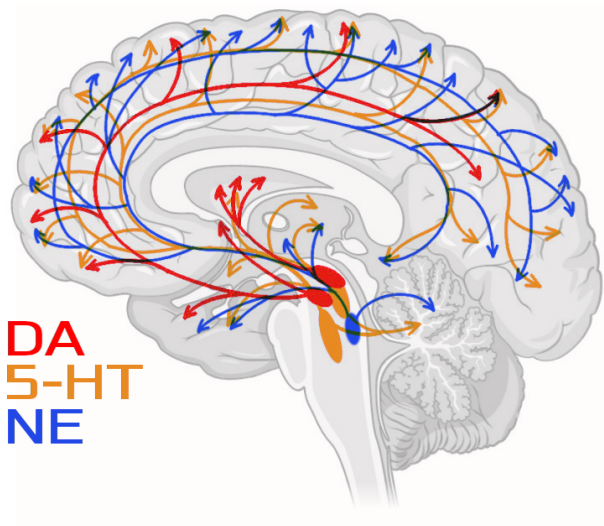
Brain areas behaviour: middle up approach



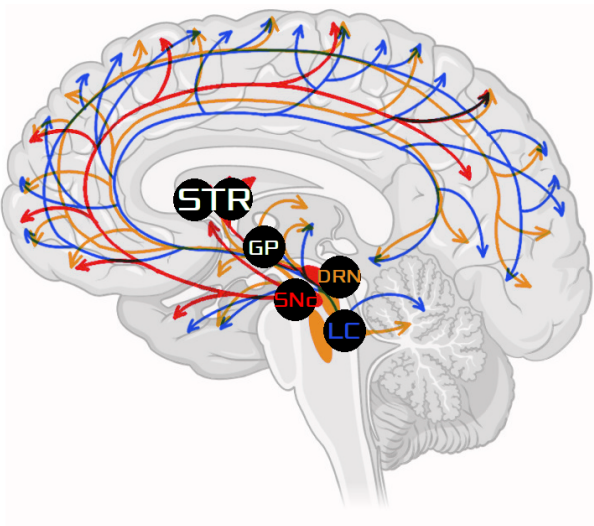
- ▶ Distinct areas: similar neurons and pathways
- ▶ Area circuits defined by projections strength and effect

Numerical model of a basal ganglia circuit to study monoamines equilibrium in induced parkinsonism

Background



Background

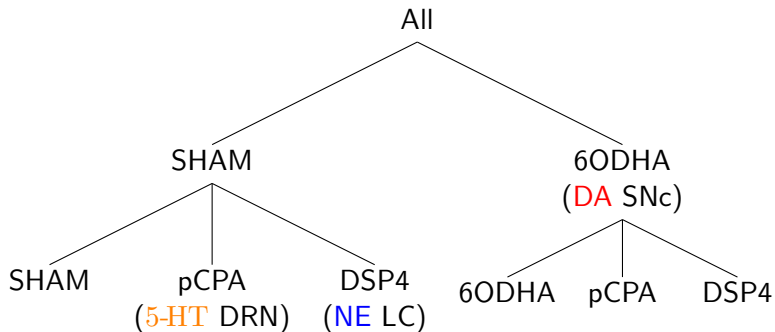


Methodology

- ▶ Understand and aggregate data
- ▶ Generate synthetic targets
- ▶ Model study loop:
 - ▶ Formulate model hypothesis
 - ▶ Optimize model
 - ▶ Validate model
- ▶ Predictions

Available data

- ▶ Average activation values of some areas in different conditions
 - ▶ GP and lesions from common study
 - ▶ Other areas from aggregated data

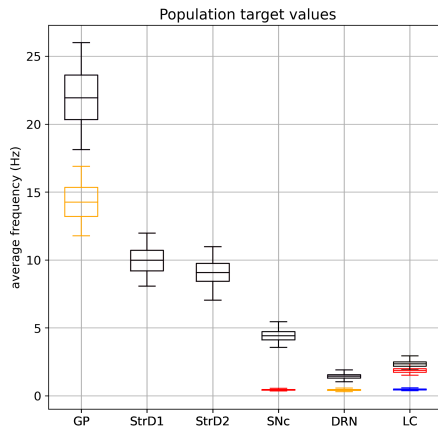
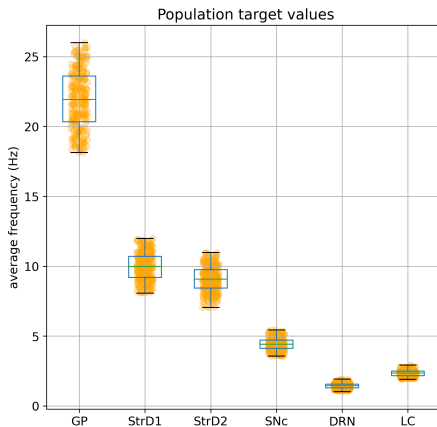


Generated data

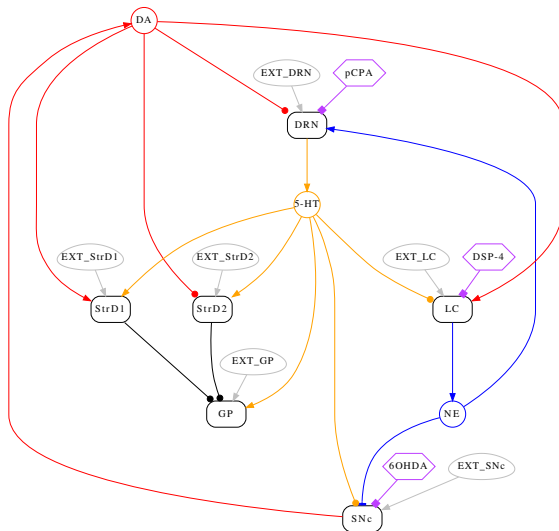
SNC: DA (6OHDA)

