Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties

MENDEN ET AL. 2013

PROSEMINAR „COMPUTATIONAL BIOMARKER DISCOVERY“
– JAKOB GEMMEL 13.10.2021

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Structure

- Motivation
- Introduction
- Methods and Materials
  - Dataset
  - Feature Selection
  - Neural Network
  - Cross Validation
- Results
- Summary & Conclusion
- Discussion

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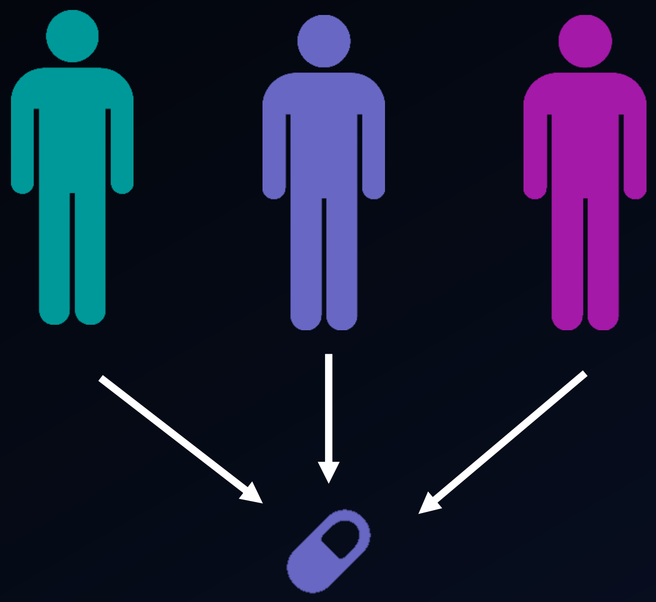
Motivation

Motivation



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Motivation

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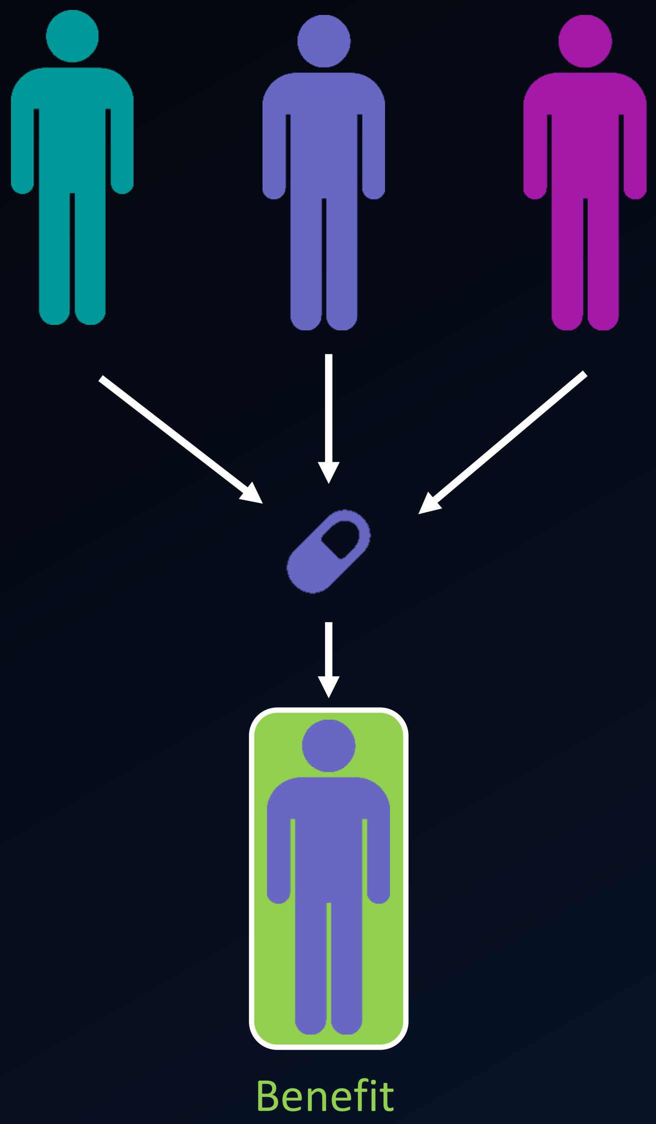

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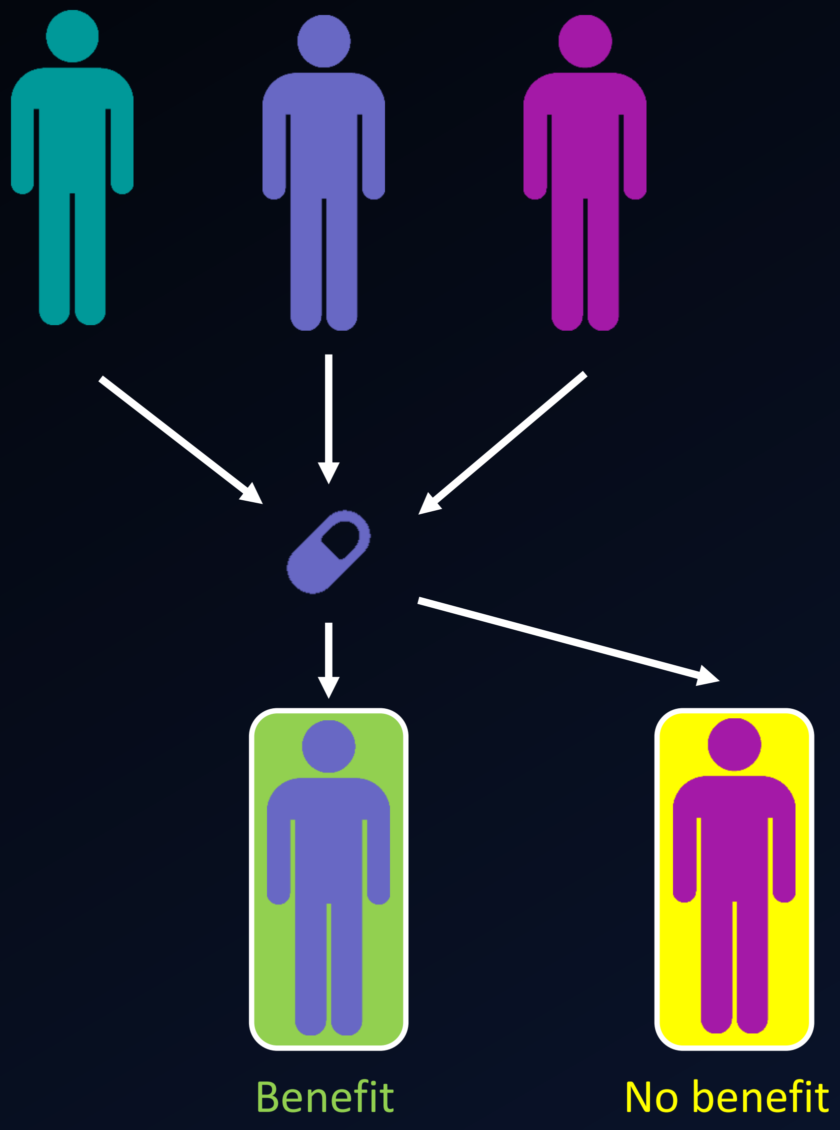
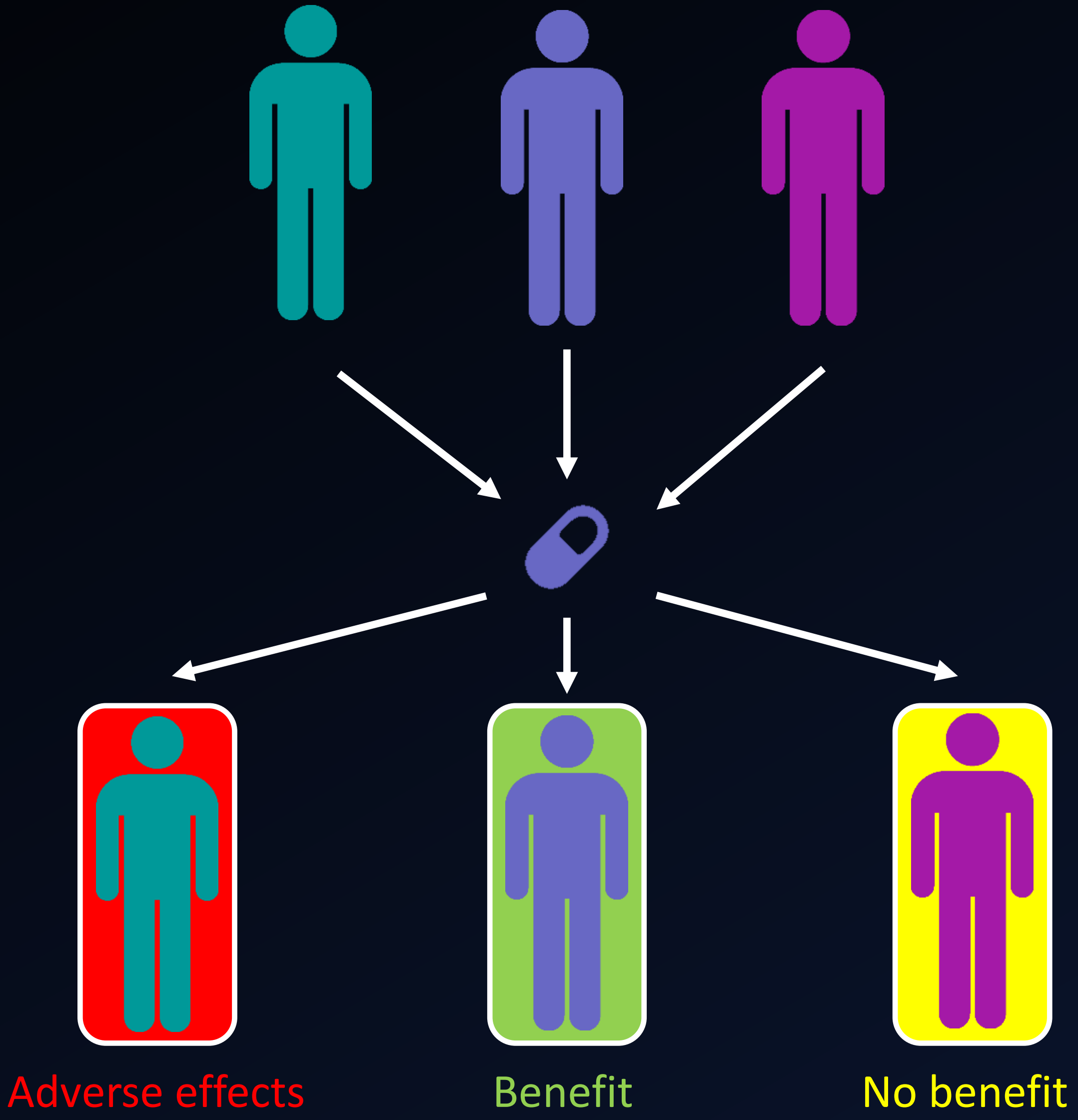
Motivation



Motivation



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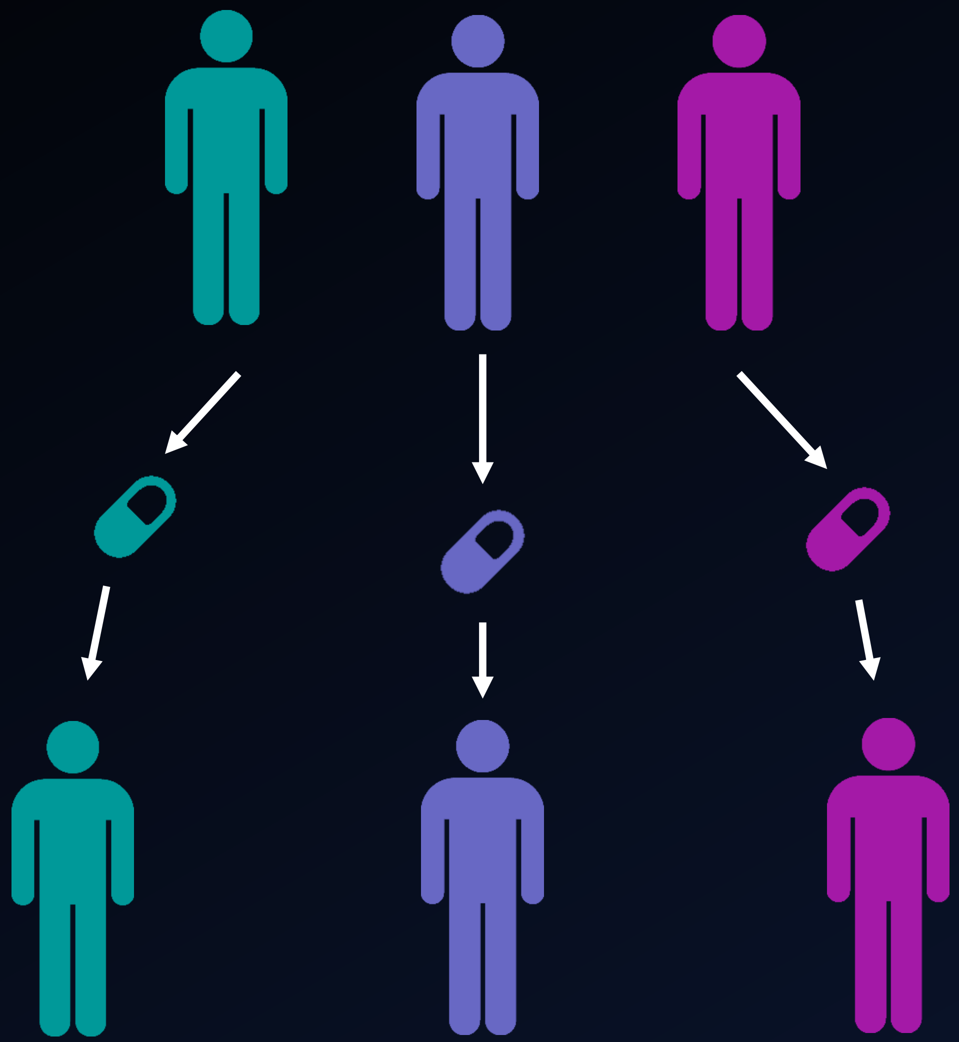
Motivation



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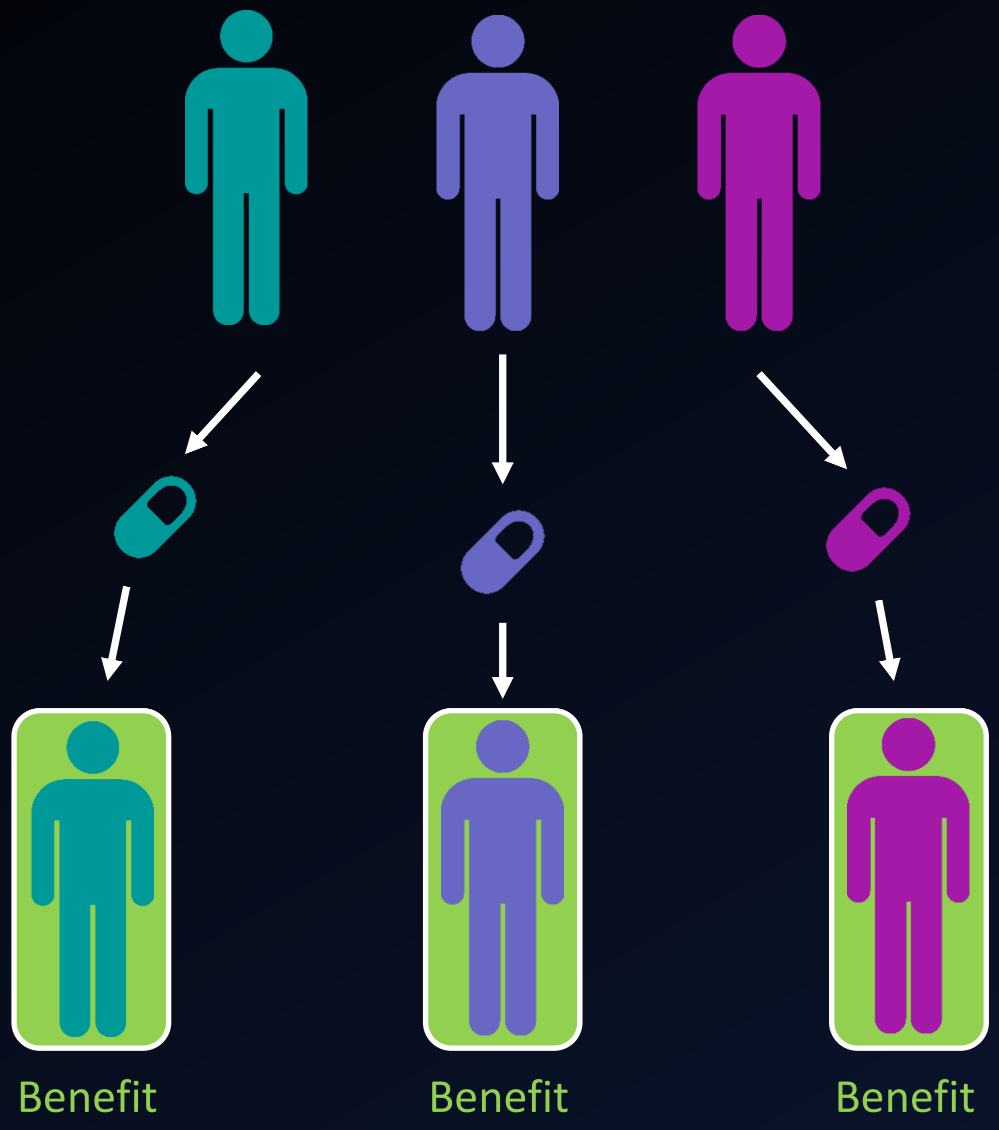
Motivation



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Introduction

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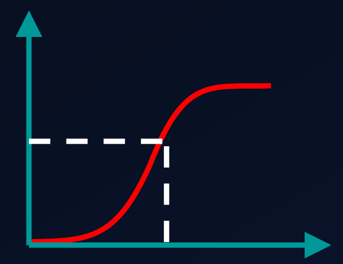
Introduction

Sensitivity



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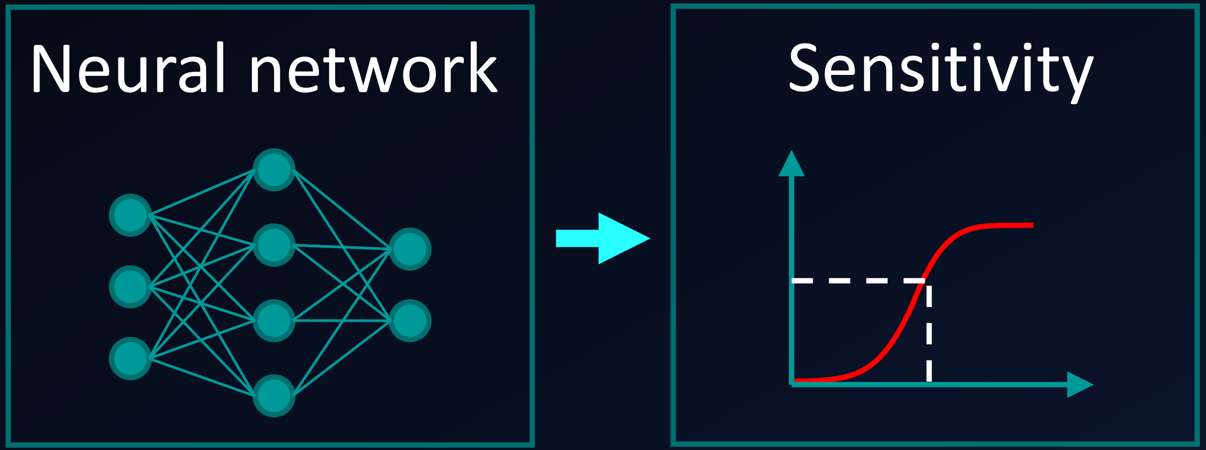
Introduction



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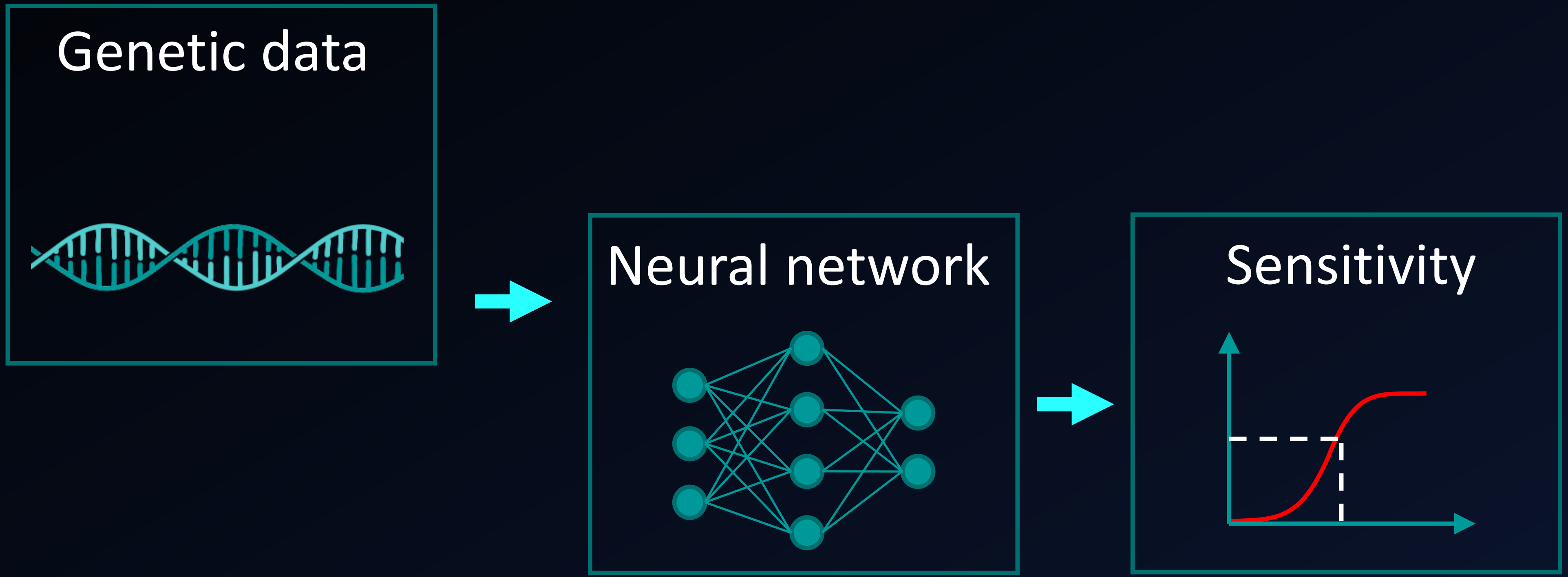
Introduction