DRN: 5-HT(pCPA)

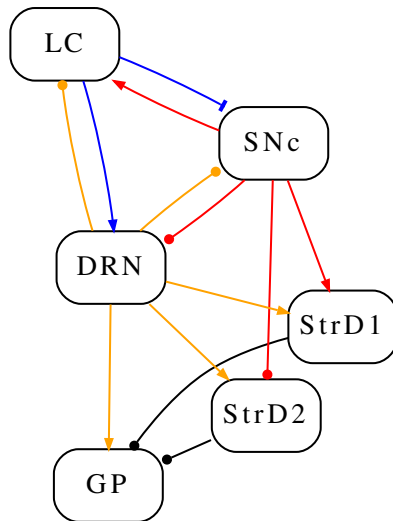
LC: NE (DSP4)



Model schema



Simplified Model schema



Model equations

$$\dot{GP} = -\frac{1}{\tau_{GP}}GP - \alpha_{GP}^{StrD1}StrD1 - \alpha_{GP}^{StrD2}StrD2 + \alpha_{GP}^{DRN}DRN + \alpha_{GP}^{ext}$$

$$\dot{StrD1} = -\frac{1}{\tau_{StrD1}}StrD1 + \alpha_{StrD1}^{SNc}SNc + \alpha_{StrD1}^{DRN}DRN + \alpha_{StrD1}^{ext}$$

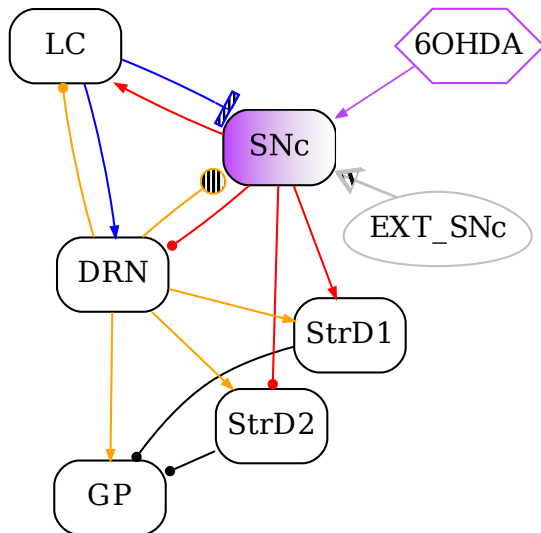
$$\dot{StrD2} = -\frac{1}{\tau_{StrD2}}StrD2 - \alpha_{StrD2}^{SNc}SNc + \alpha_{StrD2}^{DRN}DRN + \alpha_{StrD2}^{ext}$$

$$\dot{SNc} = -\frac{1}{\tau_{SNc}}SNc - \alpha_{SNc}^{DRN}DRN - \alpha_{SNc}^{LC}LC + \beta_{SNc}^{LC}LC^2 + \alpha_{SNc}^{ext}$$

$$\dot{DRN} = -\frac{1}{\tau_{DRN}}DRN - \alpha_{DRN}^{SNc}SNc + \alpha_{DRN}^{LC}LC + \alpha_{DRN}^{ext}$$

$$\dot{LC} = -\frac{1}{\tau_{LC}}LC + \alpha_{LC}^{SNc}SNc - \alpha_{LC}^{DRN}DRN + \alpha_{LC}^{ext}$$

Modelling lesions (schema)



Modelling lesions (equations)

$$\dot{GP} = -\frac{1}{\tau_{GP}}GP - \alpha_{GP}^{StrD1}StrD1 - \alpha_{GP}^{StrD2}StrD2 + \alpha_{GP}^{DRN}DRN + \alpha_{GP}^{ext}$$

$$\dot{StrD1} = -\frac{1}{\tau_{StrD1}}StrD1 + \alpha_{StrD1}^{SNc}SNc + \alpha_{StrD1}^{DRN}DRN + \alpha_{StrD1}^{ext}$$

$$\dot{StrD2} = -\frac{1}{\tau_{StrD2}}StrD2 - \alpha_{StrD2}^{SNc}SNc + \alpha_{StrD2}^{DRN}DRN + \alpha_{StrD2}^{ext}$$

$$\dot{SNc} = -\frac{1}{\tau_{SNc}}SNc - \alpha_{SNc}^{DRN}DRN - \alpha_{SNc}^{LC}LC + \beta_{SNc}^{LC}LC^2 + \alpha_{SNc}^{ext}$$

$$\dot{DRN} = -\frac{1}{\tau_{DRN}}DRN - \alpha_{DRN}^{SNc}SNc + \alpha_{DRN}^{LC}LC + \alpha_{DRN}^{ext}$$

$$\dot{LC} = -\frac{1}{\tau_{LC}}LC + \alpha_{LC}^{SNc}SNc - \alpha_{LC}^{DRN}DRN + \alpha_{LC}^{ext}$$

Matrix representation and subjects

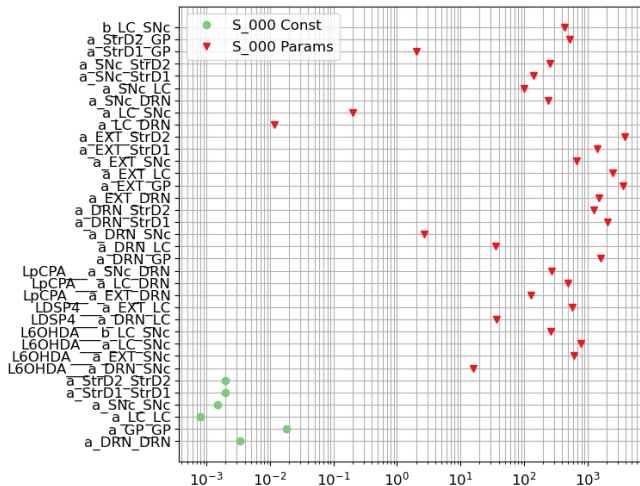
$$\dot{\mathbf{y}}(t) = A\mathbf{y}(t) + C(\mathbf{y}(t) \circ \mathbf{y}(t)) + \mathbf{b}$$

$$S_i = \{(A, C, \mathbf{b}), (\textcolor{red}{A}, \textcolor{red}{C}, \textcolor{red}{\mathbf{b}}), (\textcolor{brown}{A}, \textcolor{brown}{C}, \textcolor{brown}{\mathbf{b}}), (\textcolor{blue}{A}, \textcolor{blue}{C}, \textcolor{blue}{\mathbf{b}}), \dots\} =$$

$$\{S_i^{SHAM}, S_i^{\textcolor{red}{6OHDA}}, S_i^{\textcolor{brown}{pCPA}}, S_i^{\textcolor{blue}{DSP4}}, \dots\}$$

Free parameters

30 free parameters (20 + 4 + 3 + 3) + 6 constants



Stability conditions

$$\dot{\mathbf{y}}(t) = A\mathbf{y}(t) + C(\mathbf{y}(t) \circ \mathbf{y}(t)) + \mathbf{b}$$

When linearized in first approximation:

$$\dot{\mathbf{y}}(t) = \tilde{A}\mathbf{y}(t) + g(\mathbf{y}(t))$$

can be proved *exponentially asymptotically stable* if:

$$\sigma(\tilde{A}) \subset \mathbb{C}^-$$

- ▶ \tilde{A} depends on $\bar{\mathbf{y}}$
- ▶ Must be approximated

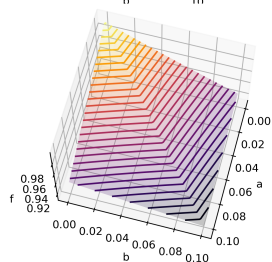
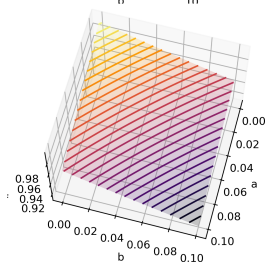
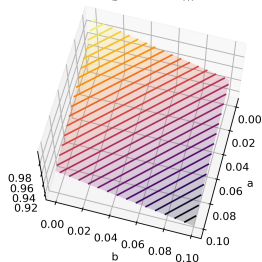
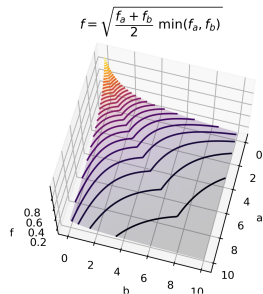
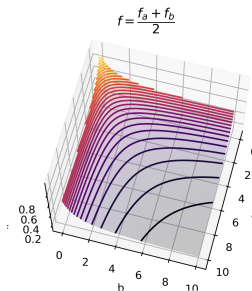
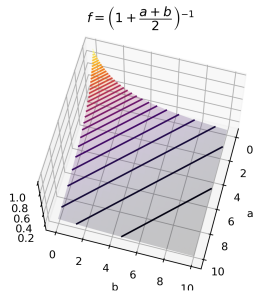
Fitness Measures

Fitness measure

Single figure of merit, normalized to $[0, 1]$.

- ▶ Distance (MSE)
- ▶ Barrier / limit
- ▶ Simulation end time
- ▶ Stability
- ▶ Parameter constraints

Combining fitness measures



Simulation time

Basic area behaviour:

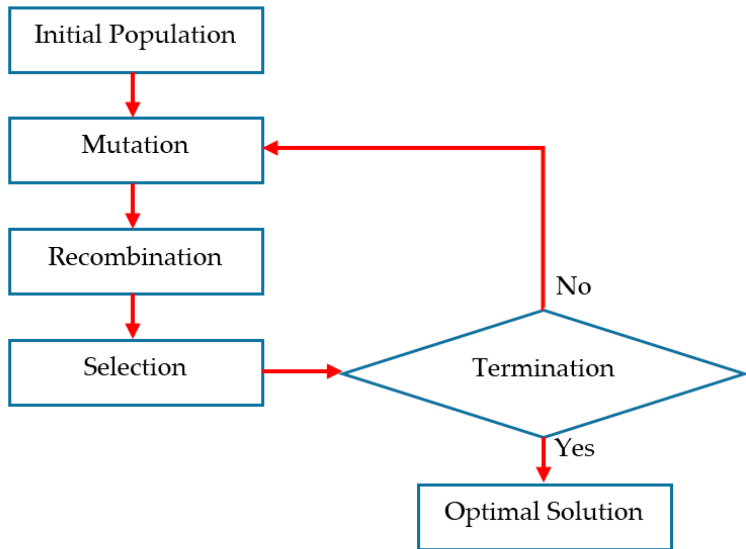
$$y'(t) = -\frac{1}{\tau}y(t) + k$$

$$\longrightarrow y(t) = -k\tau e^{-\frac{t}{\tau}} + k\tau$$

$$0.99k\tau = -k\tau e^{-\frac{t}{\tau}} + k\tau \implies t = \log(0.01)\tau \approx 5\tau$$