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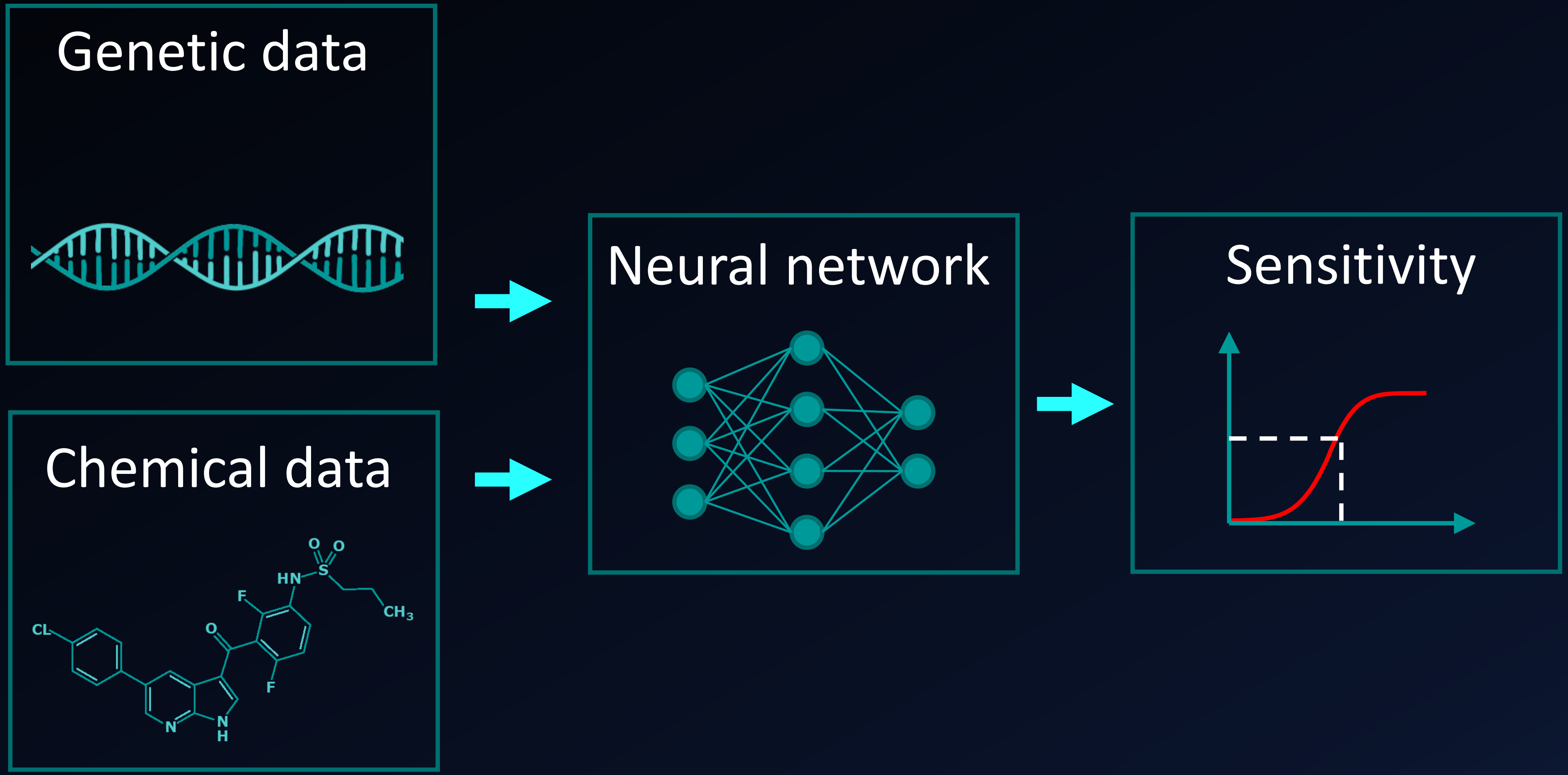
Introduction



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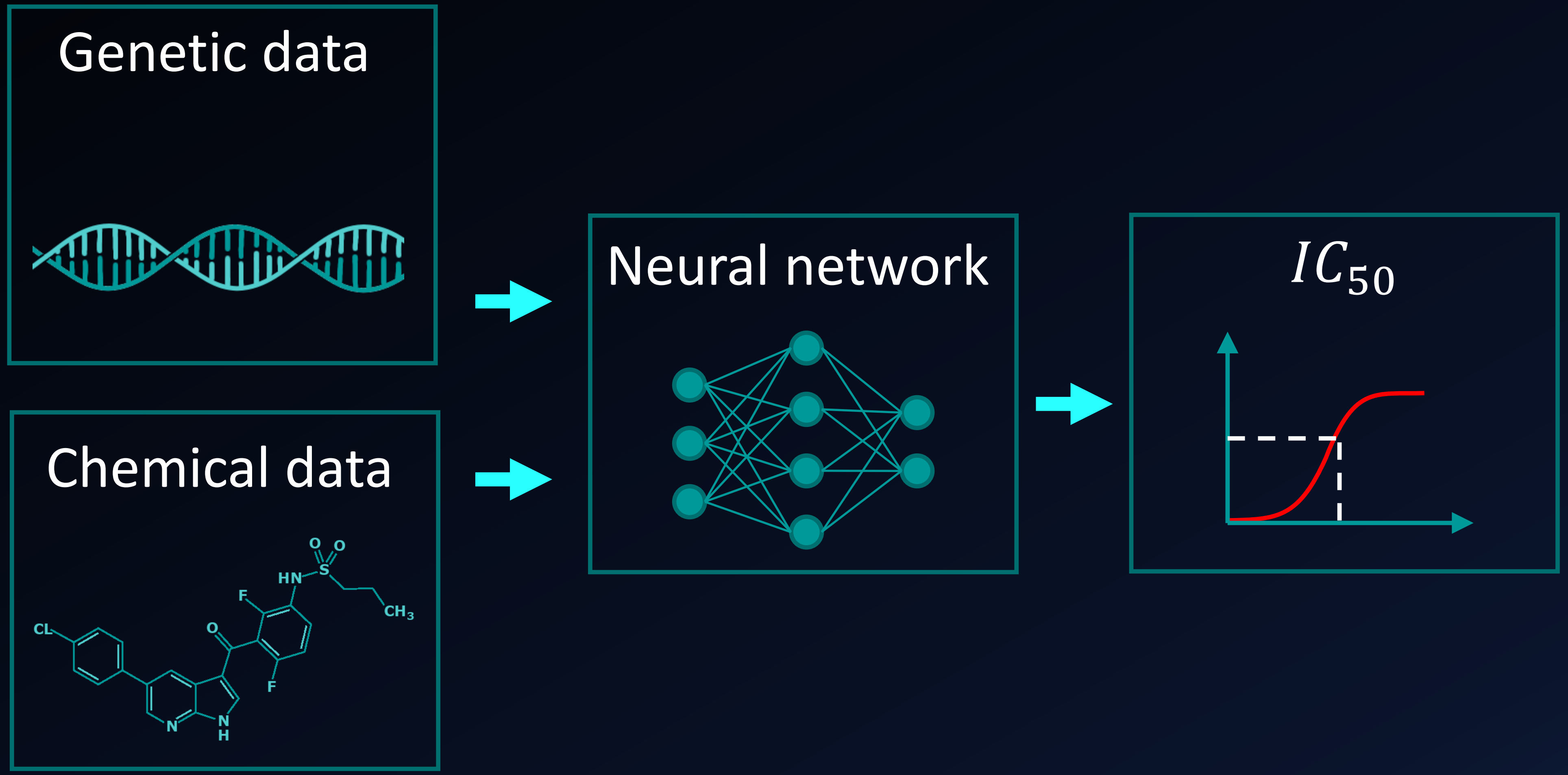
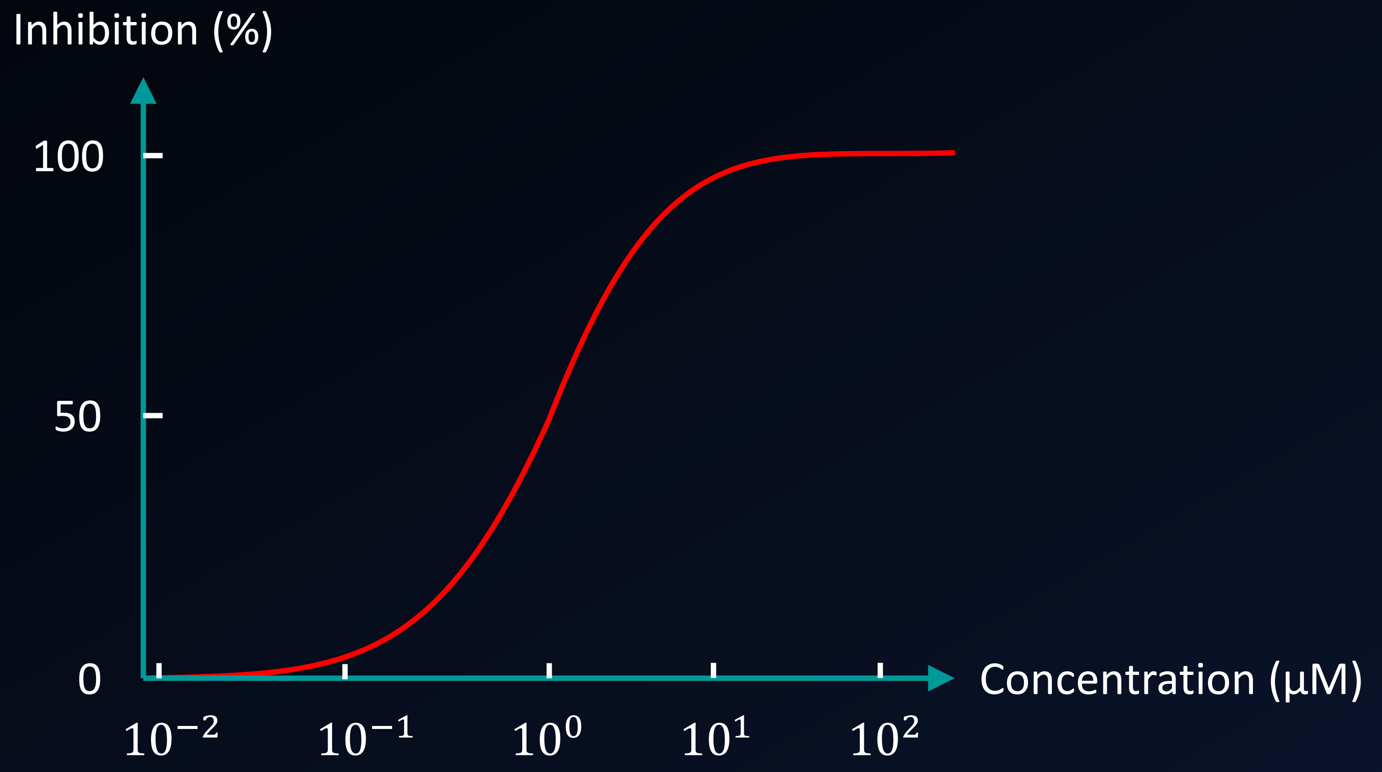
Introduction



Introduction - IC_{50} Value



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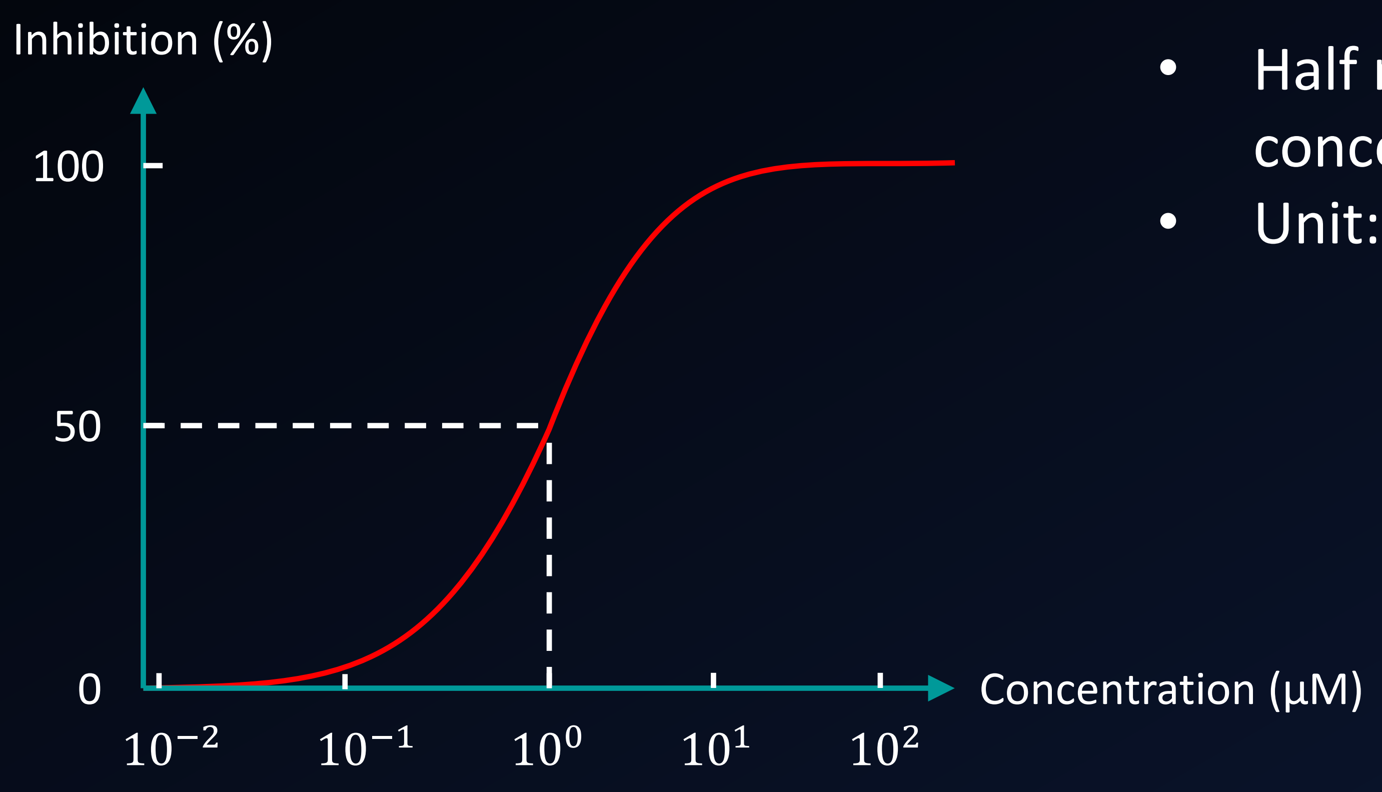
Introduction - IC_{50} Value



- Half maximal inhibitory concentration
- Unit: µM

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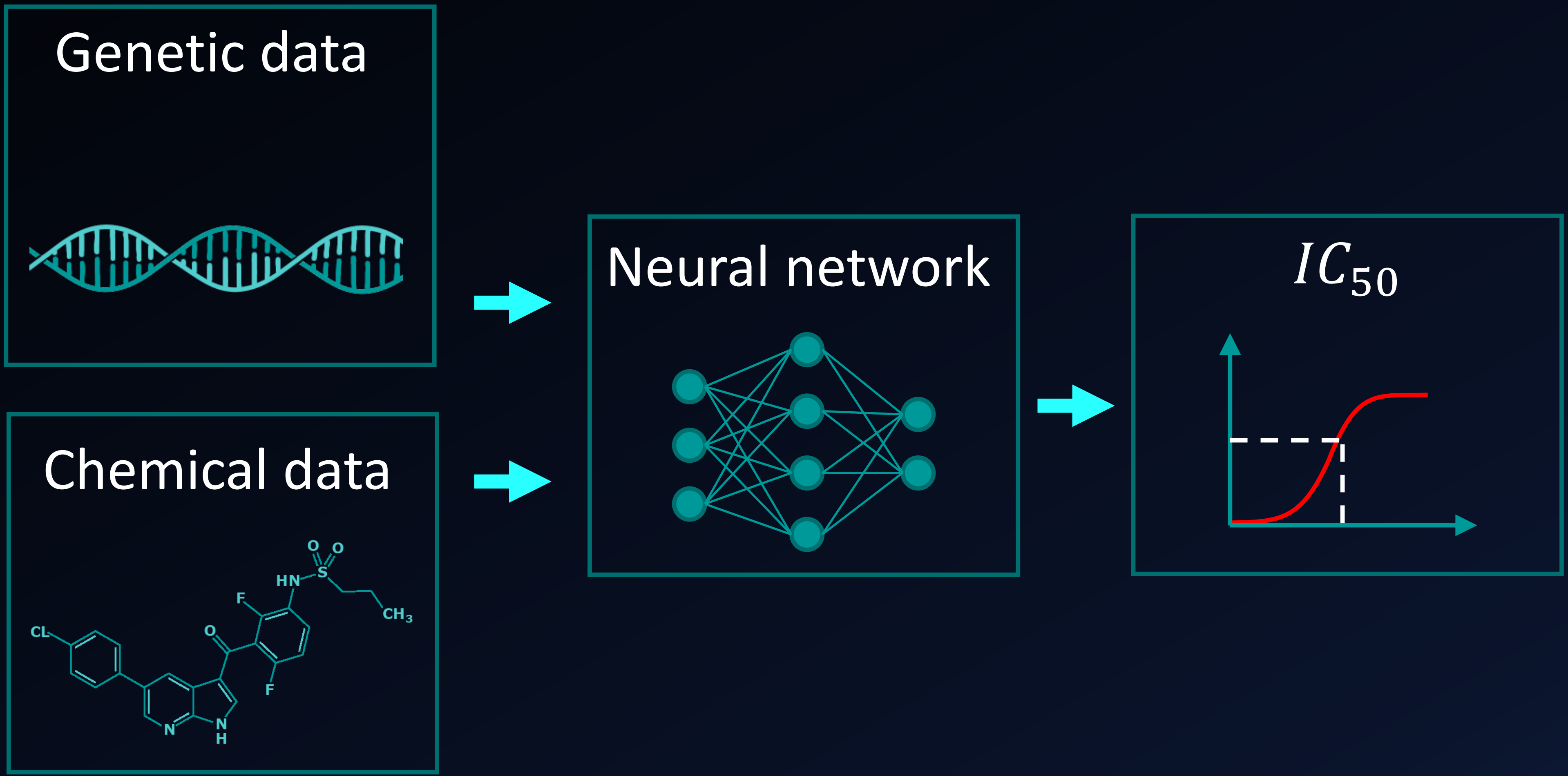
Methods and Materials - Overview