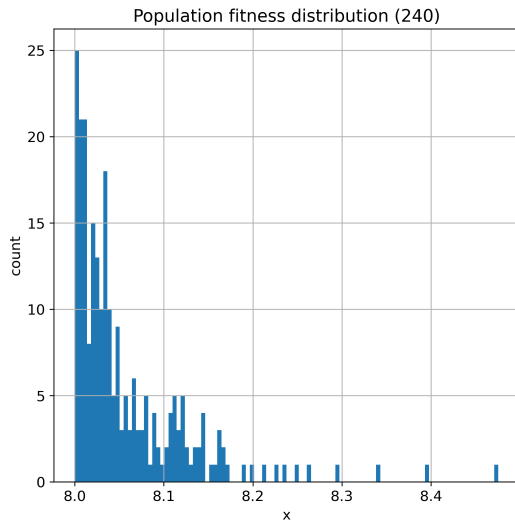
$$\max(\tau) \leq 20\text{ms} \implies 0.1\text{s simulation}$$

Optimization algorithm: Differential Evolution



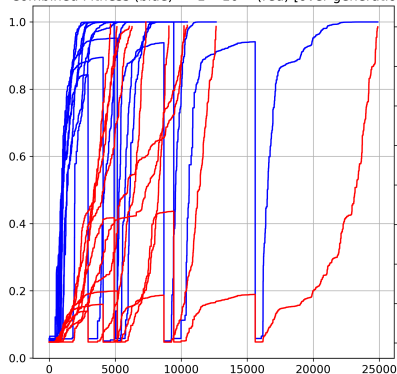
Results and predictions

Population fitness distribution



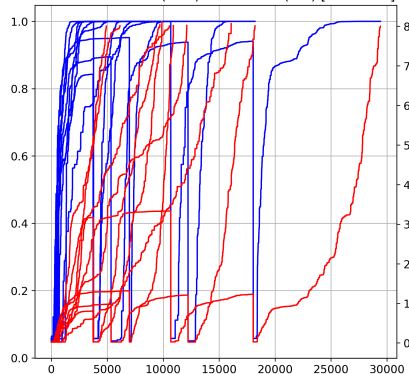
Optimization performance

Combined Fitness (blue) = $1 - 10^{-y}$ (red) [over generations]



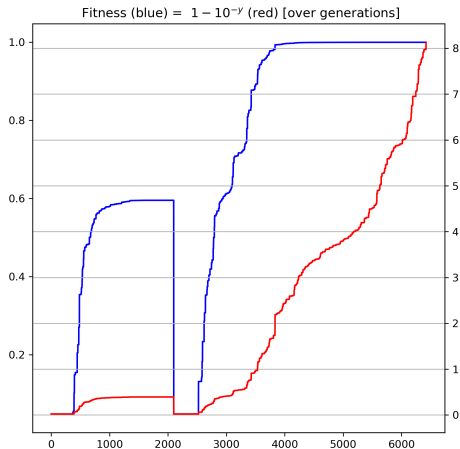
- $\sim 15K$ generations average
- 90 competitors
- 240 subjects

Combined Fitness (blue) = $1 - 10^{-y}$ (red) [over time]

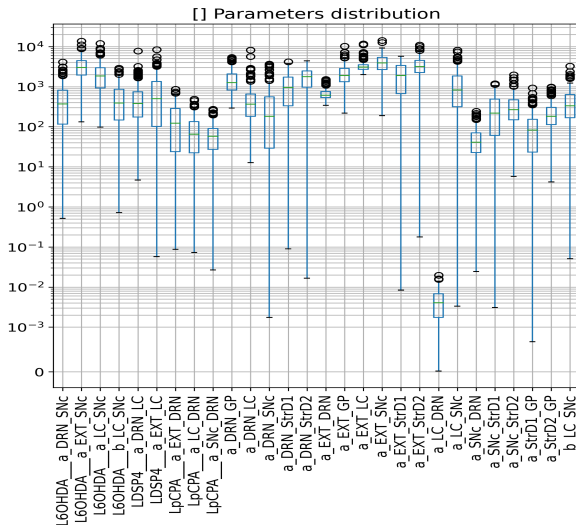


- ~ 2 hours per subject (6h arithmetic avg.)
- 16 4Ghz cores (32 threads)
- ~ 15 days

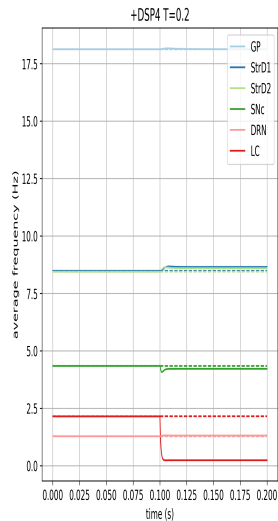
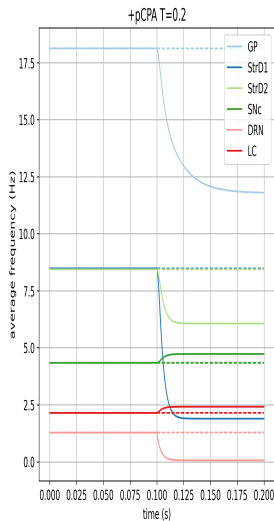
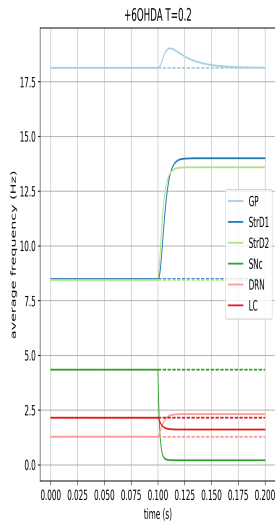
Outer optimization cycles: numerical anomaly?



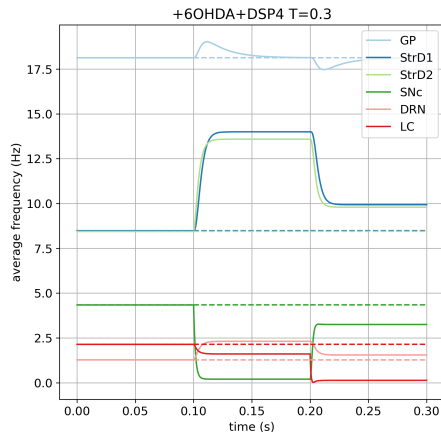
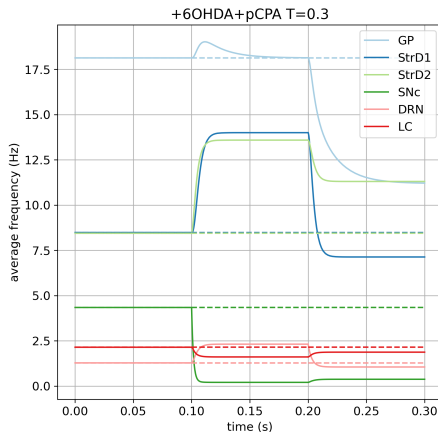
Parameters space distribution



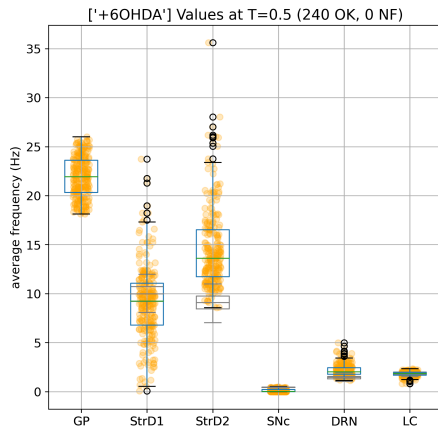
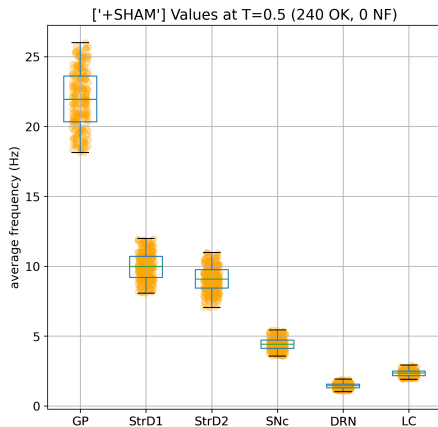
Solutions dynamic behaviour example 1



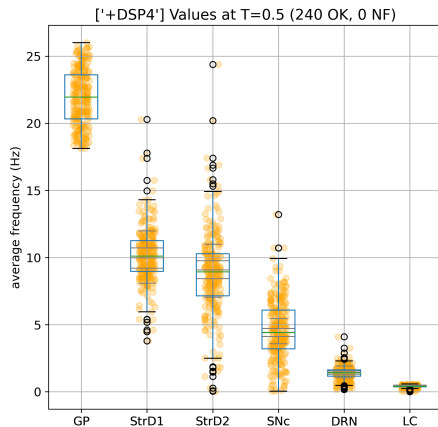
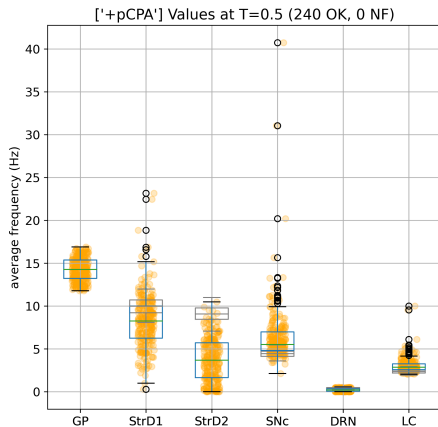
Solutions dynamic behaviour example 2



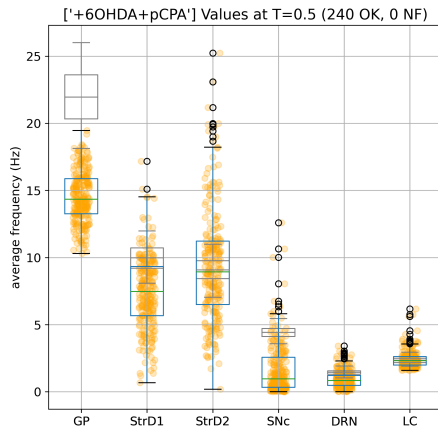
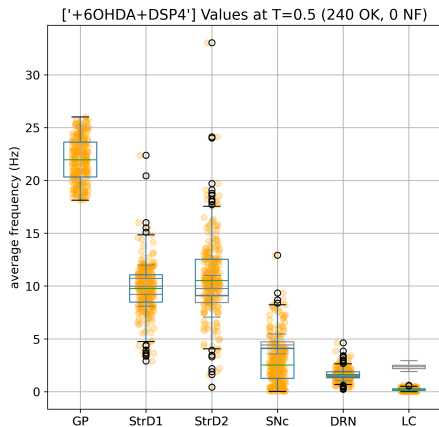
Fitted data and predictions by lesion 1