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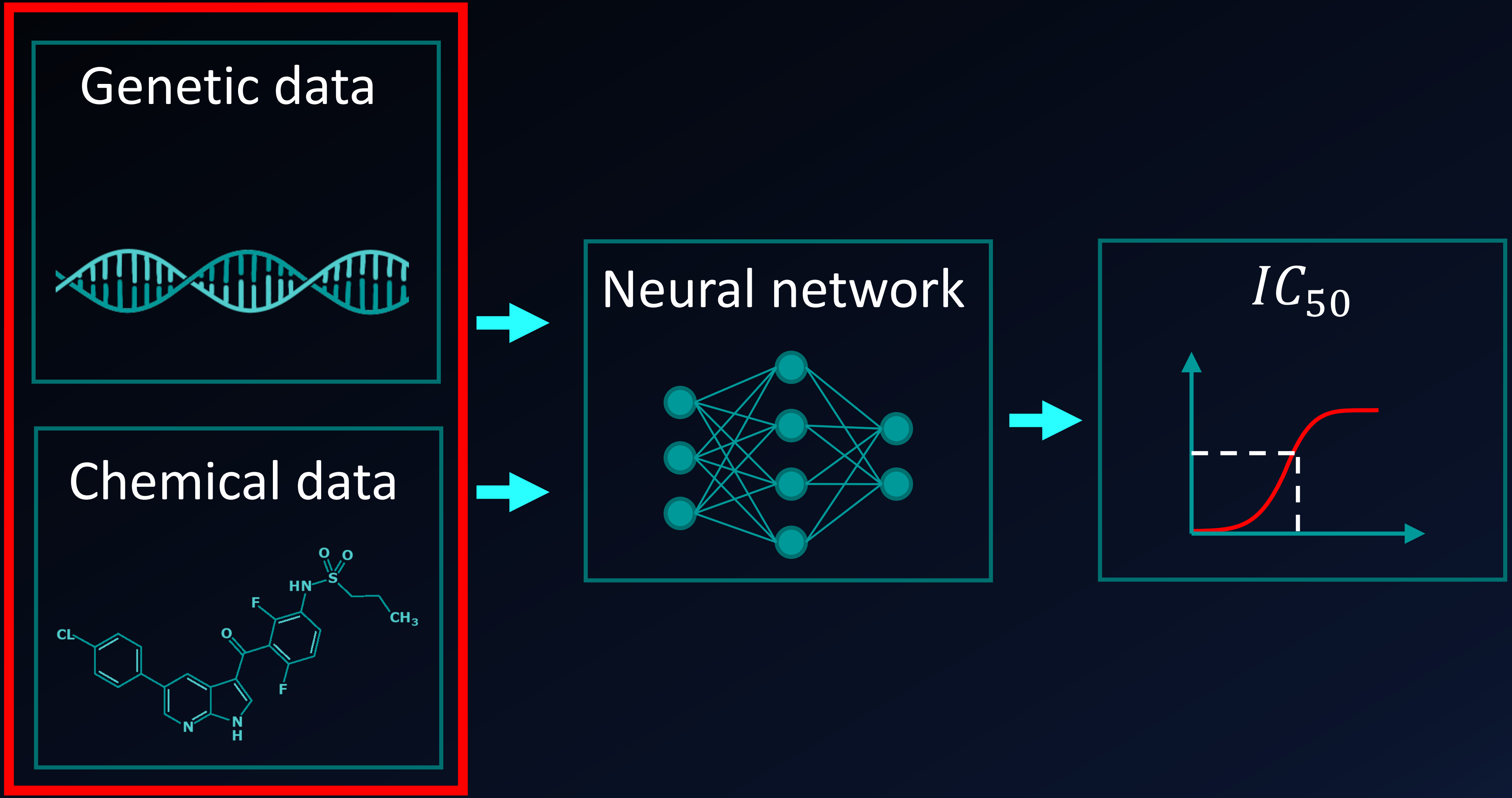
Methods and Materials - Overview



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Methods and Materials - The Dataset

- Genomics of Drug Sensitivity in Cancer
  - 988 cell lines
  - 518 compounds
  - 446.146 dose–response curves

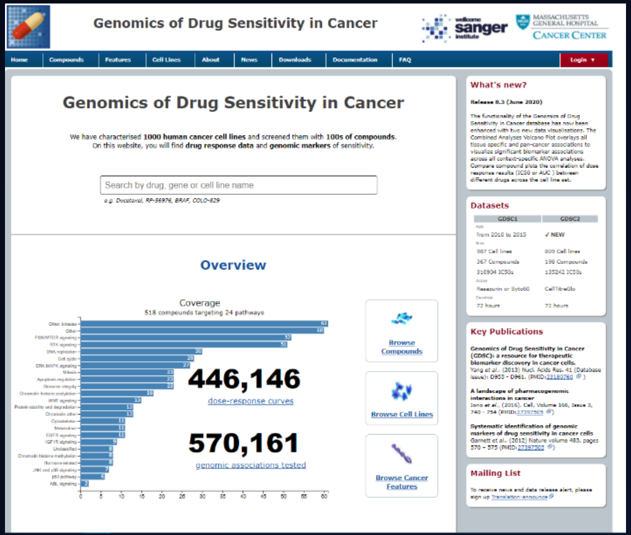

Fig. 1

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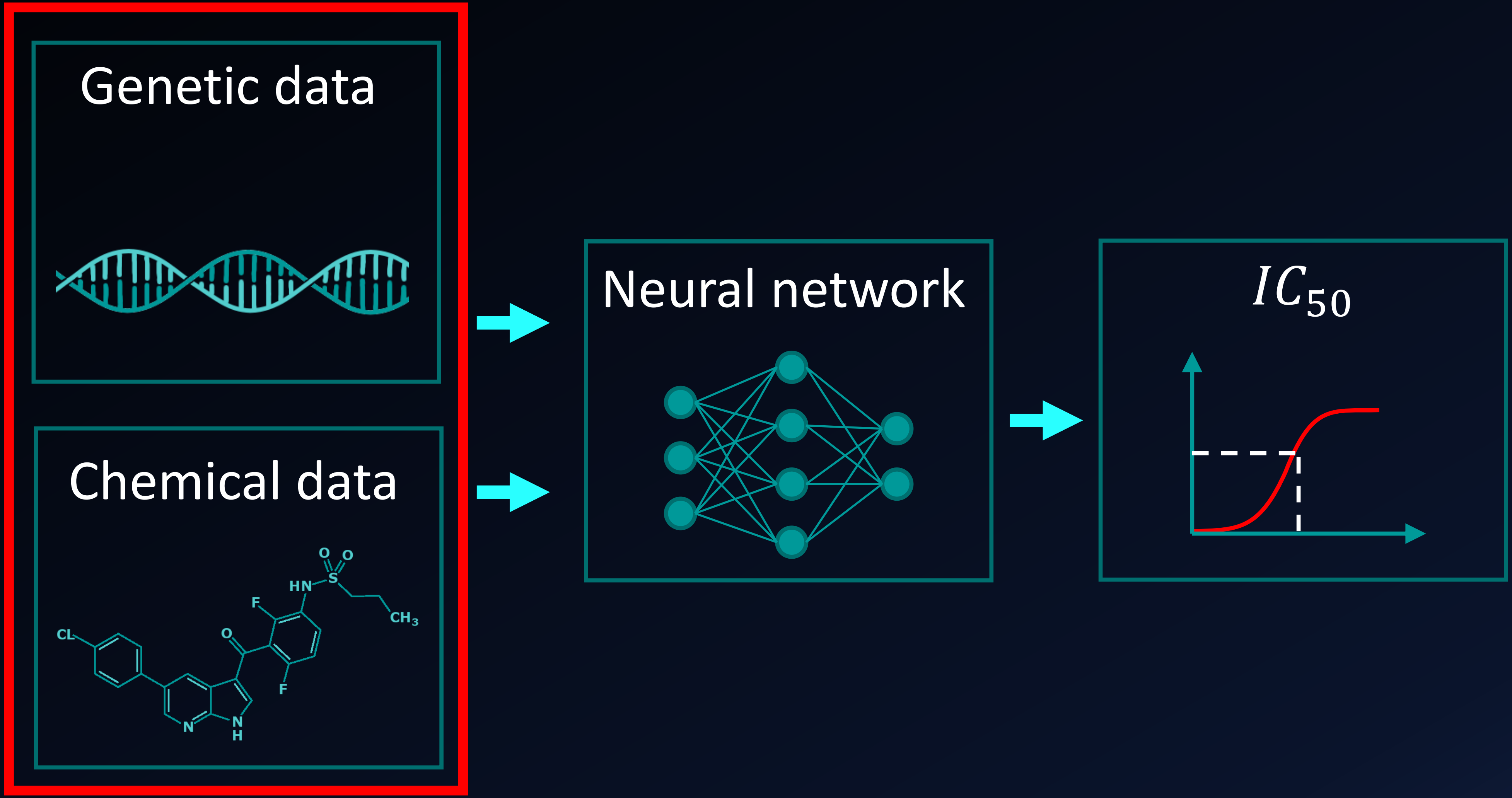
Methods and Materials - Overview



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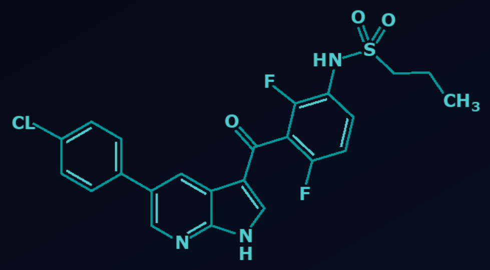
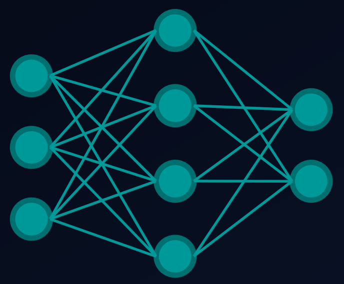
Methods and Materials - Overview

Genetic data

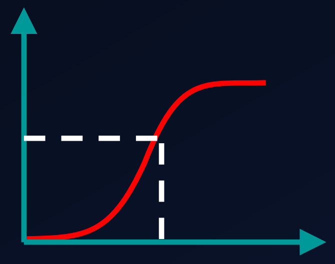
Chemical data



Neural network



IC_{50}



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Methods and Materials – Feature Selection

Genomic Features

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Methods and Materials – Feature Selection

Genomic Features

Whole cell line genome

$$\text{Microsatellite instability status} = \begin{cases} 1 & \text{if unstable} \\ 0 & \text{if stable} \end{cases}$$

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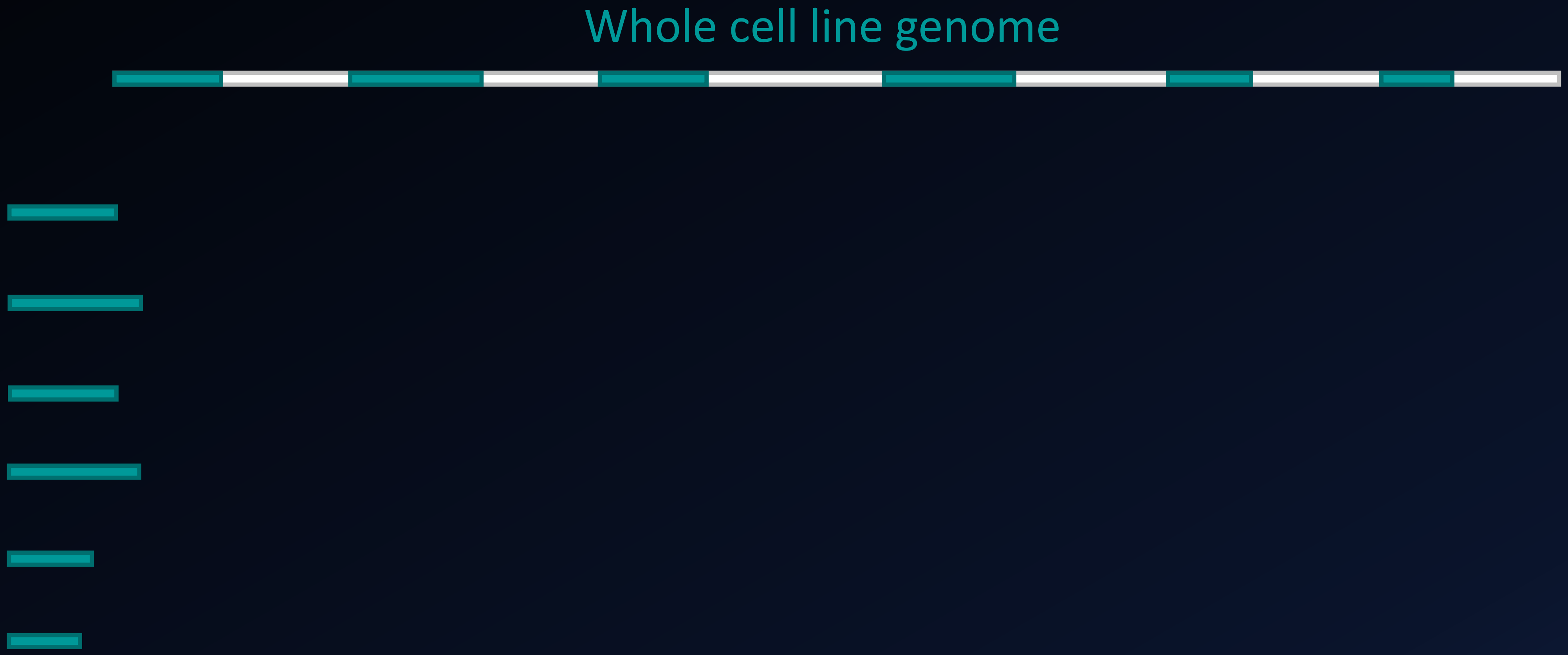
Methods and Materials – Feature Selection

Genomic Features



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Methods and Materials – Feature Selection

Genomic Features

77 oncogenes

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Methods and Materials – Feature Selection

Genomic Features

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Methods and Materials – Feature Selection

Genomic Features

15

Methods and Materials – Feature Selection

Genomic Features

$$\text{Sequence variation} = \begin{cases} 1 & \text{if mutation} \\ 0 & \text{if wildtype} \end{cases}$$

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Methods and Materials – Feature Selection

Genomic Features

$$\text{Sequence variation} = \begin{cases} 1 & \text{if mutation} \\ 0 & \text{if wildtype} \end{cases}$$

$$\text{Copy number variation} = \begin{cases} 1 & \text{if amplification} \\ 0 & \text{if wildtype} \\ -1 & \text{if deletion} \end{cases}$$

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Methods and Materials – Feature Selection

Genomic Features

1 MIS + 77 Oncogenes × 2 Features = 155 Genomic Input Features

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Methods and Materials – Feature Selection

Genomic Features

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1 MIS + 77 Oncogenes × 2 Features = ~~155~~ Genomic Input Features

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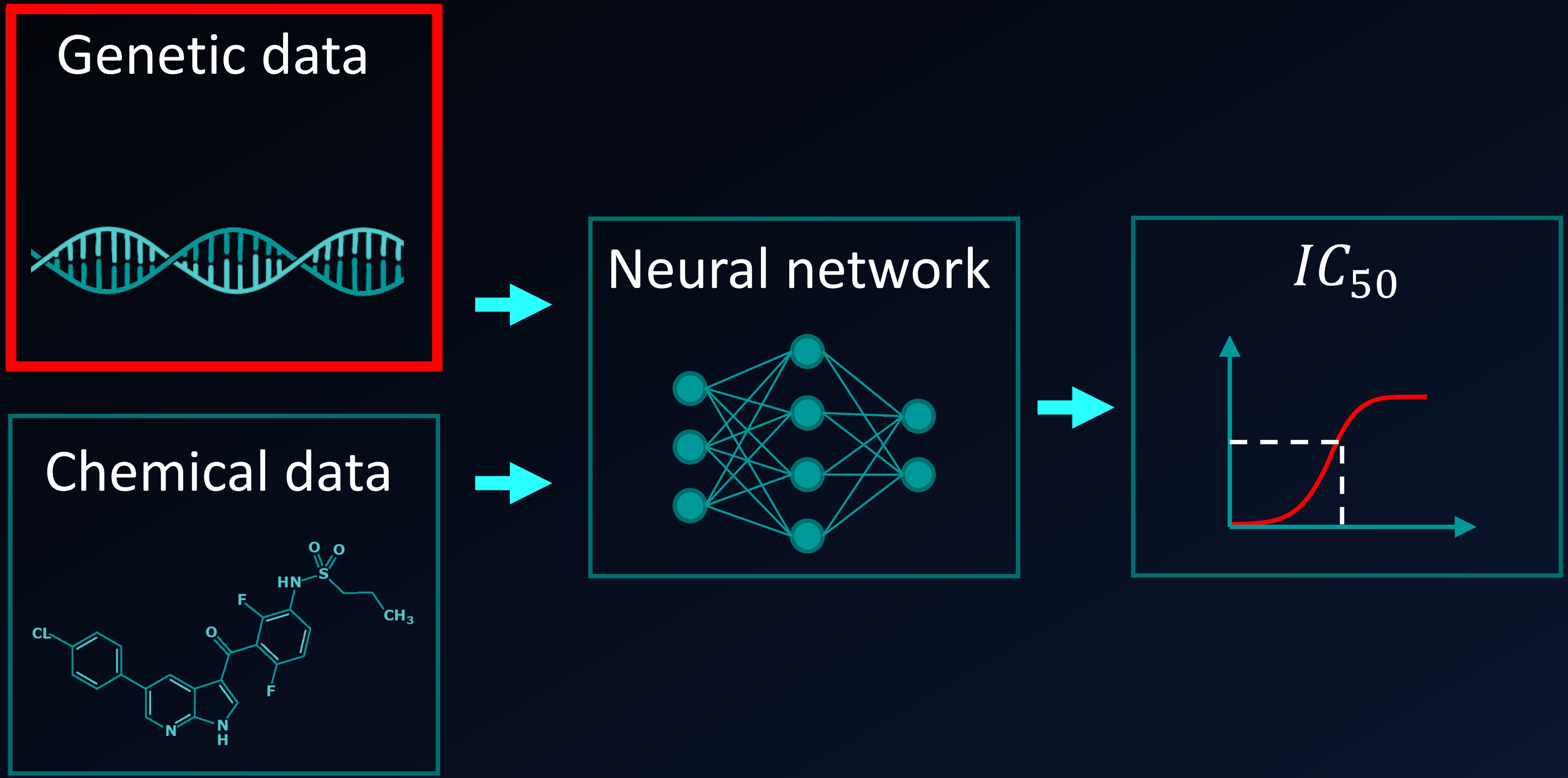
Methods and Materials - Overview



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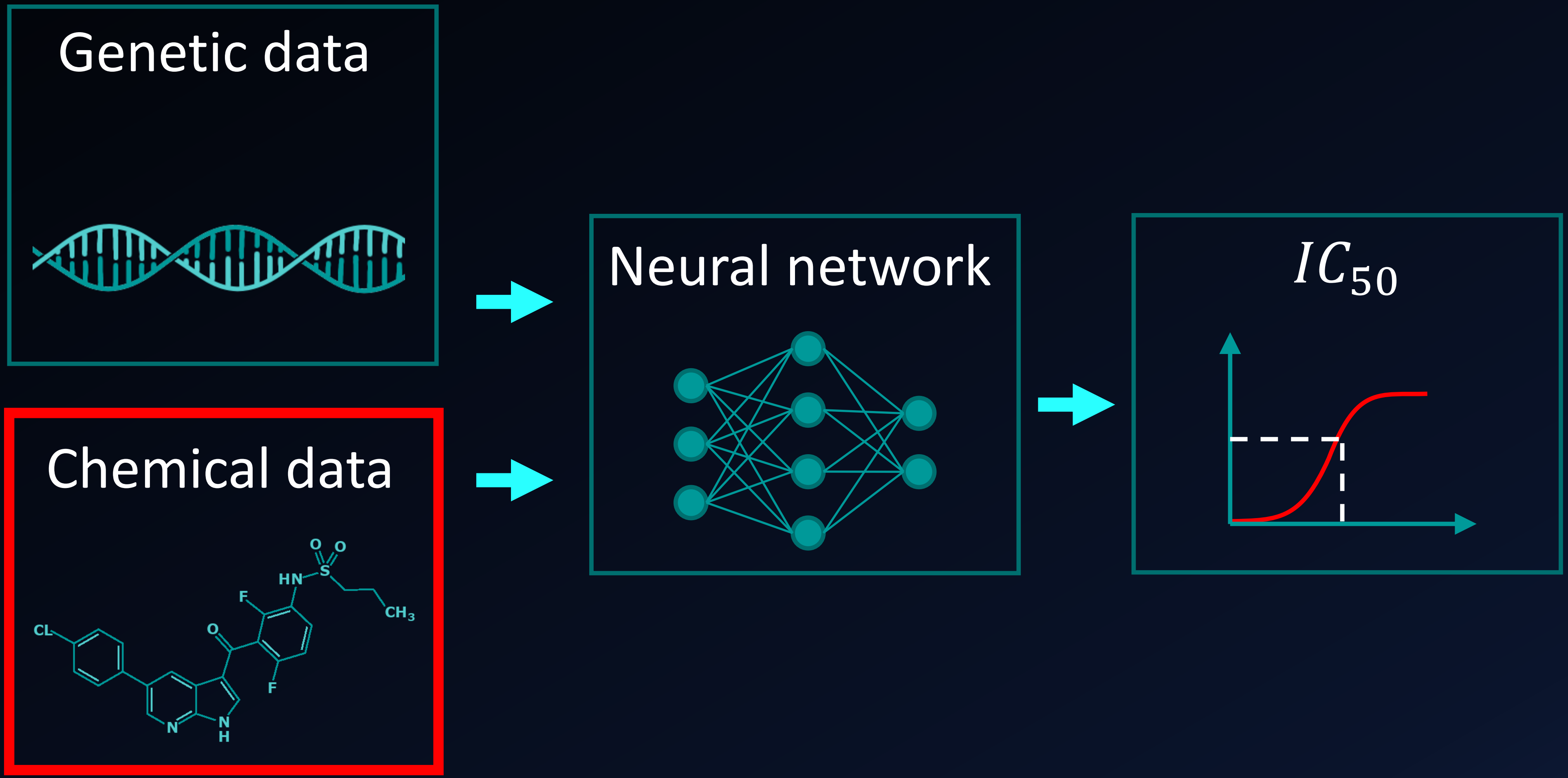
Methods and Materials - Overview



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Feature Selection

Drug Features

Why use drug features?

Feature Selection

Drug Features

Why use drug features?

- More data for machine learning ($\times 10^2$)

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Feature Selection

Drug Features

Why use drug features?

- More data for machine learning ($\times\ 10^2$)
- New areas of application

18

Feature Selection

Drug Features

Why use drug features?

- More data for machine learning ($\times\ 10^2$)
- New areas of application

But how to describe molecule features for the neural network?