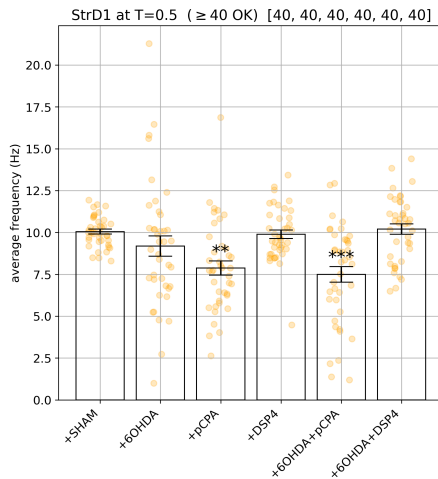
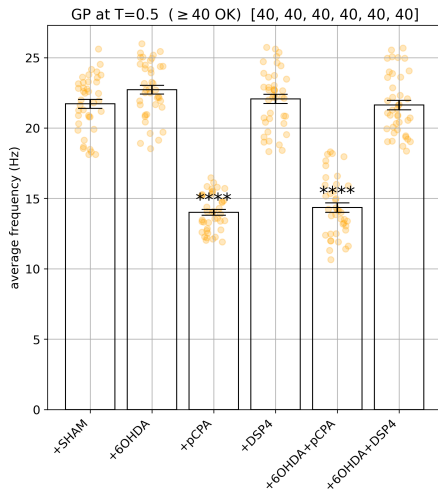
Fitted data and predictions by lesion 2



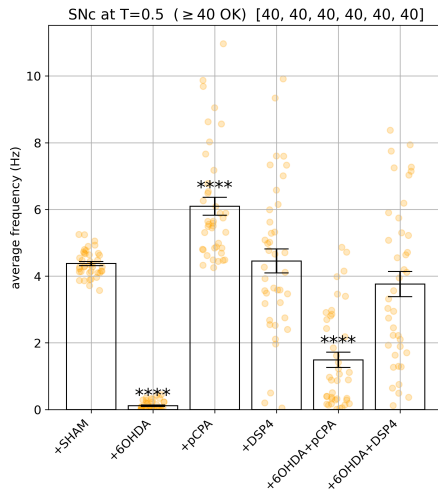
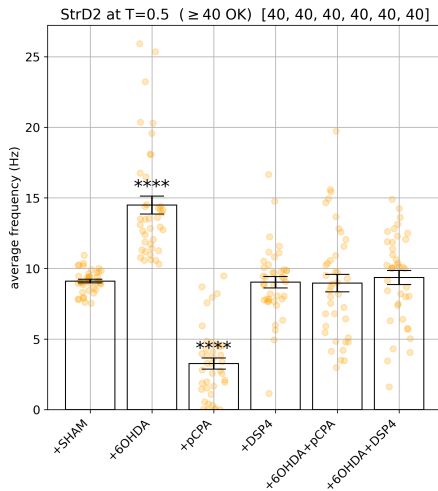
Fitted data and predictions by lesion 3



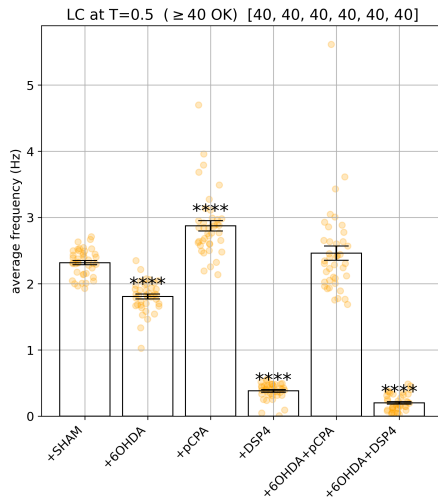
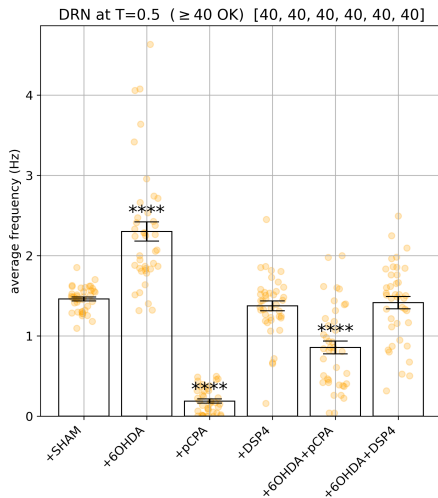
Fitted data and predictions by area 1



Fitted data and predictions by area 2



Fitted data and predictions by area 3



Parameter sensitivity analysis results

SHAM

a_DRN_GP	0.47	0.088	0.088	0.086	0.11	0.081
a_DRN_LC	0.037	0.042	0.046	0.072	0.05	0.067
a_DRN_SNC	0.023	0.027	0.031	0.04	0.034	0.024
a_DRN_StrD1	0.15	0.12	0.076	0.075	0.093	0.07
a_DRN_StrD2	0.46	0.12	0.25	0.12	0.15	0.11
a_EXT_DRN	0.46	0.43	0.74	0.55	1	0.4
a_EXT_GP	0.53	0.1	0.1	0.099	0.12	0.092
a_EXT_LC	0.17	0.29	0.43	0.79	0.39	0.72
a_EXT_SNC	0.12	0.27	0.45	0.66	0.41	0.2
a_EXT_StrD1	0.19	0.16	0.087	0.085	0.11	0.079
a_EXT_StrD2	0.49	0.12	0.33	0.12	0.15	0.11
a_LC_DRN	0.079	0.084	0.083	0.082	0.1	0.076
a_LC_SNC	0.049	0.083	0.14	0.21	0.13	0.067
a_SNC_DRN	0.1	0.1	0.14	0.093	0.19	0.081
a_SNC_LC	0.28	0.32	0.36	0.41	0.41	0.32
a_SNC_StrD1	0.08	0.08	0.055	0.054	0.067	0.05
a_SNC_StrD2	0.14	0.069	0.11	0.067	0.084	0.063
a_StrD1_GP	0.2	0.056	0.056	0.055	0.069	0.051
a_StrD2_GP	0.53	0.099	0.098	0.096	0.12	0.09
b_LC_SNC	0.073	0.12	0.19	0.29	0.18	0.093
	GP	StrD1	StrD2	SNC	DRN	LC

6OHDA

a_DRN_GP	0.038	0.02	0.015	0.29	0.015	0.0068
a_DRN_LC	0.0021	0.0084	0.0064	0.047	0.0065	0.0052
a_DRN_SNC	0.0024	0.0092	0.0076	0.054	0.0078	0.0036
a_DRN_StrD1	0.012	0.021	0.013	0.26	0.014	0.0061
a_DRN_StrD2	0.04	0.028	0.024	0.4	0.021	0.0096
a_EXT_DRN	0.028	0.044	0.04	0.29	0.054	0.027
a_EXT_GP	0.031	0.024	0.018	0.33	0.018	0.008
a_EXT_LC	0.0093	0.033	0.029	0.21	0.029	0.05
a_EXT_SNC	0.0067	0.022	0.021	0.089	0.021	0.011
a_EXT_StrD1	0.011	0.024	0.015	0.29	0.015	0.0069
a_EXT_StrD2	0.029	0.029	0.025	0.41	0.021	0.0097
a_LC_DRN	0.0046	0.02	0.015	0.28	0.015	0.0066
a_LC_SNC	0.0046	0.015	0.015	0.081	0.014	0.0081
a_SNC_DRN	0.0041	0.018	0.013	0.26	0.013	0.0059
a_SNC_LC	0.017	0.072	0.053	1	0.054	0.024
a_SNC_StrD1	0.0031	0.013	0.0098	0.18	0.0098	0.0044
a_SNC_StrD2	0.0038	0.016	0.012	0.23	0.012	0.0054
a_StrD1_GP	0.012	0.013	0.0097	0.19	0.01	0.0044
a_StrD2_GP	0.044	0.023	0.018	0.34	0.017	0.0079
b_LC_SNC	0.0032	0.012	0.01	0.087	0.0099	0.0054
	GP	StrD1	StrD2	SNC	DRN	LC

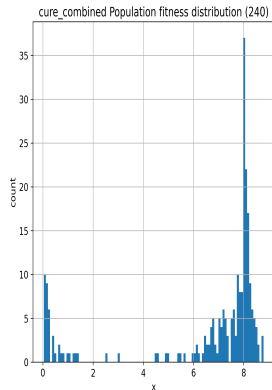
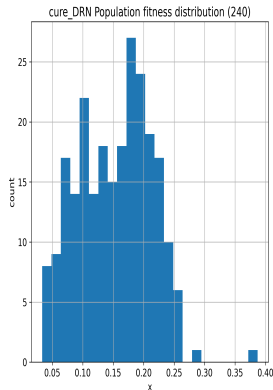
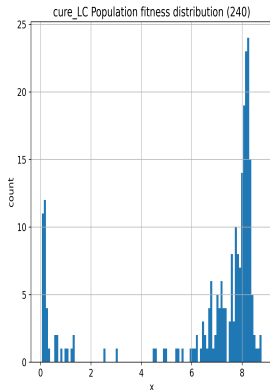
Treatment Hypothesis

$$S_i^{6OHDA} = \dot{\mathbf{y}}(t) = \mathbf{A}\mathbf{y}(t) + \mathbf{C}(\mathbf{y}(t) \circ \mathbf{y}(t)) + \mathbf{b}$$

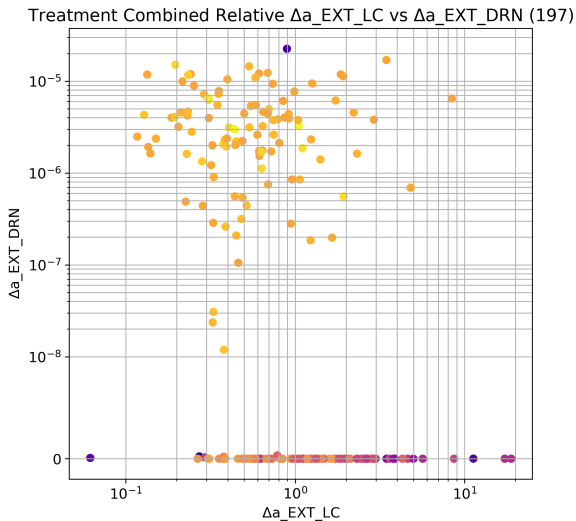
External stimulation of DRN or LC:

$$\begin{aligned} S_i^{6OHDA+cLC} &= (\mathbf{A}, \mathbf{C}, b_{cLC}) \\ S_i^{6OHDA+cDRN} &= (\mathbf{A}, \mathbf{C}, b_{cDRN}) \\ S_i^{6OHDA+cCOMB} &= (\mathbf{A}, \mathbf{C}, b_{cCOMB}) \end{aligned}$$