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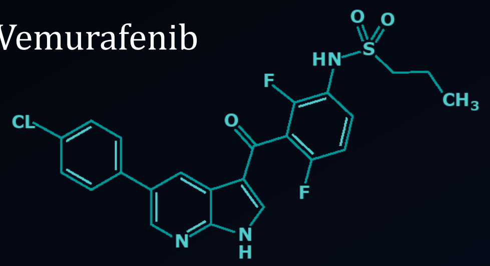
Feature Selection

Drug Features

Vemurafenib



Molecule structure

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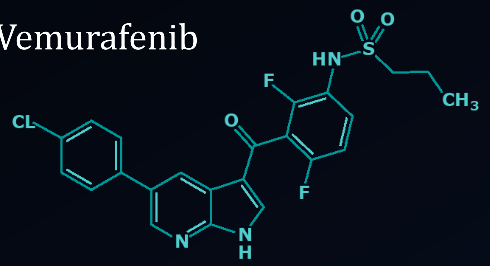
Feature Selection

Drug Features

Vemurafenib



C(=O)(C=1C=2C(NC1)
=NC=C(C2)C3=CC=C(C
l)C=C3)C4=C(F)C(NS(C
CC)(=O)=O)=CC=C4F

Molecule structure

SMILES - format

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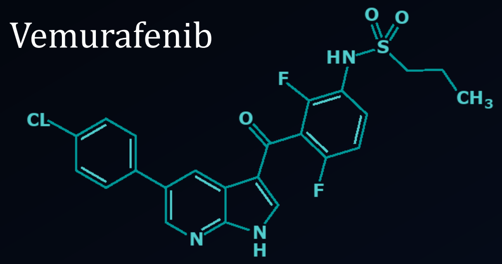
Feature Selection

Drug Features



C(=O)(C=1C=2C(NC1)=NC=C(C2)C3=CC=C(Cl)C=C3)C4=C(F)C(NS(CCC)(=O)=O)=CC=C4F

Atom count: 51
Bond count: 130
Rotating bond count: 70
Acidic group count: 0
Basic group count: 0
Rule of five: 1
…

Molecule structure → SMILES - format → PaDel - descriptor

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Feature Selection

Drug Features

Atom count: 51
Bond count: 130
Rotating bond count: 70
Acidic group count: 0
Basic group count: 0
Ruel of five: 1
…

} 689 chemical features

PaDel - descriptor

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Feature Selection

155 Genomic Features + 689 Chemical Features = 827 Input Features

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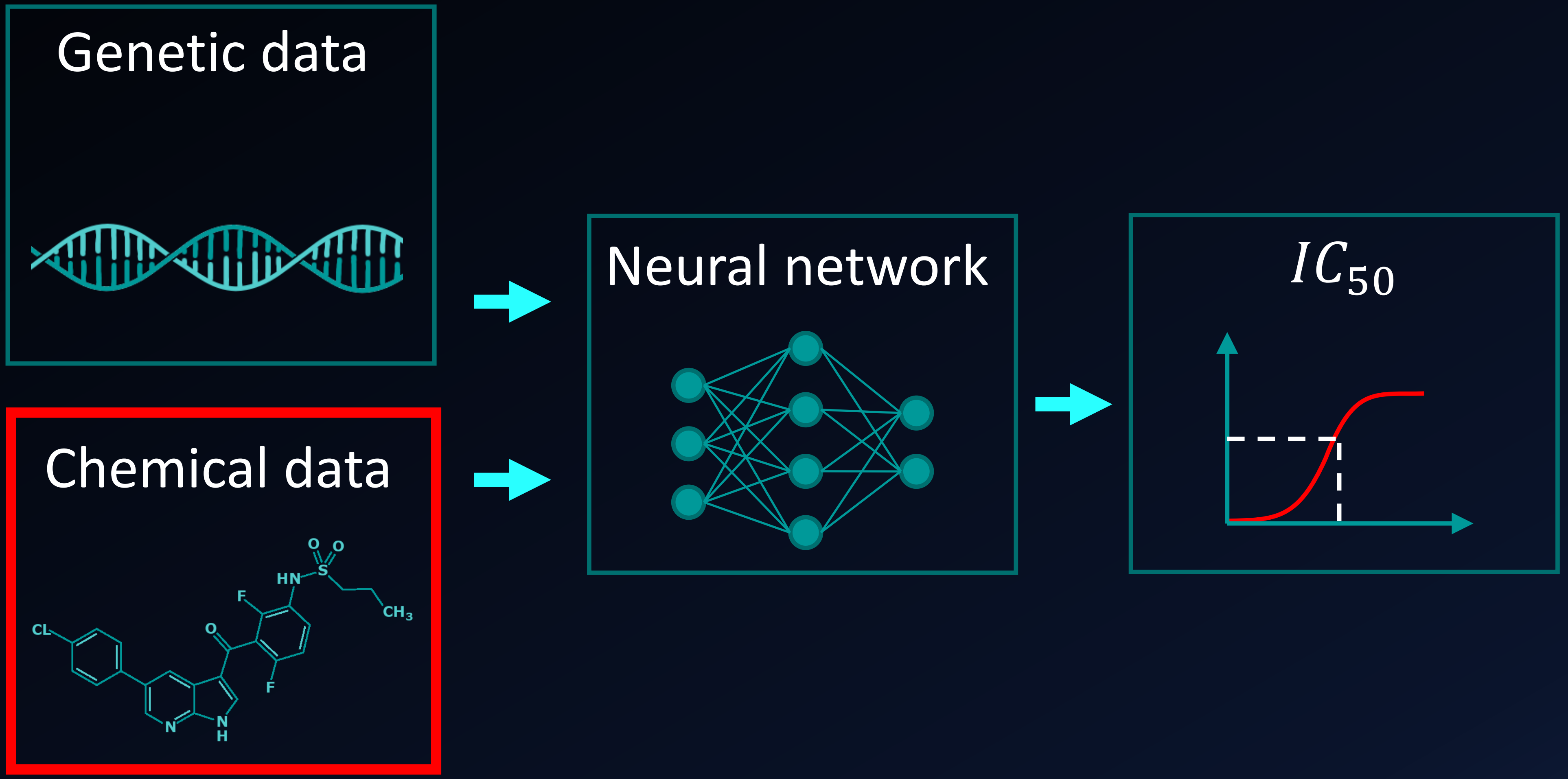
Methods and Materials - Overview



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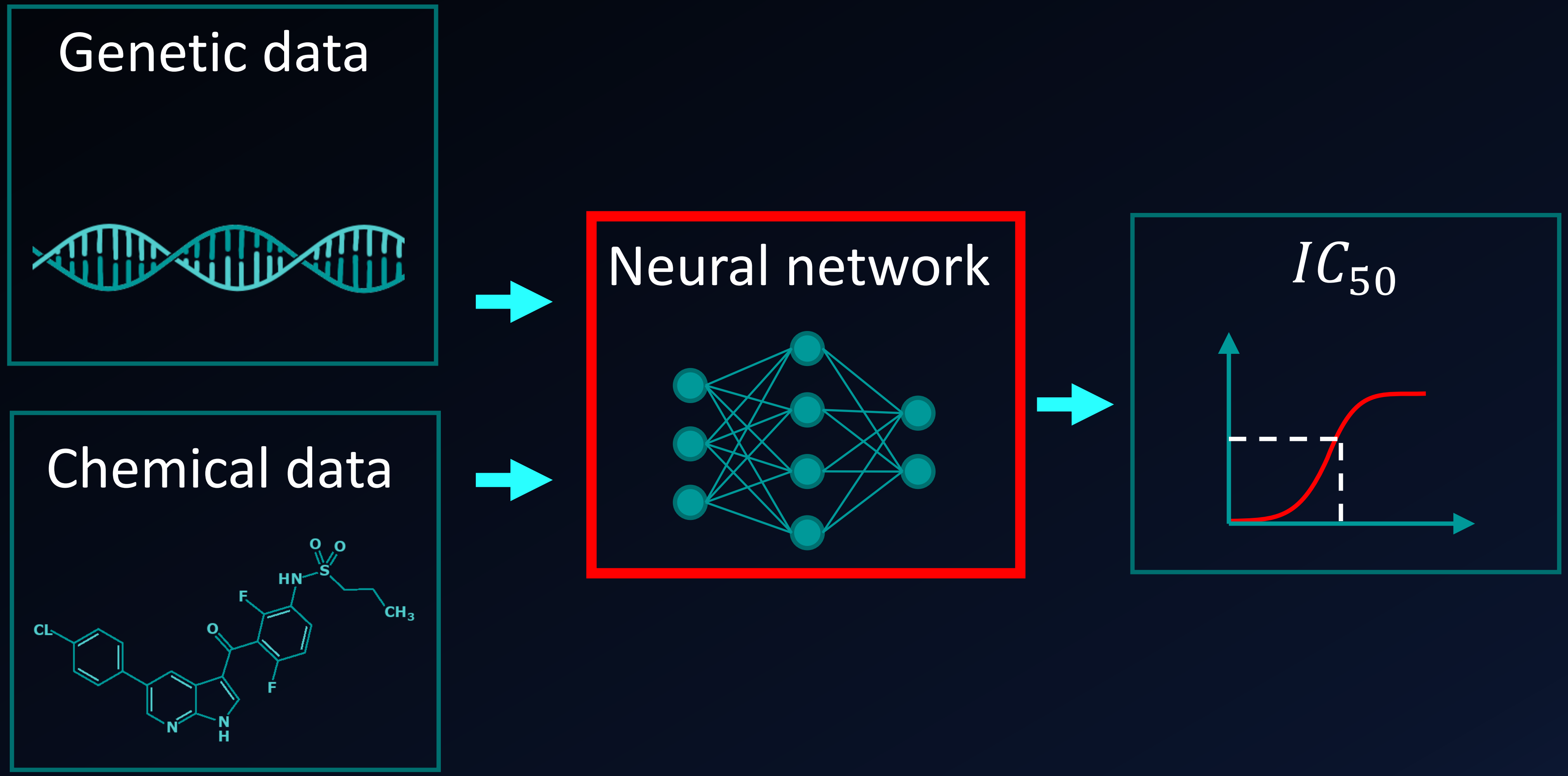
Methods and Materials - Overview



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Methods and Materials - Neural Network

Neuron

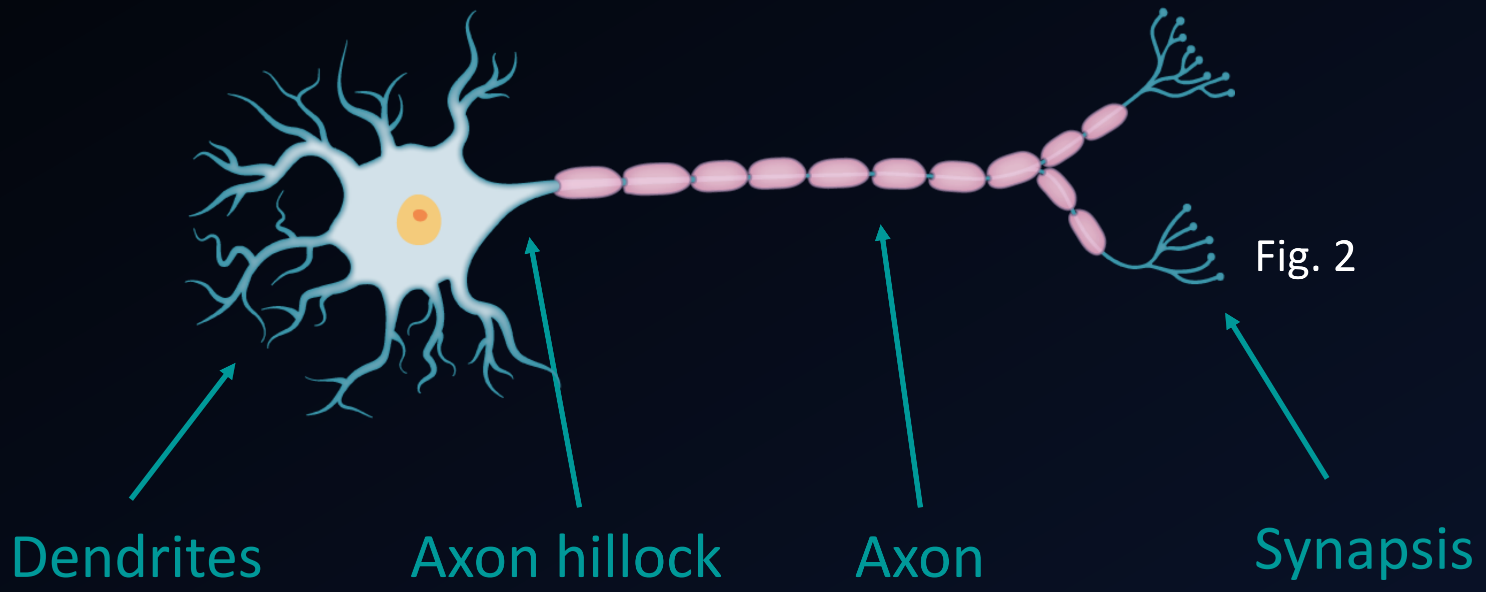

Fig. 2

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Methods and Materials - Neural Network

Artificial Neuron

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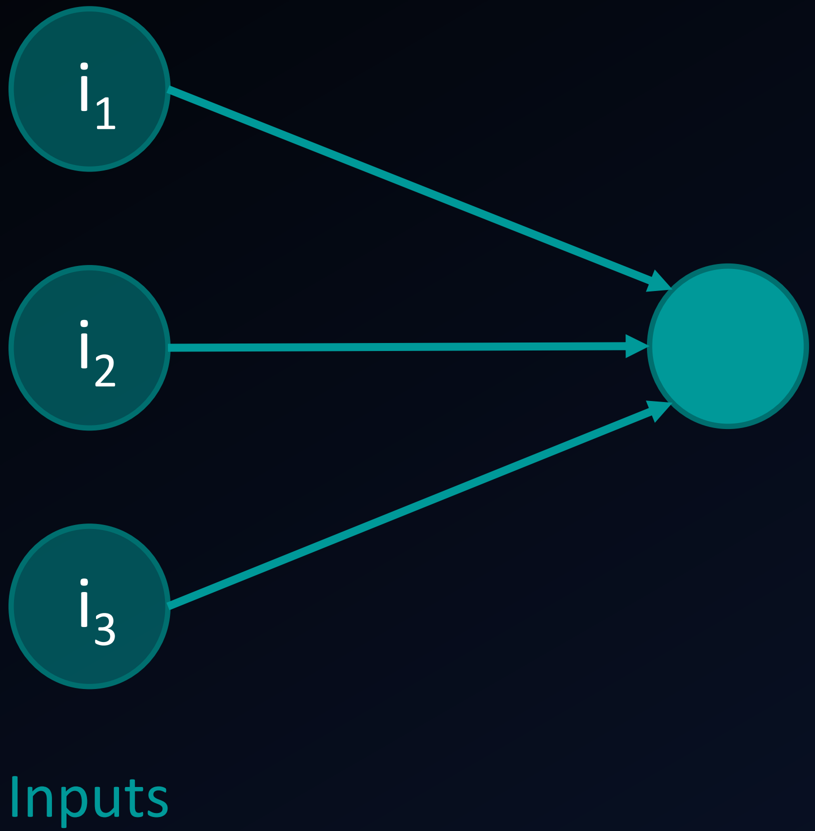
Methods and Materials - Neural Network

Artificial Neuron



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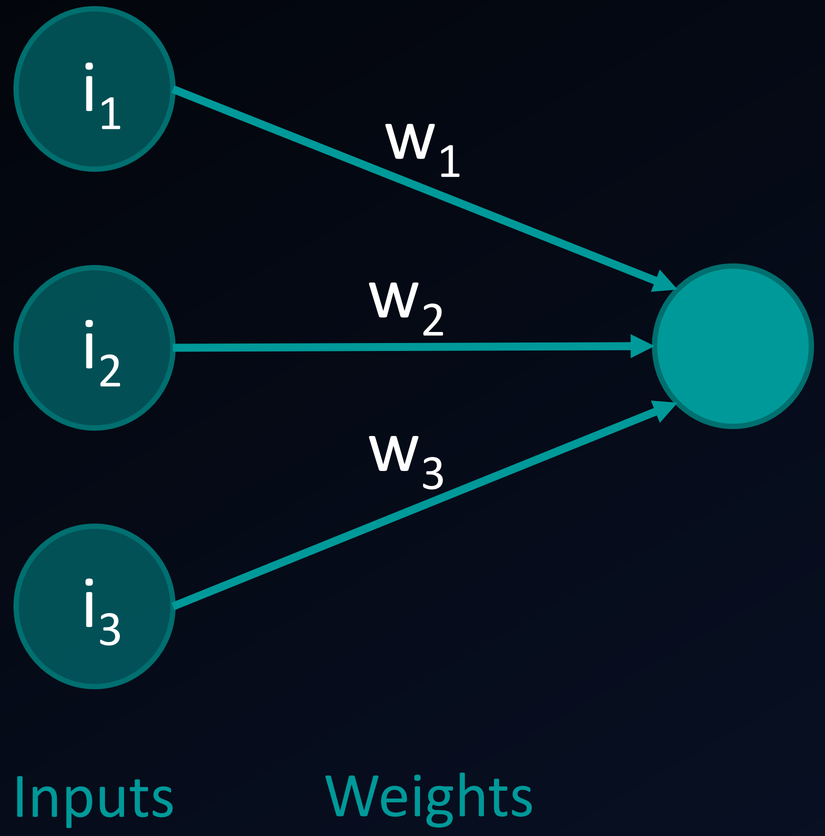
Methods and Materials - Neural Network

Artificial Neuron



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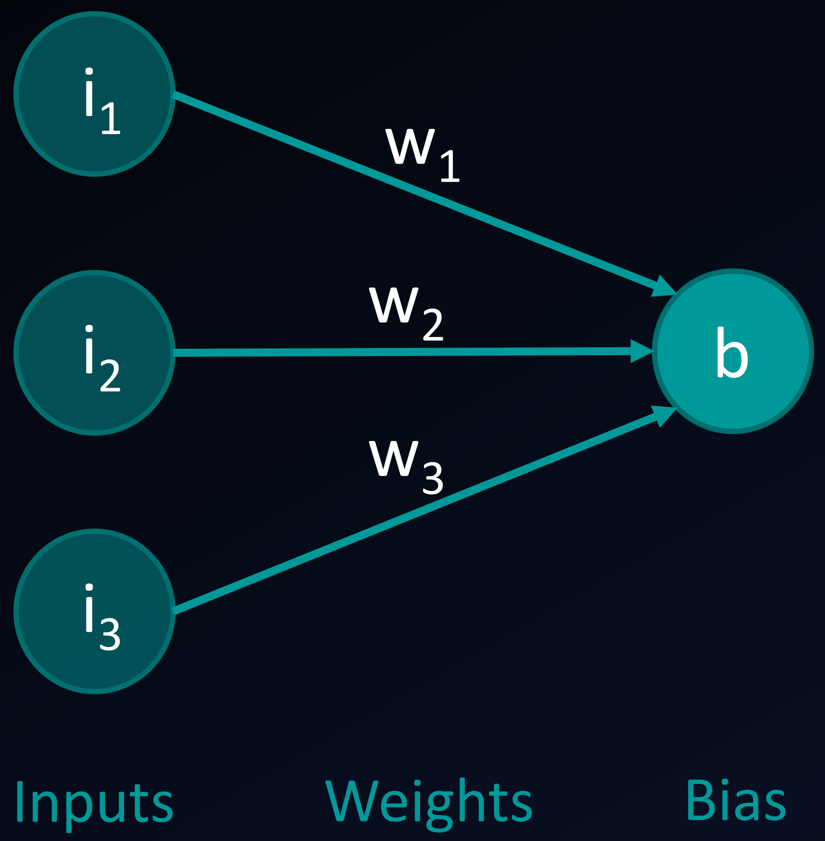
Methods and Materials - Neural Network

Artificial Neuron



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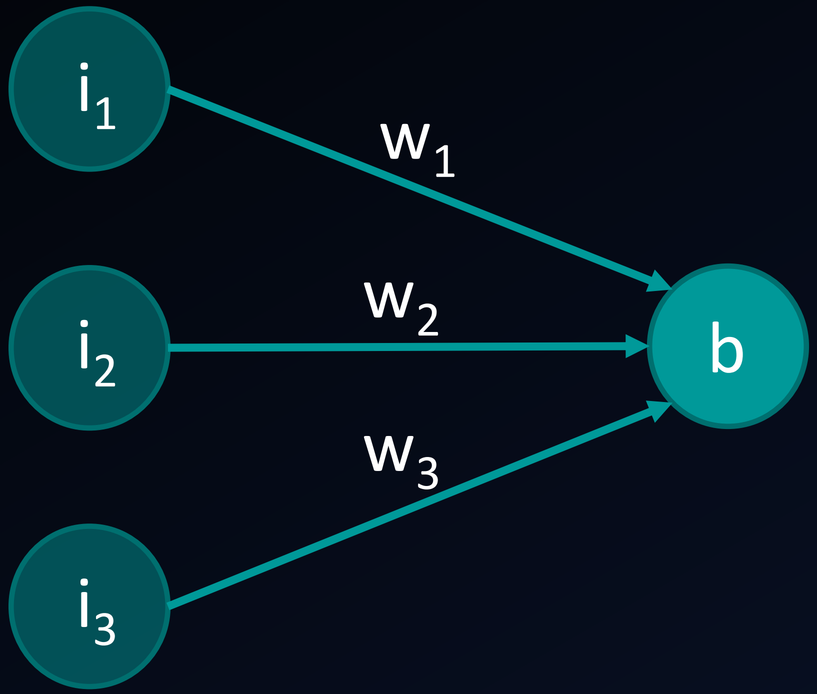
Methods and Materials - Neural Network