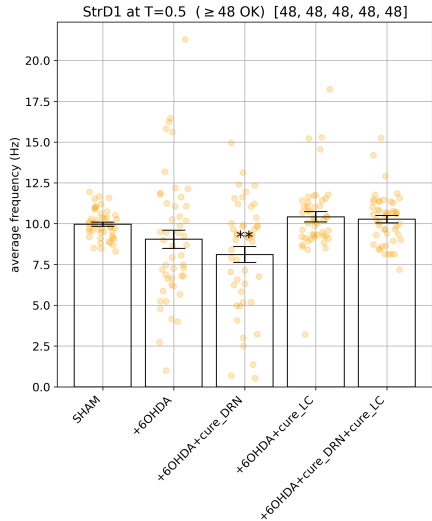
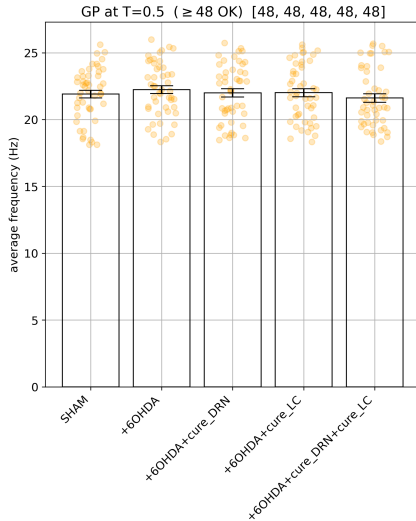
Treatment fitness results



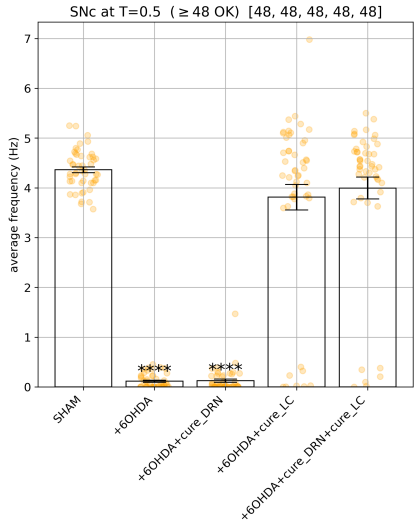
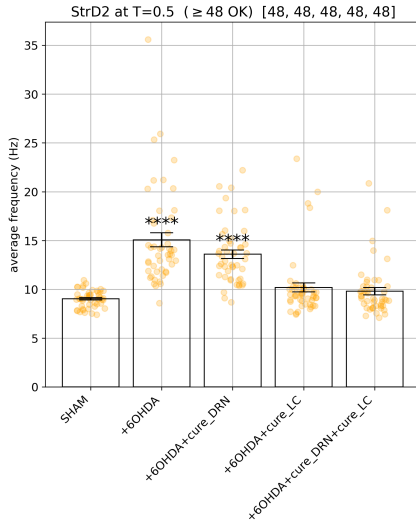
Role of DRN stimulation in combined treatment



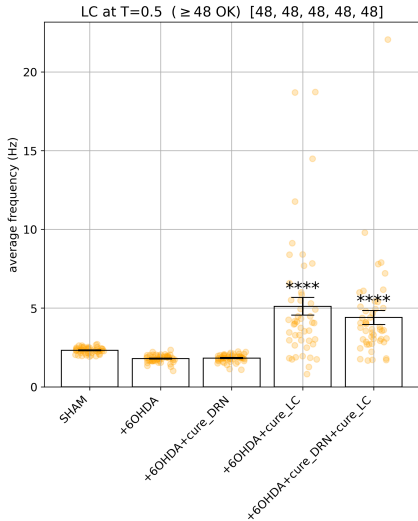
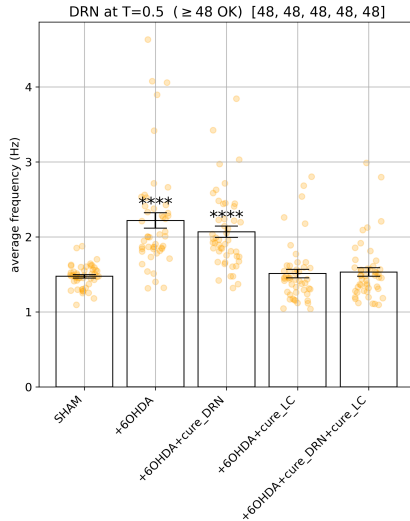
Treatment by area 1



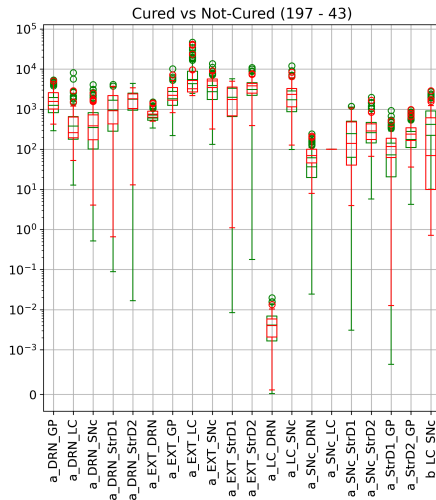
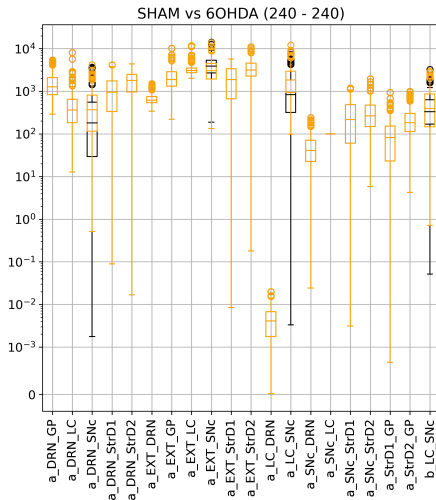
Treatment by area 2



Treatment by area 3



Curable vs Non-Curable



Conclusions

- ▶ Identified structures involved in Parkinson disease
- ▶ Collected and aggregated data about plausible circuit
- ▶ Identified a model able to reproduce bio-compatible synthetic data
- ▶ Predicted a potential treatment direction
 - ▶ In agreement with articles recently published!

Thanks for your attention!

Questions?

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