Artificial Neuron



$$\sigma(\sum_{k=0}^{n} \mathrm{i}_\mathrm{k} \mathrm{w}_\mathrm{k} + \mathrm{b})$$

Inputs Weights Bias Activation function

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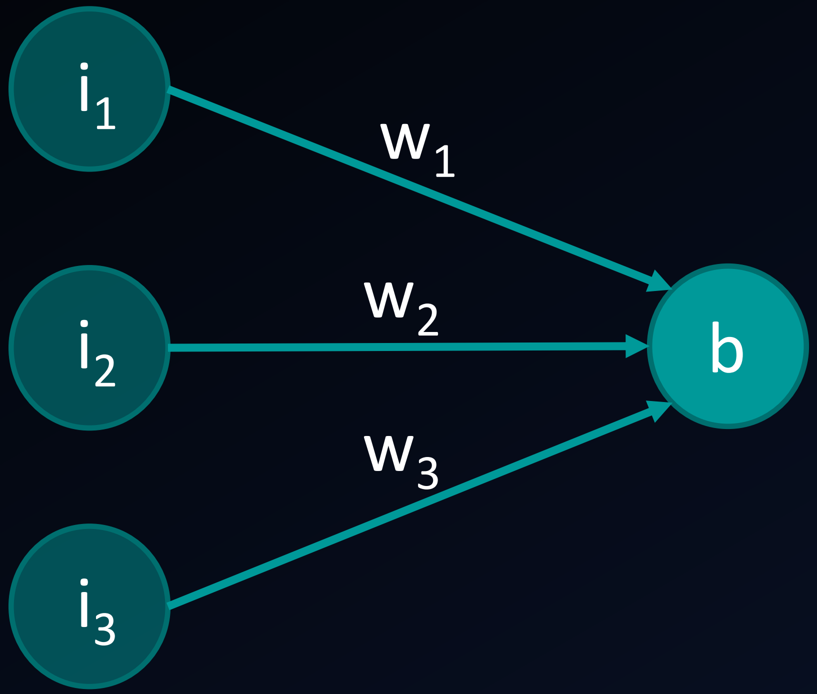
Methods and Materials - Neural Network

Artificial Neuron



$$\sigma(i_1w_1 + i_2w_2 + i_3w_3 + b)$$

Inputs Weights Bias Activation function

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Methods and Materials - Neural Network

Activation Function

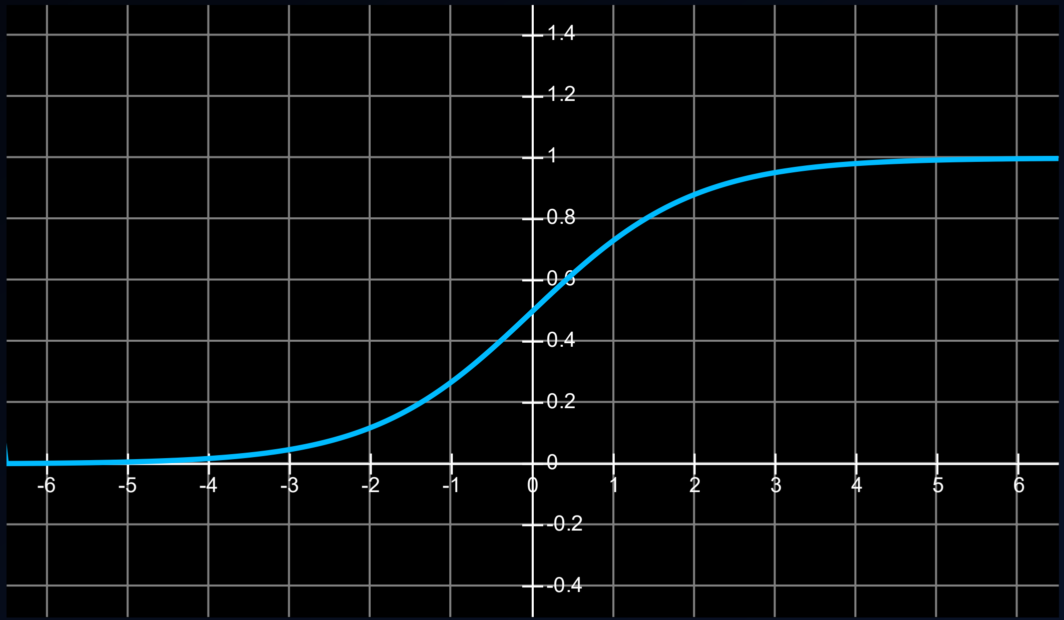

Fig. 3

Sigmoid function

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Methods and Materials - Neural Network

Activation Function

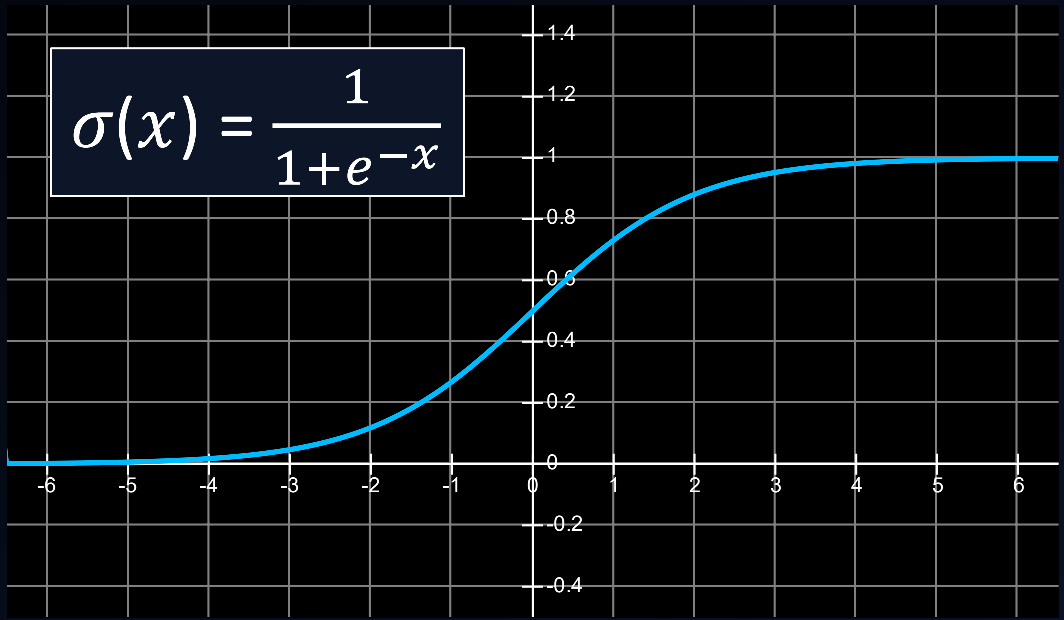

Fig. 3

Sigmoid function

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Methods and Materials - Neural Network

Artificial Neural Network

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Methods and Materials - Neural Network

Artificial Neural Network

Input layer

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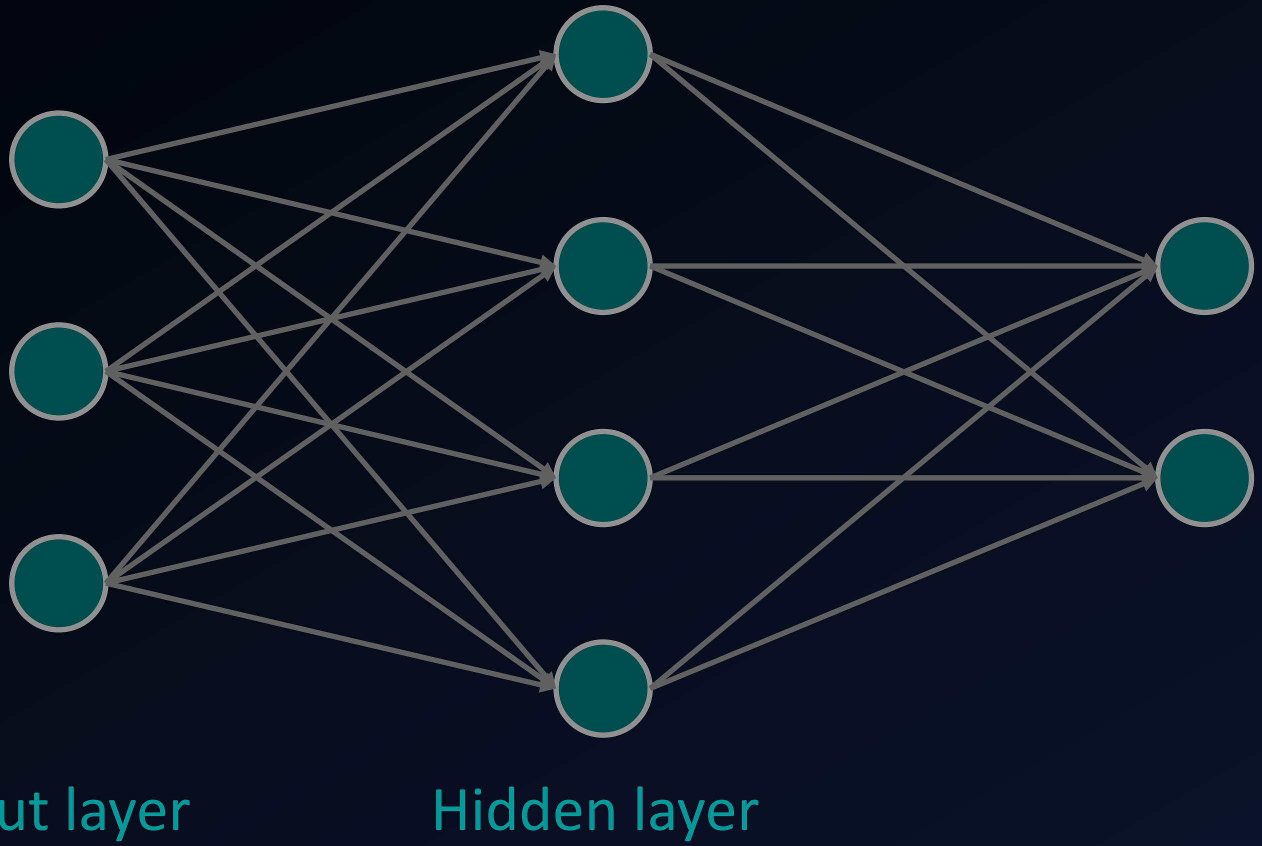
Methods and Materials - Neural Network

Artificial Neural Network



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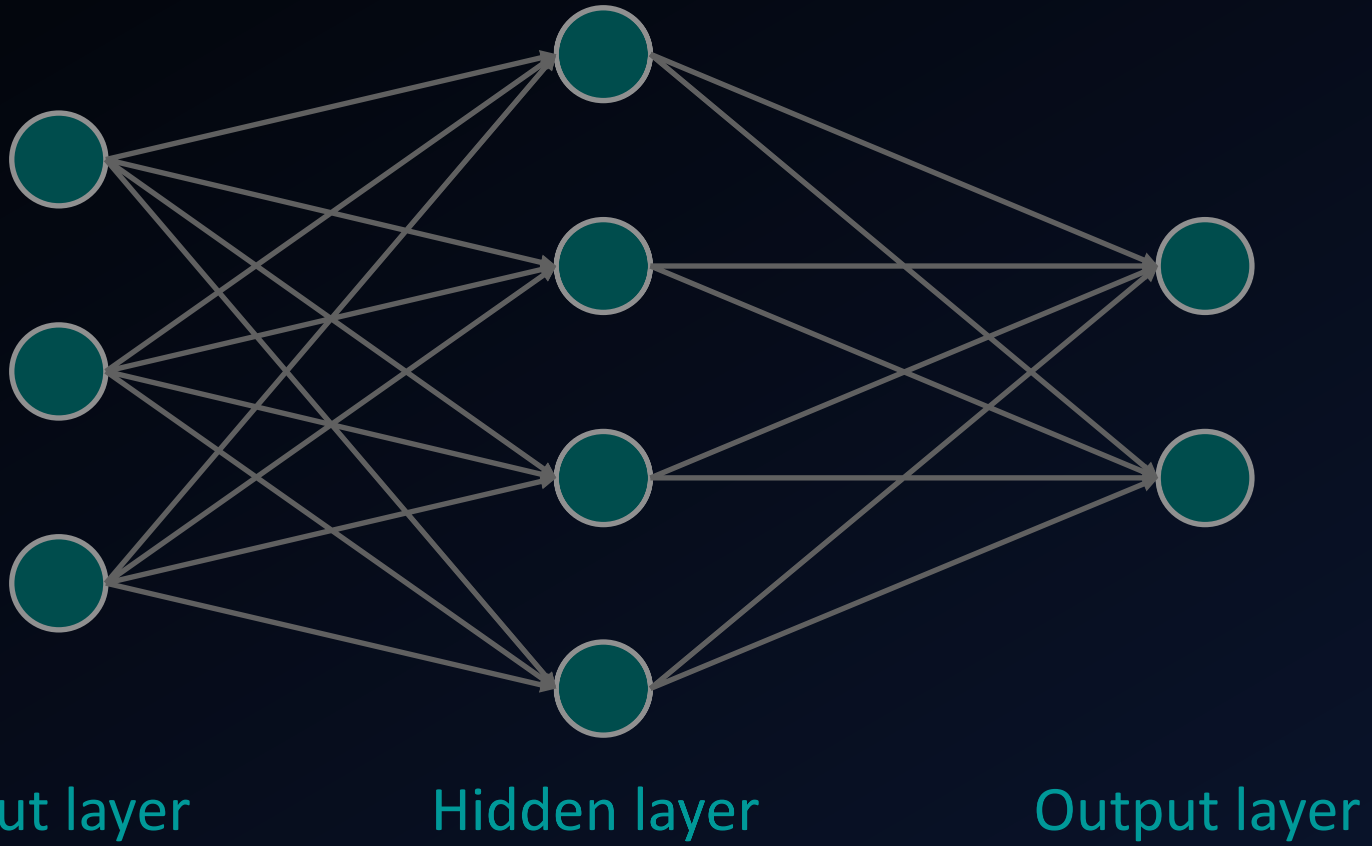
Methods and Materials - Neural Network

Artificial Neural Network



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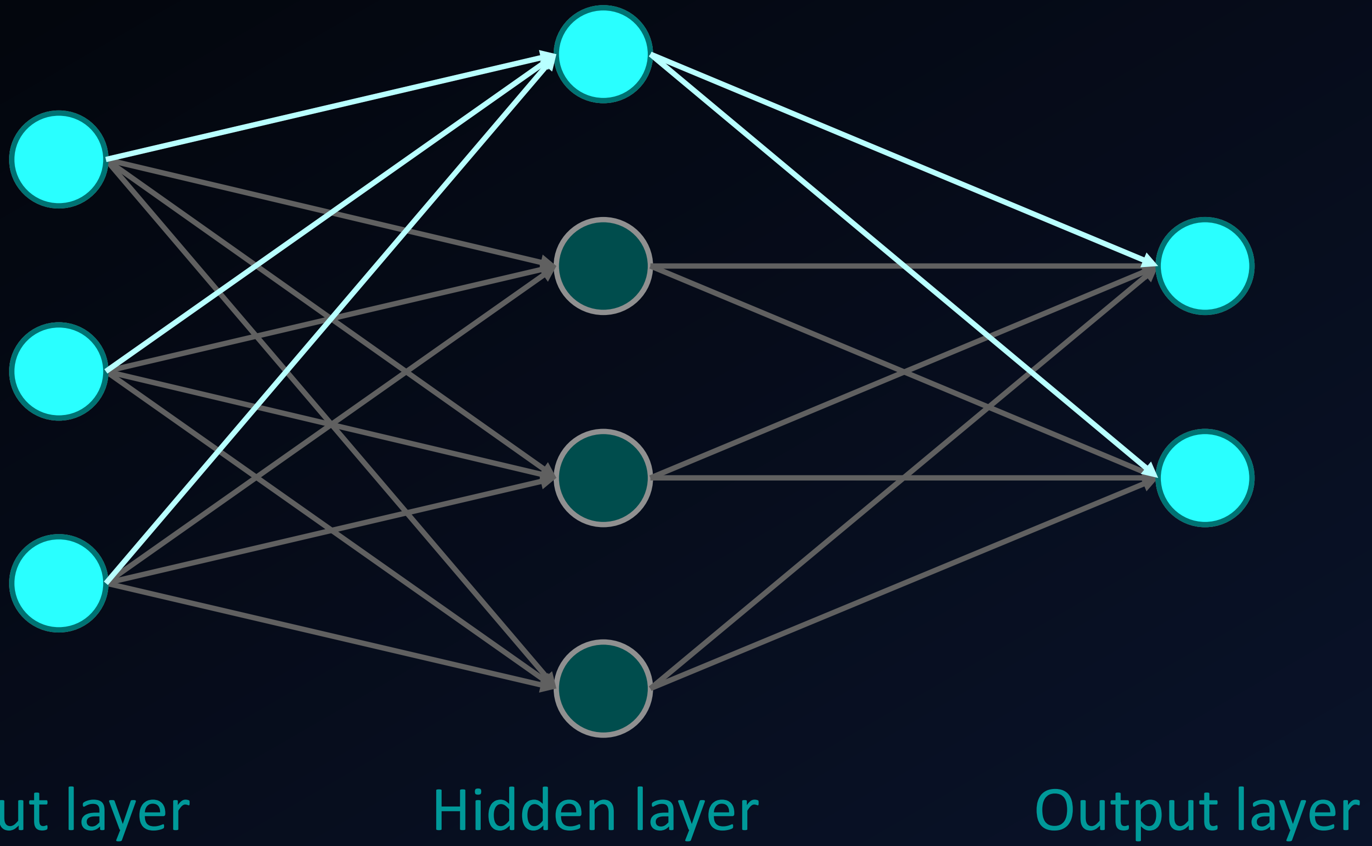
Methods and Materials - Neural Network

Artificial Neural Network



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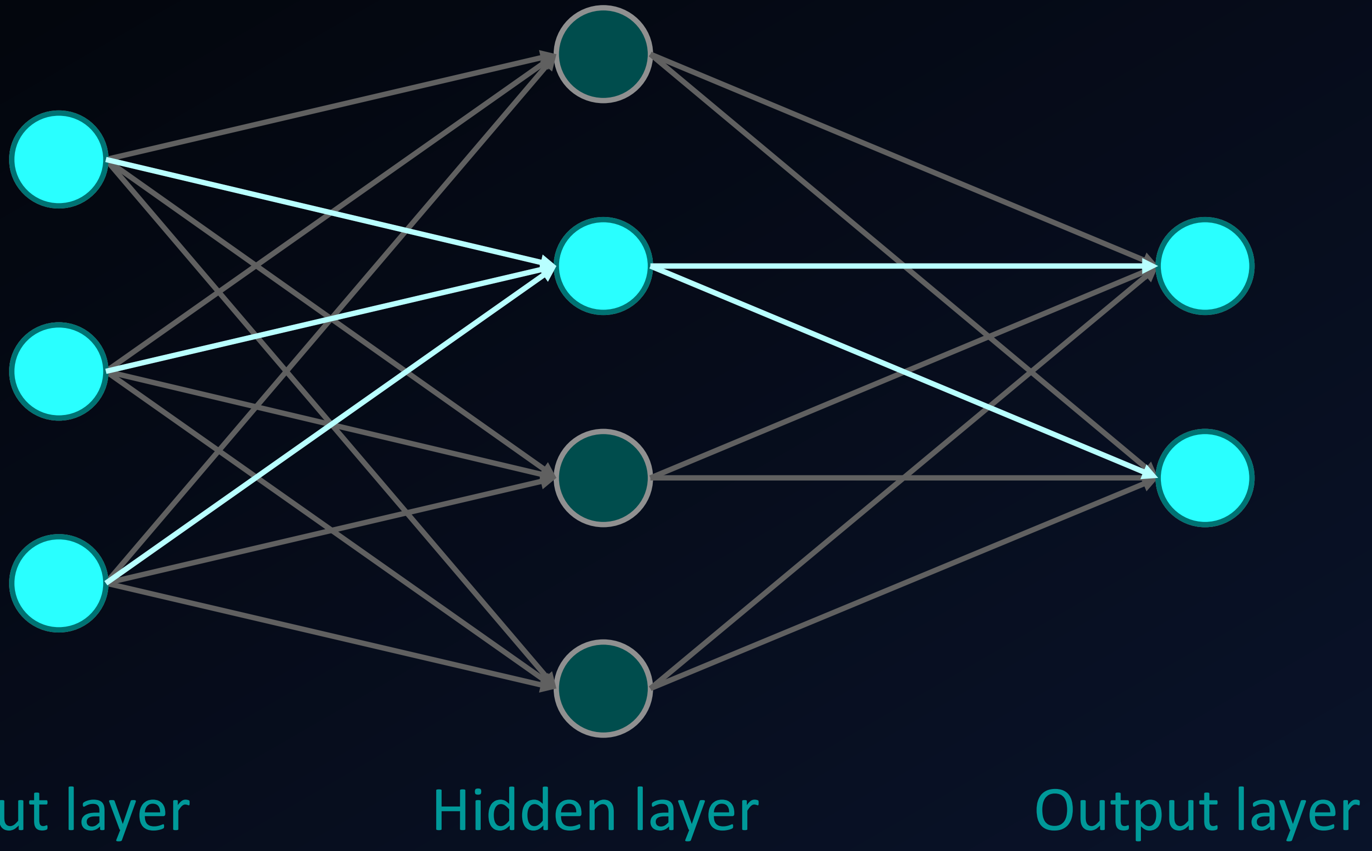
Methods and Materials - Neural Network

Artificial Neural Network



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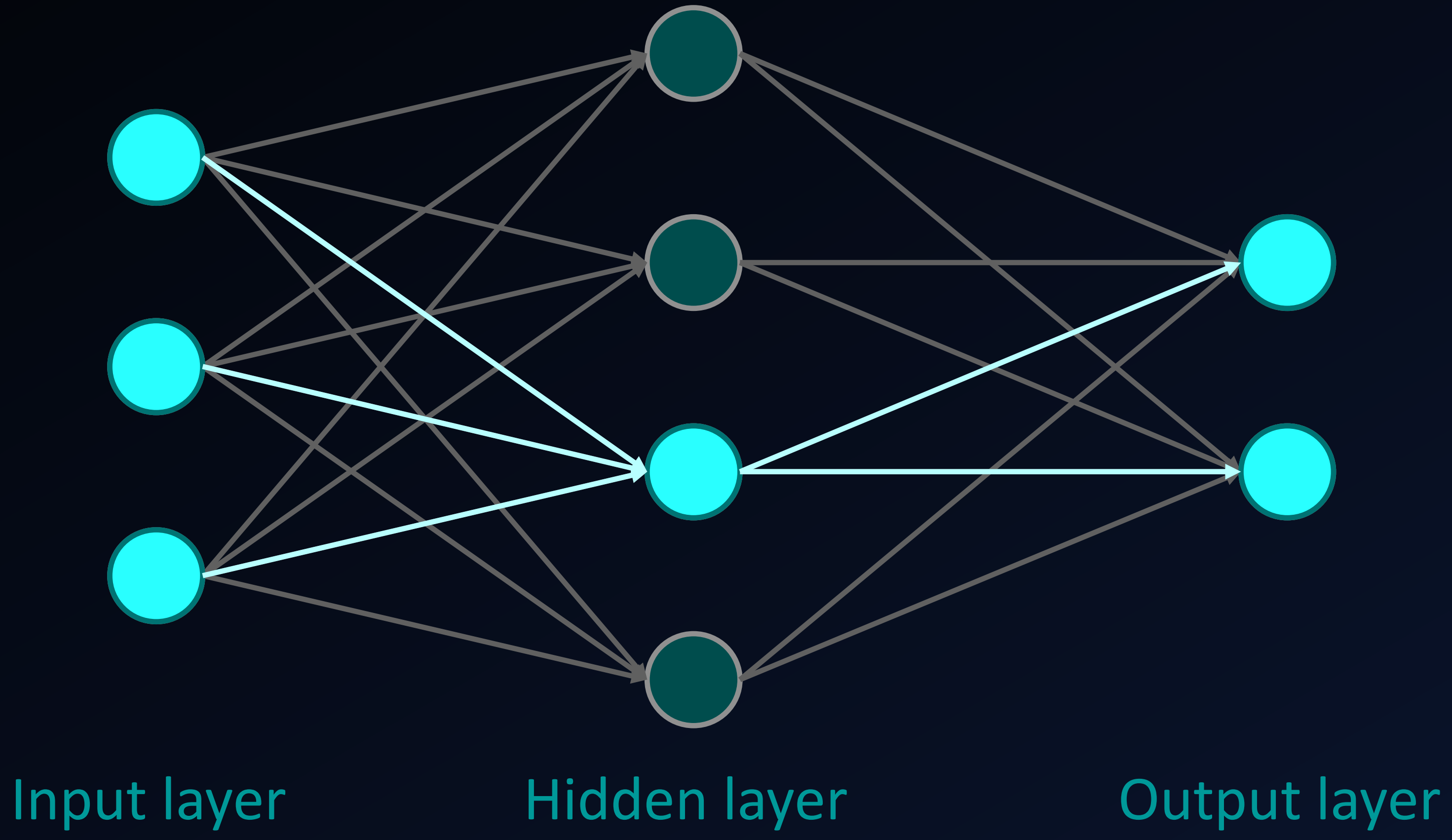
Methods and Materials - Neural Network

Artificial Neural Network



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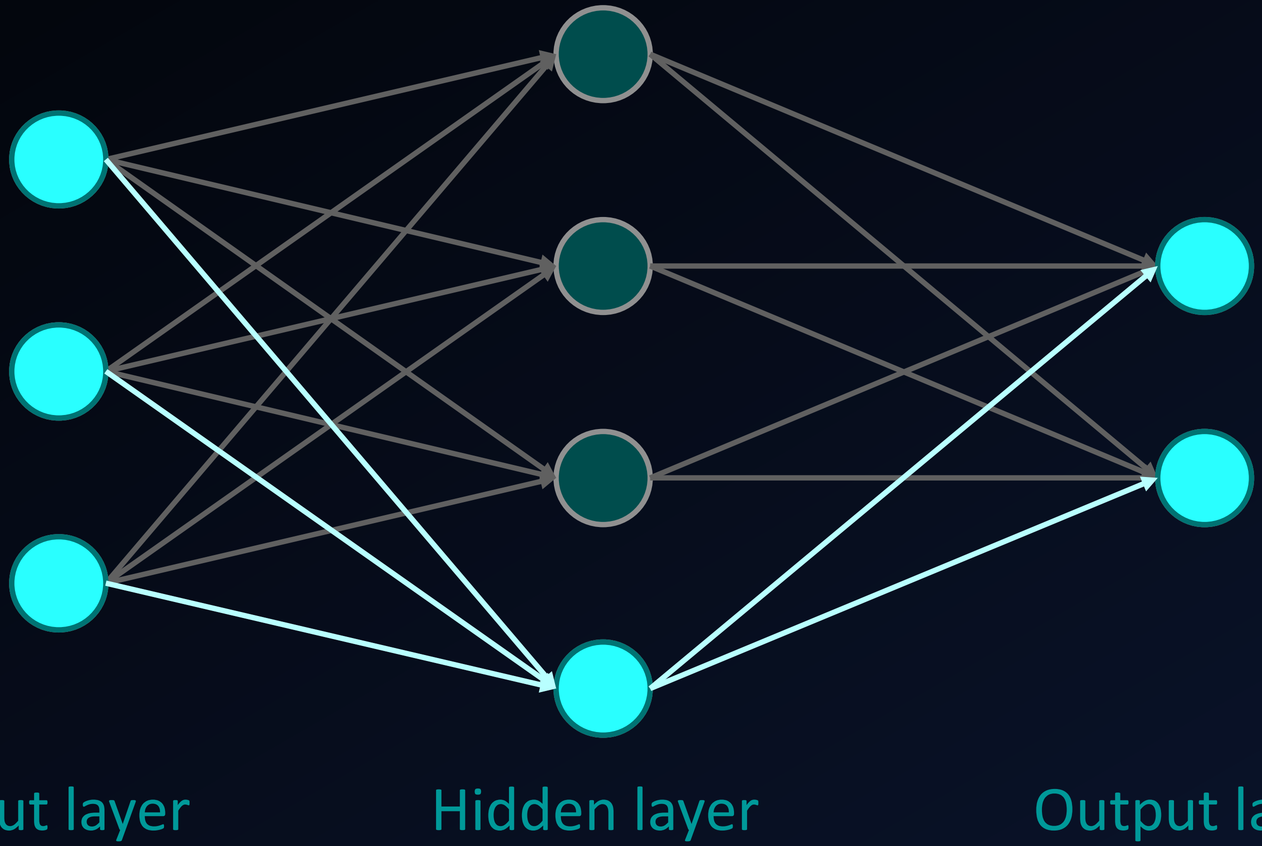
Methods and Materials - Neural Network

Artificial Neural Network



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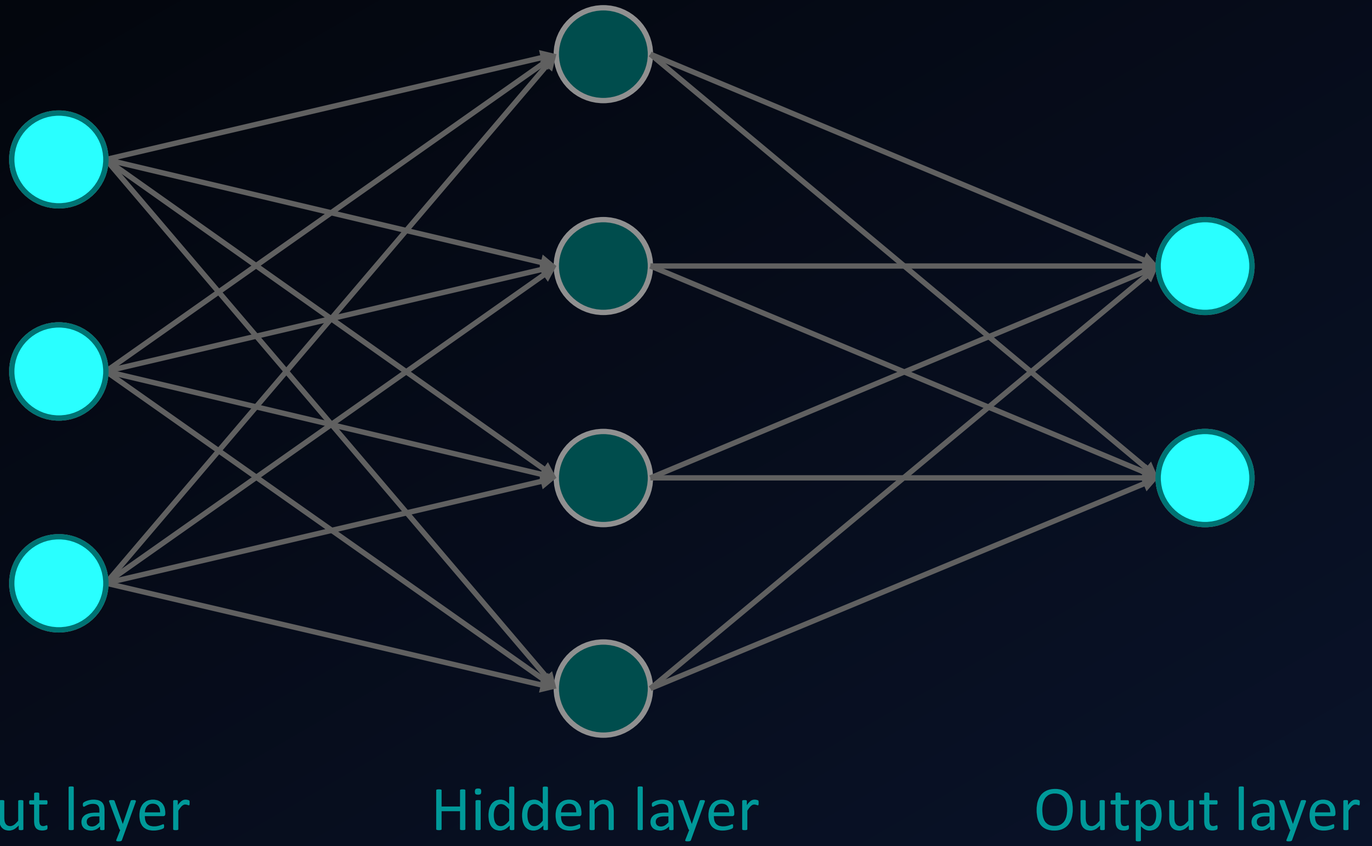
Methods and Materials - Neural Network

Artificial Neural Network



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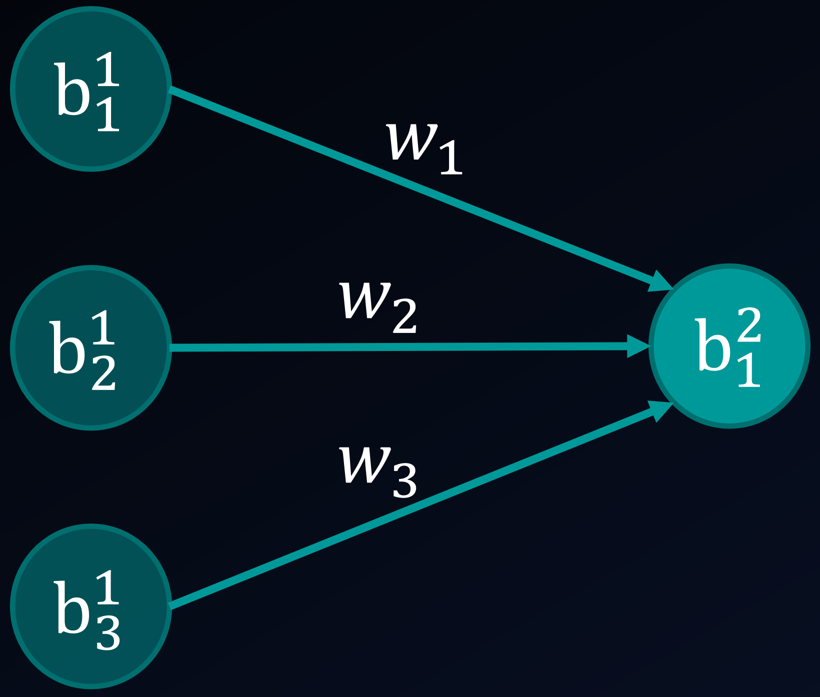
Methods and Materials - Neural Network

Backpropagation



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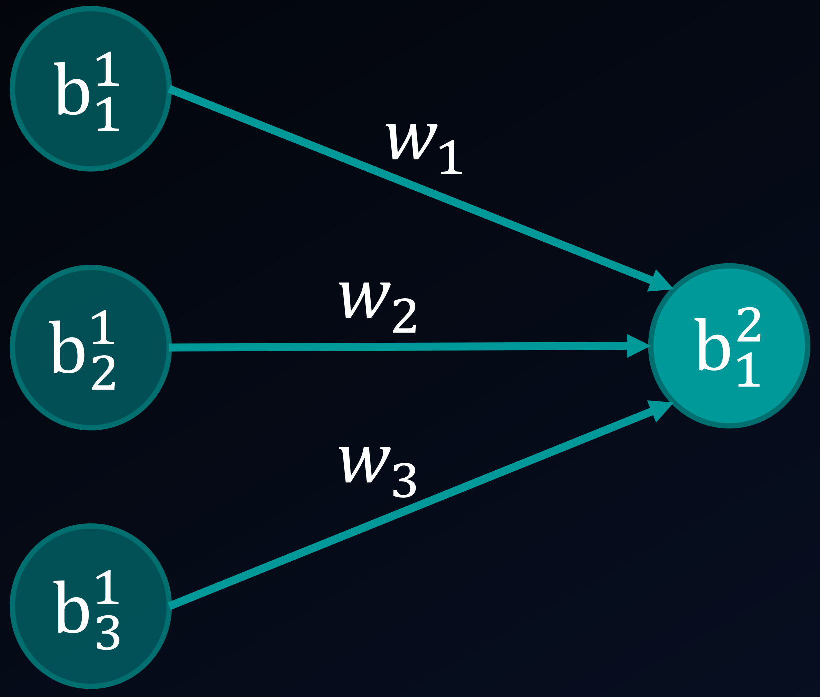
Methods and Materials - Neural Network

Backpropagation



Cost function

$C(y, \hat{y})$

y : Observed values
$\hat{y}$: Predicted values

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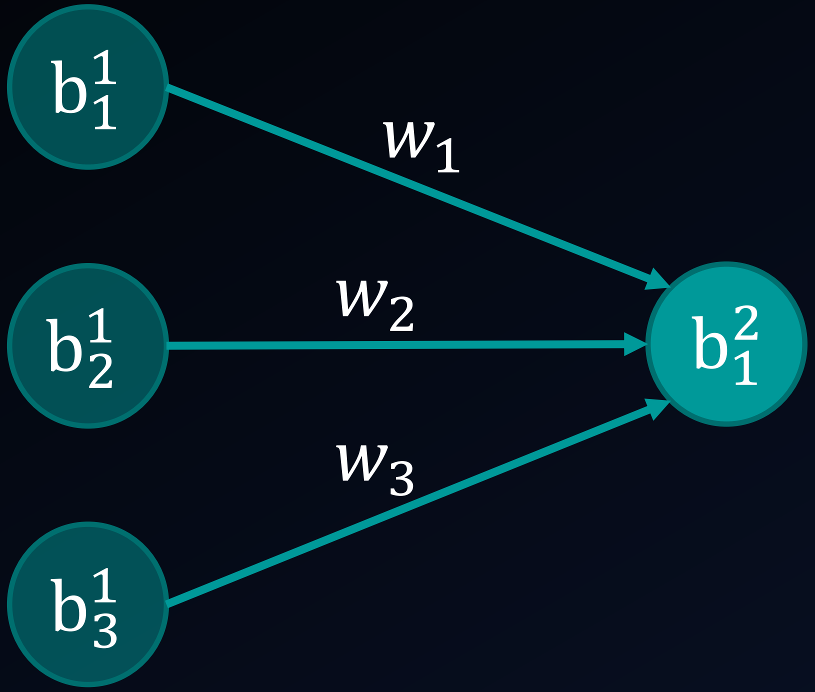
Methods and Materials - Neural Network

Backpropagation



MSE (Mean Squared Error)

$$C(y, \hat{y}) = \frac{1}{n}\sum_{k=0}^{n}(y_k - \widehat{y_k})^2$$

y : Observed values

$\hat{y}$: Predicted values

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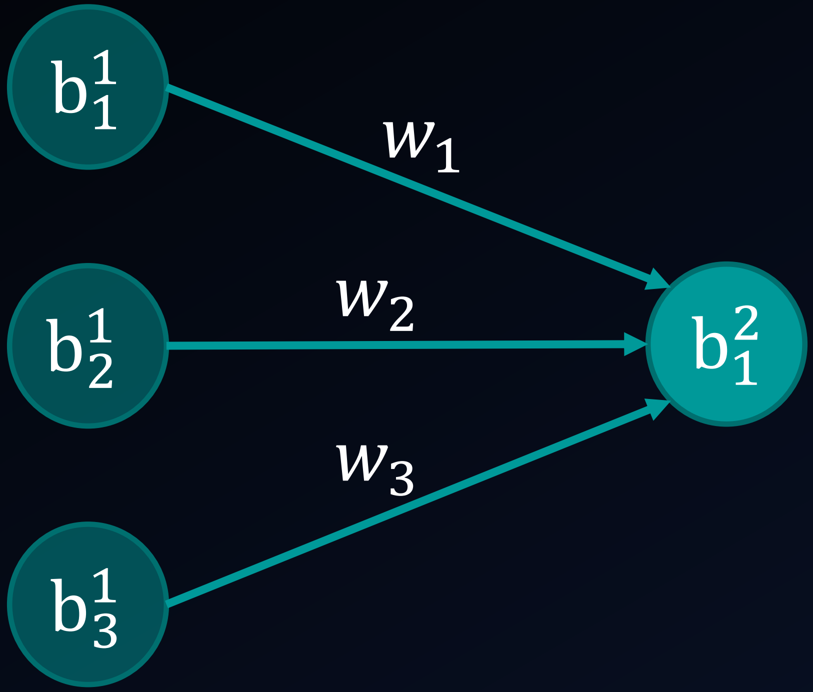
Methods and Materials - Neural Network

Backpropagation



Gradient descent

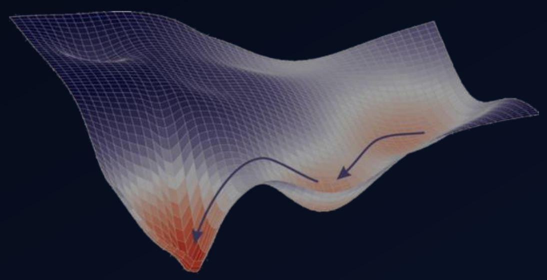


Fig. 4

→ Iteratively find local minima of cost function

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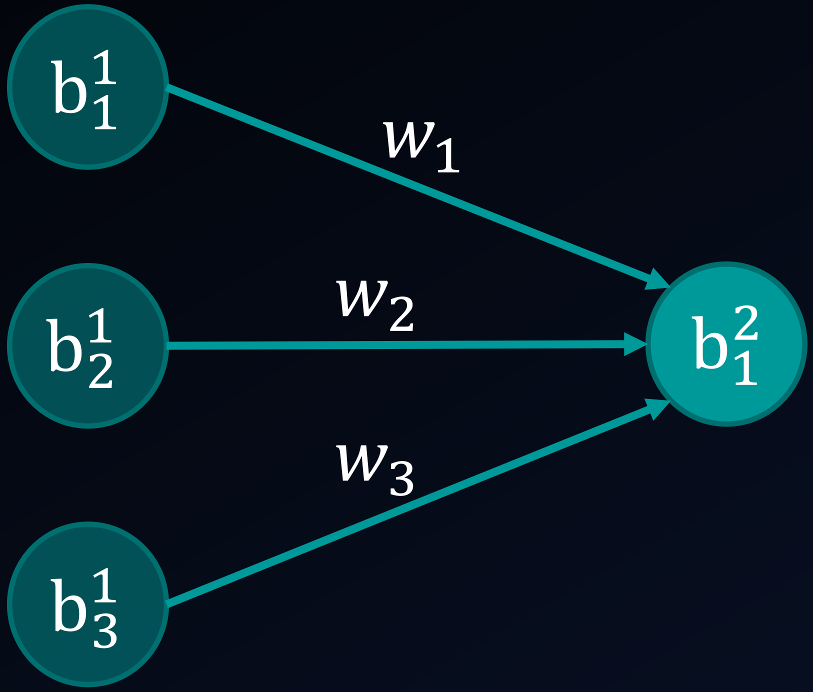
Methods and Materials - Neural Network

Backpropagation



$$\partial C = \begin{pmatrix} \frac{\partial C}{\partial w_1} \\ \frac{\partial C}{\partial w_2} \\ \frac{\partial C}{\partial w_3} \\ \frac{\partial C}{\partial b_1^2} \\ \dots \end{pmatrix}$$

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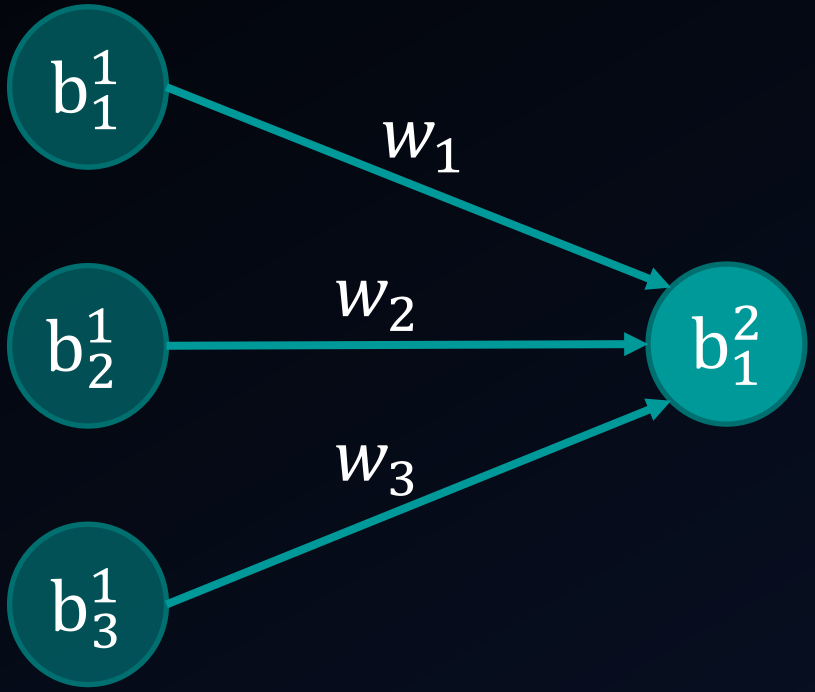
Methods and Materials - Neural Network

Backpropagation



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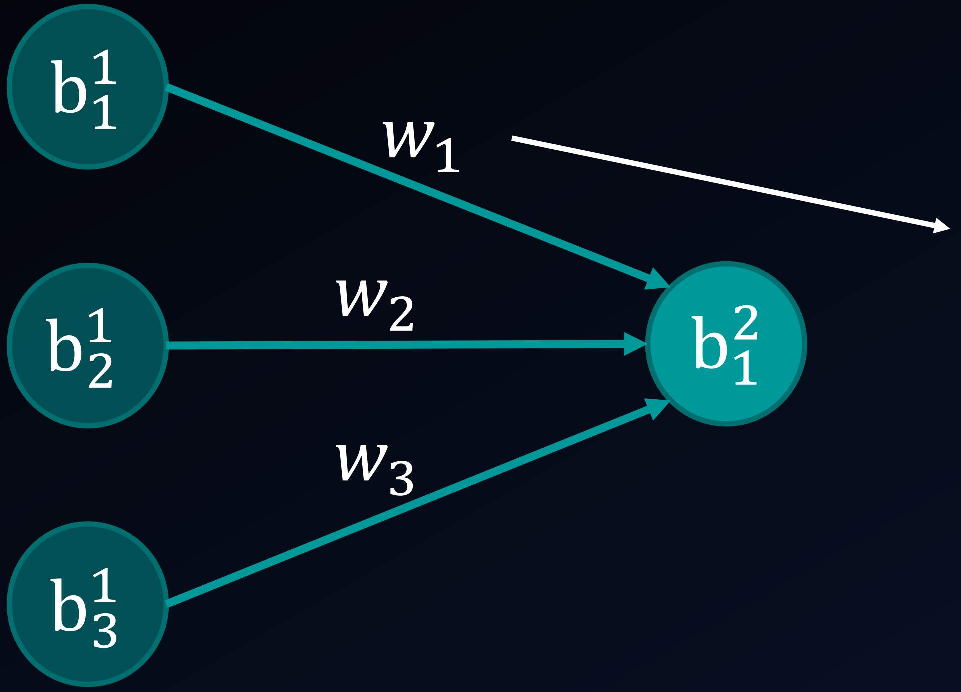
Methods and Materials - Neural Network

Backpropagation



$w_{1_{(t+1)}} =$

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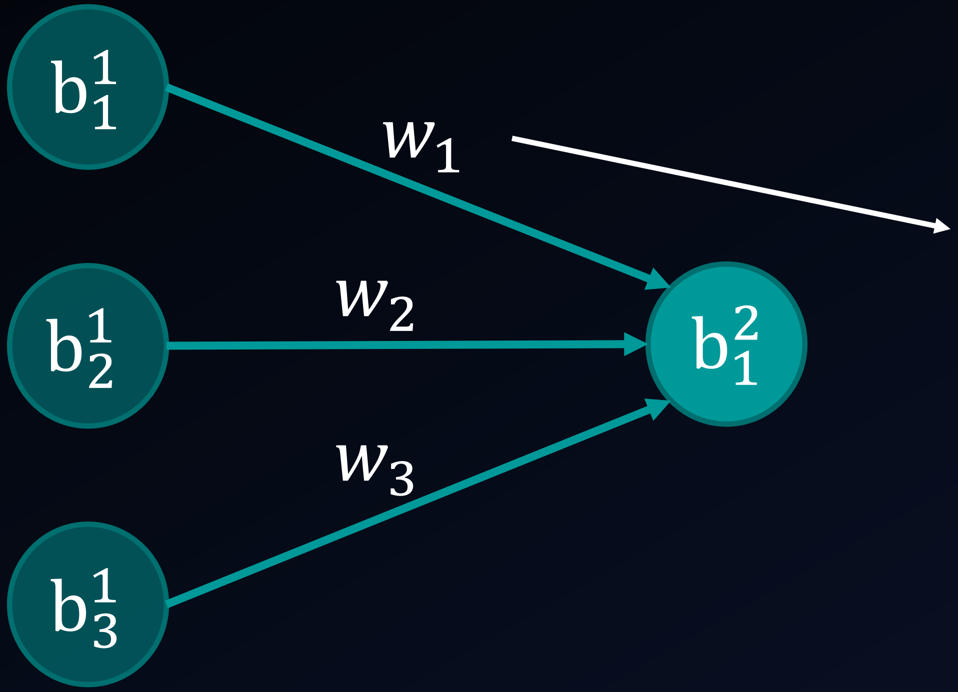
Methods and Materials - Neural Network

Backpropagation



$$w_{1_{(t+1)}} = w_{1_{(t)}}$$

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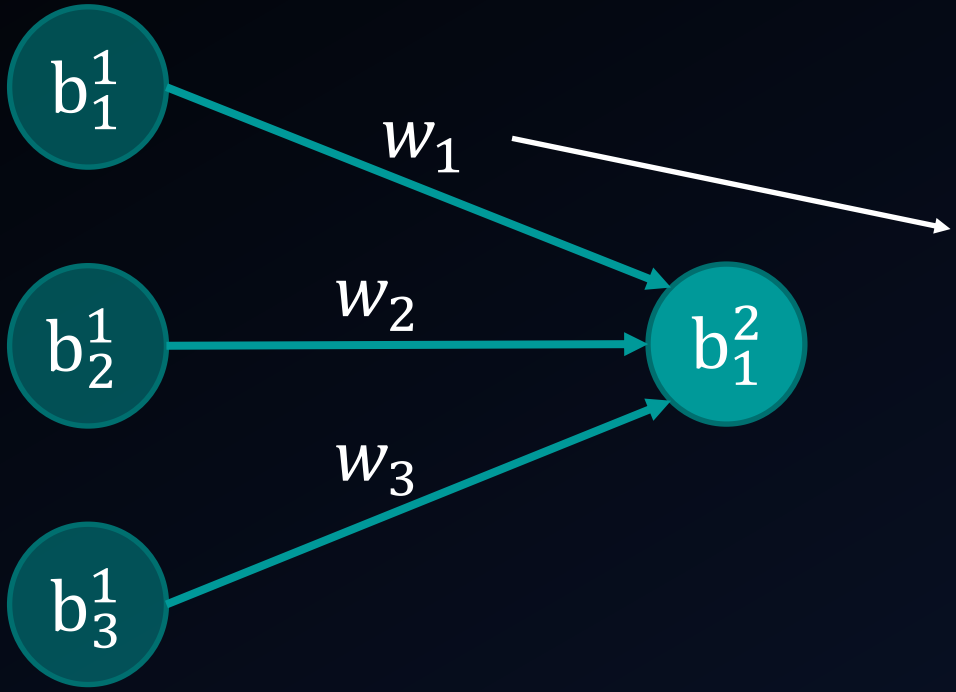
Methods and Materials - Neural Network

Backpropagation



$$w_{1_{(t+1)}} = w_{1_{(t)}} - \frac{\partial C_{(t)}}{\partial w_{1_{(t)}}}$$

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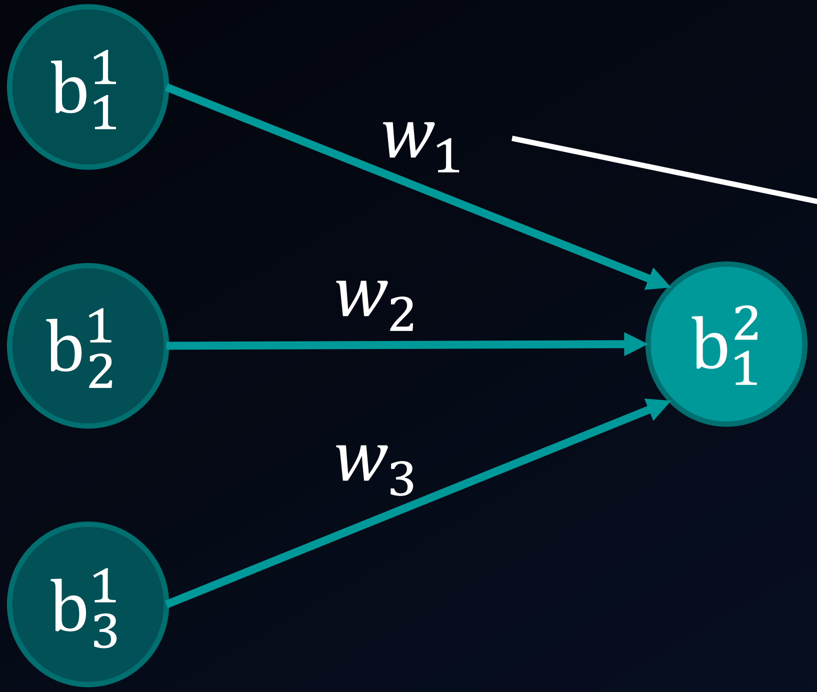
Methods and Materials - Neural Network

Backprojection



$$w_{1_{(t+1)}} = w_{1_{(t)}} - \frac{\partial C_{(t)}}{\partial w_{1_{(t)}}}$$

$$b^2_{1_{(t+1)}} =$$

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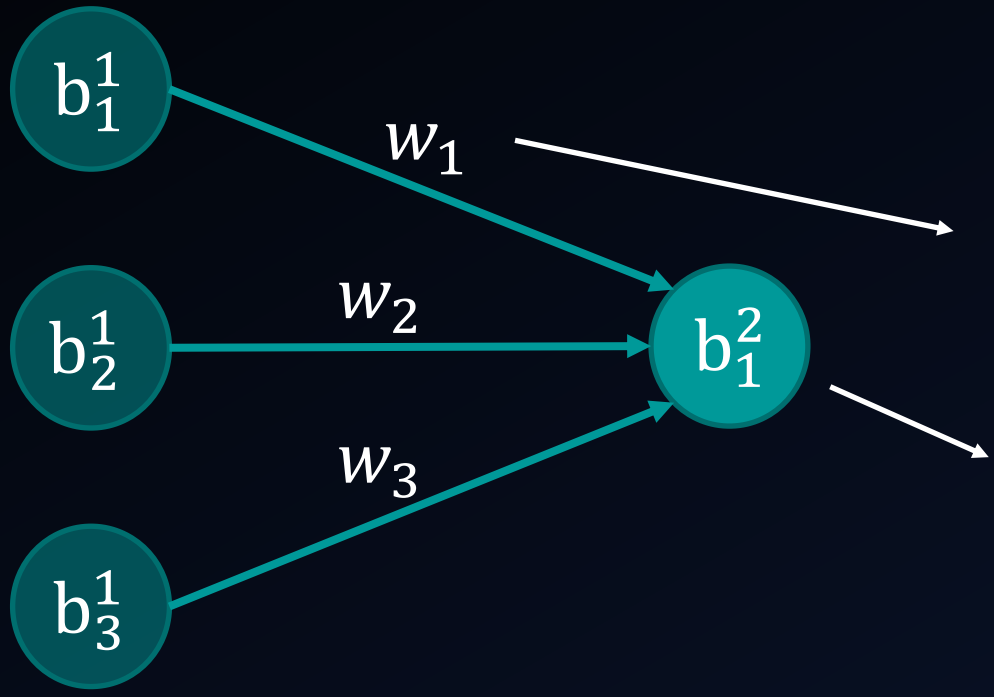
Methods and Materials - Neural Network

Backpropagation



$$w_{1(t+1)} = w_{1(t)} - \frac{\partial C_{(t)}}{\partial w_{1(t)}}$$

$$b^2_{1(t+1)} = b^2_{1(t)}$$

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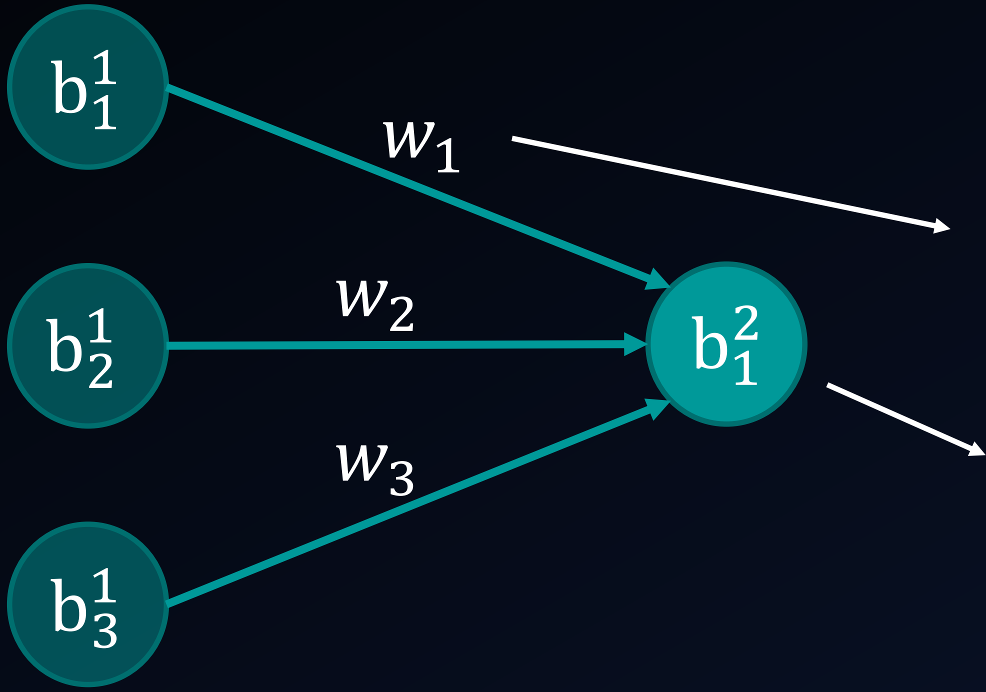
Methods and Materials - Neural Network

Backpropagation



$$w_{1(t+1)} = w_{1(t)} - \frac{\partial C_{(t)}}{\partial w_{1(t)}}$$

$$b^2_{1(t+1)} = b^2_{1(t)} - \frac{\partial C_{(t)}}{\partial b^2_{1(t)}}$$

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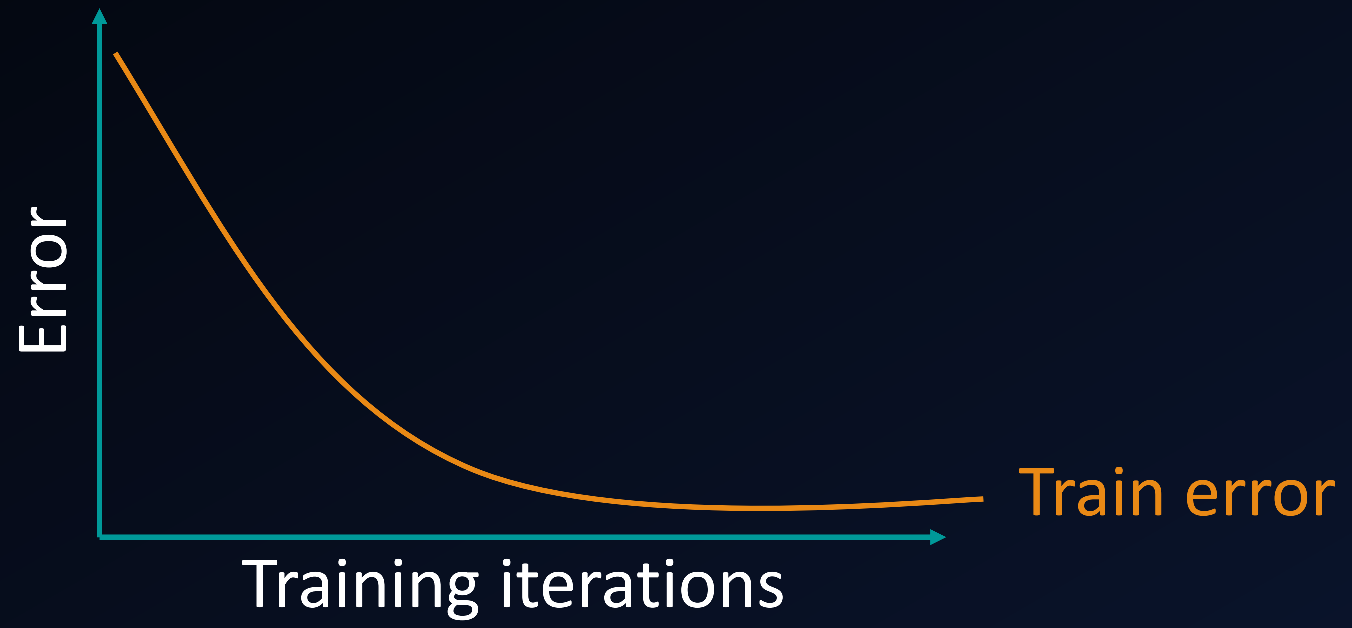
Methods and Materials - Neural Network

Training

Methods and Materials - Neural Network

Training



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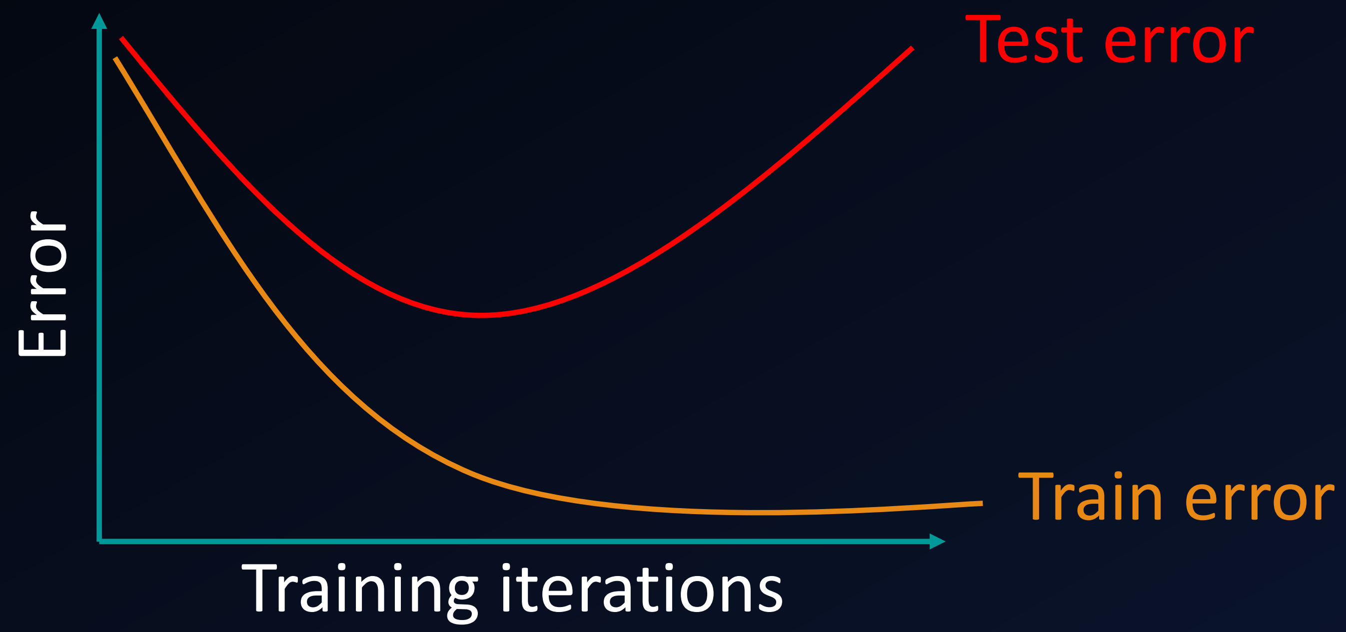
Methods and Materials - Neural Network

Training



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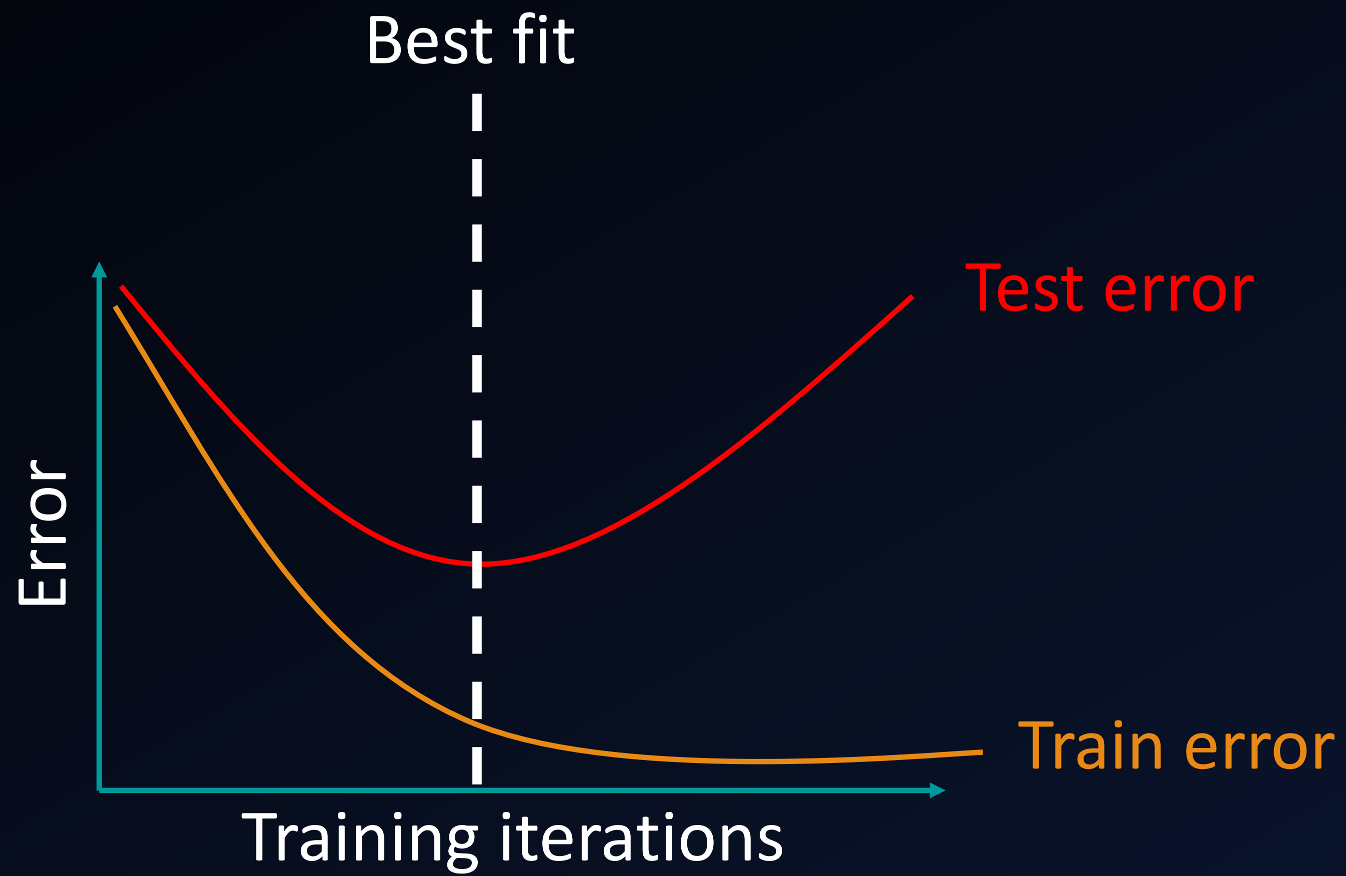
Methods and Materials - Neural Network

Training



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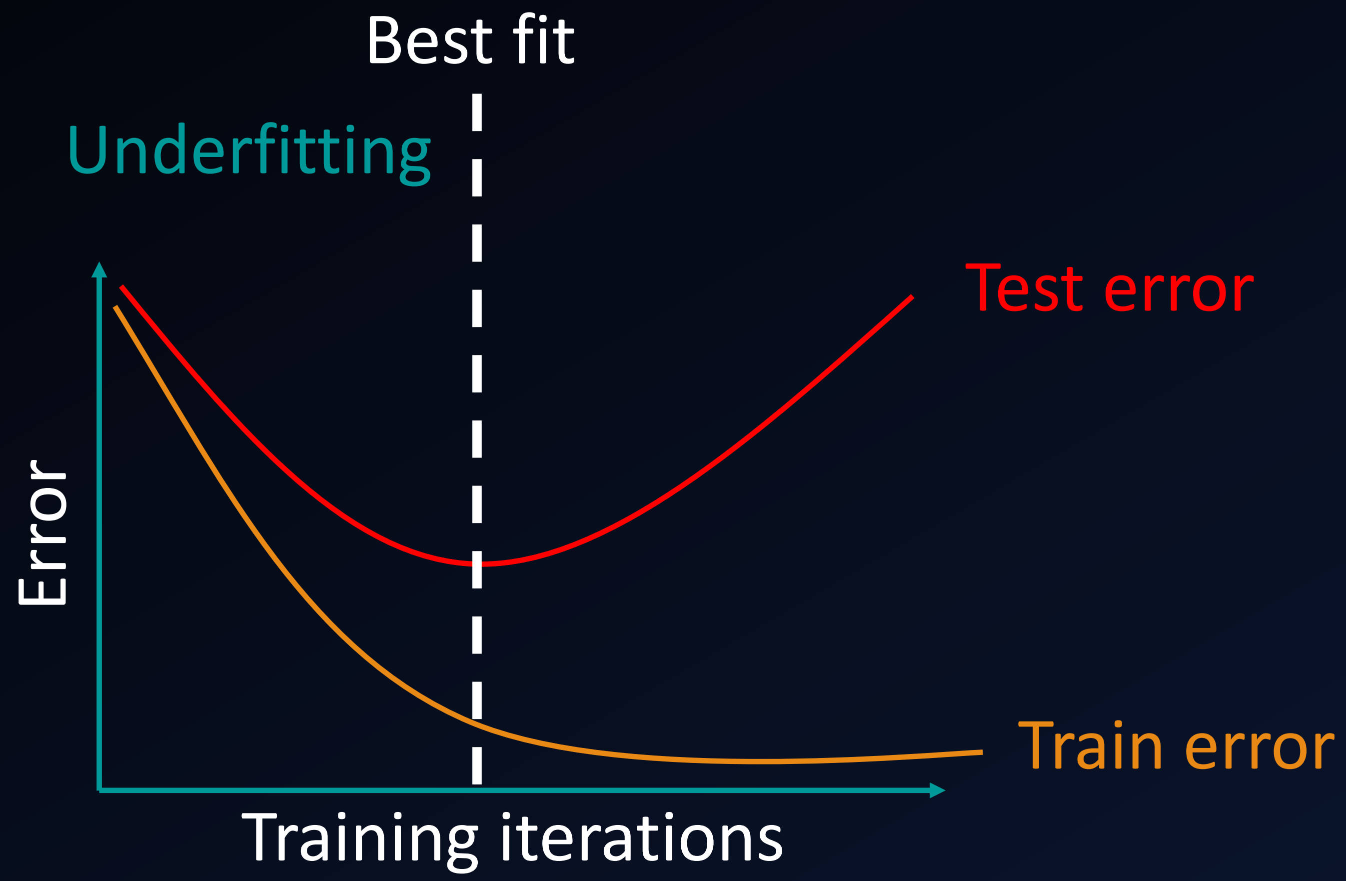
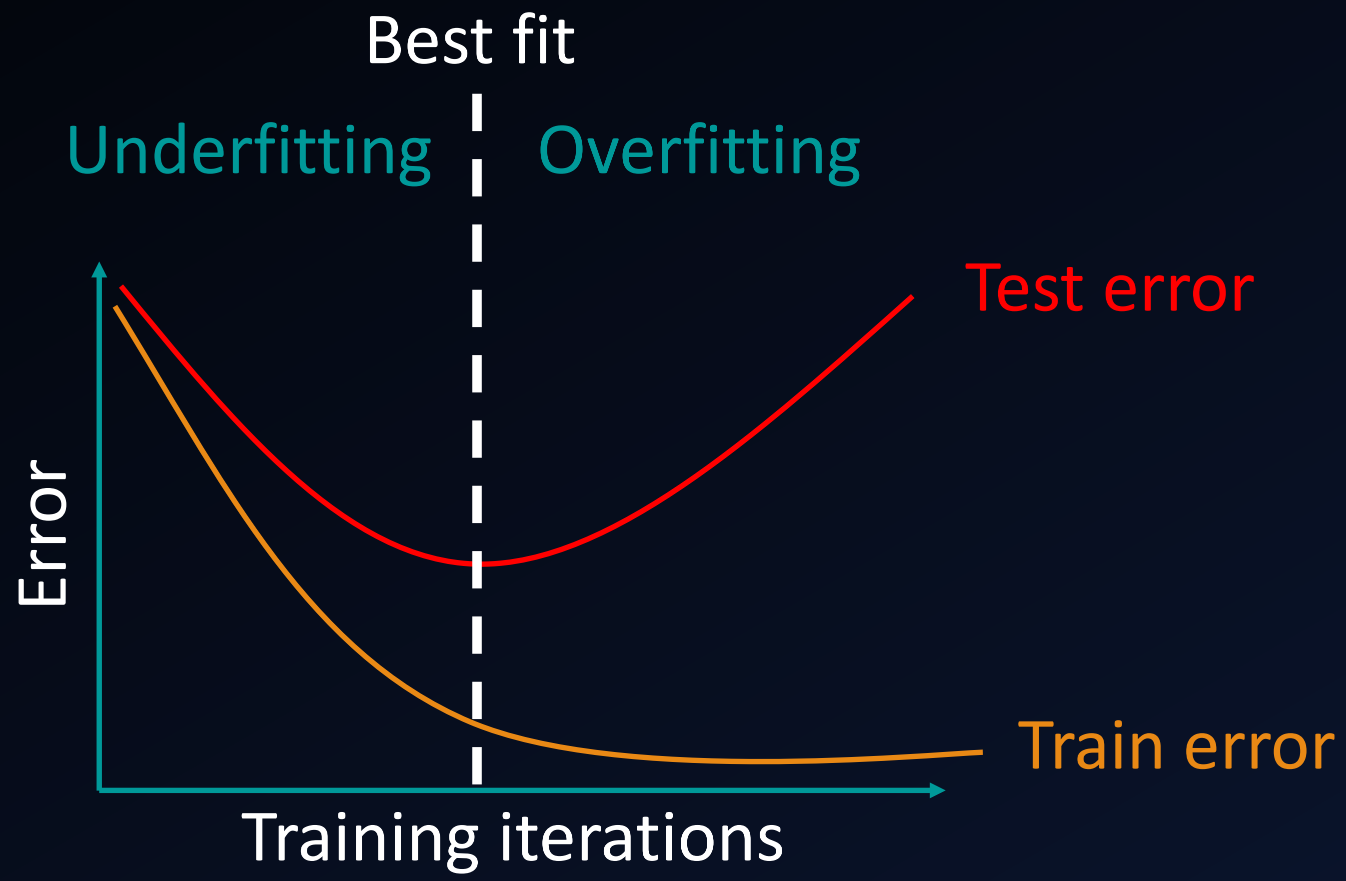
Methods and Materials - Neural Network

Training



Methods and Materials - Neural Network

Training



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Methods and Materials - Neural Network

Training

So how to teach?

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Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation

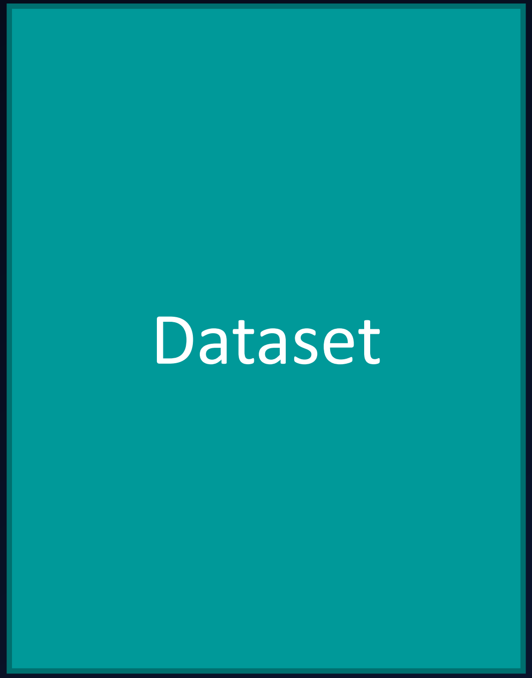
32

Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation



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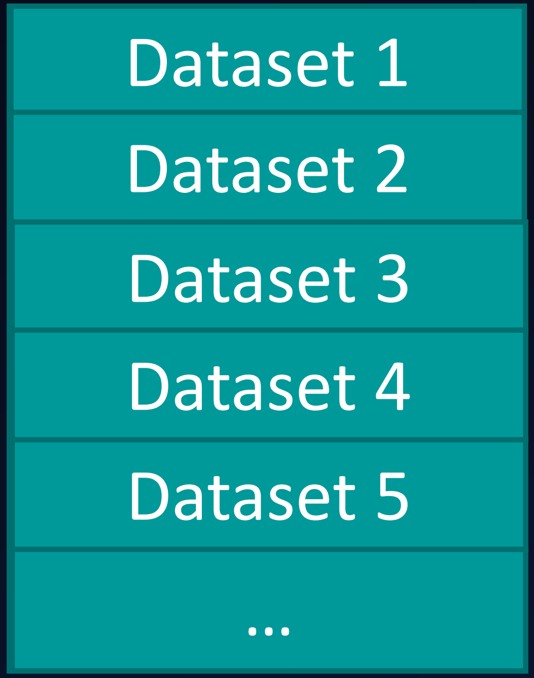
Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation

1. Partition data



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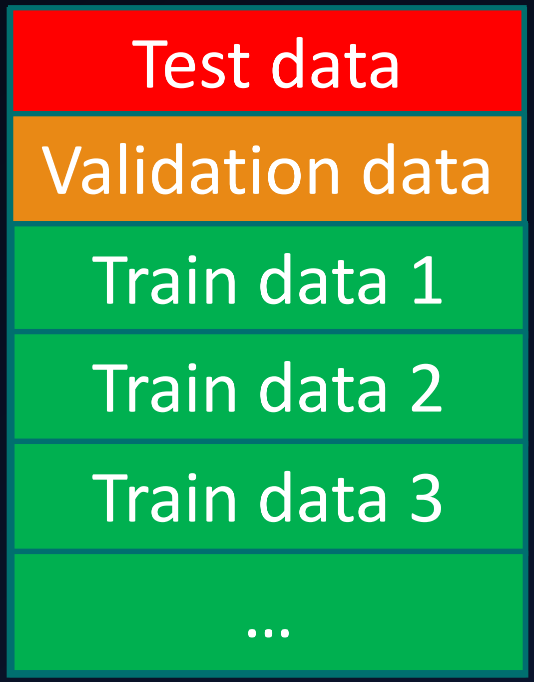
Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation

1. Partition data
2. Declare test-, validation- and train- datasets



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Methods and Materials - Neural Network

Training

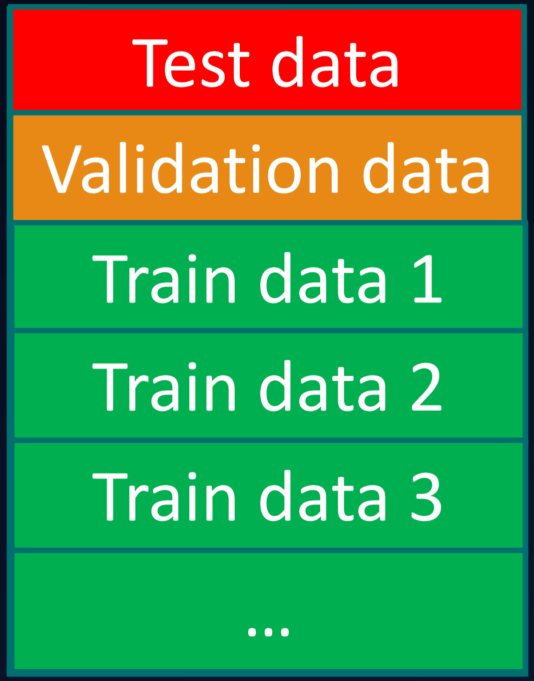
So how to teach?

- Cross validation

1. Partition data

2. Declare test-, validation- and train- datasets

4. Train on the train data



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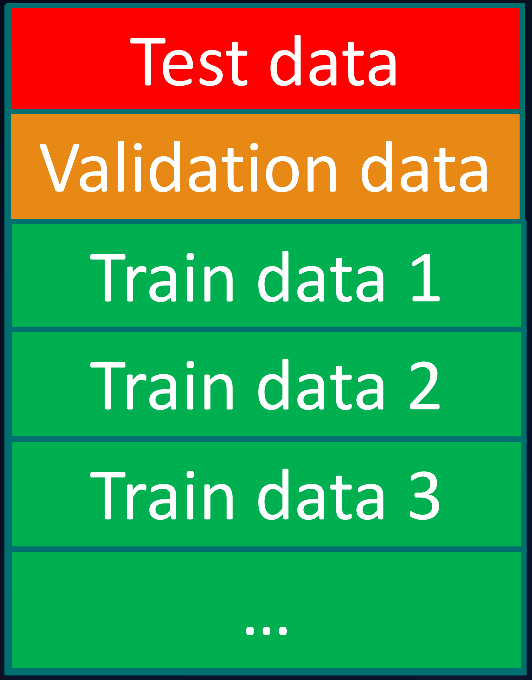
Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation

1. Partition data
2. Declare test-, validation- and train- datasets
4. Train on the train data
5. After each iteration check progress on the validation data



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Methods and Materials - Neural Network

Training

So how to teach?

- Cross validation

1. Partition data
2. Declare test-, validation- and train- datasets
4. Train on the train data
5. After each iteration check progress on the validation data
6. Finally test the model on the test data

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Methods and Materials - Neural Network

8 Fold - Cross Validation

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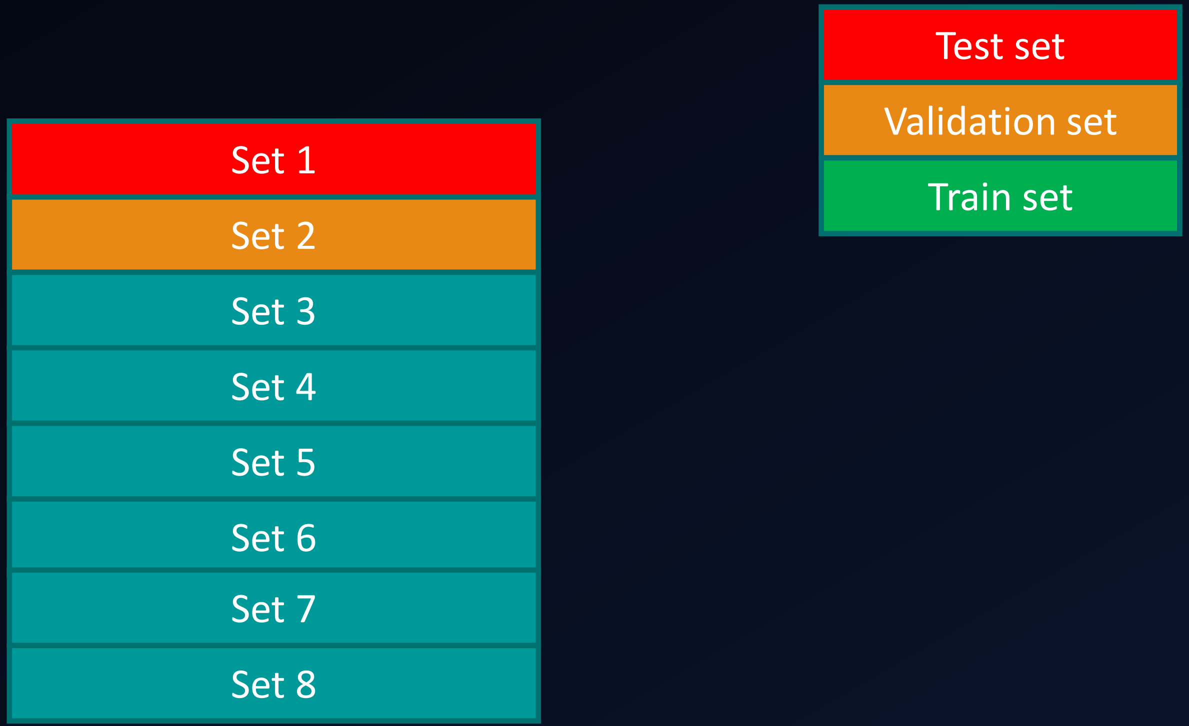
Methods and Materials - Neural Network

8 Fold - Cross Validation



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Methods and Materials - Neural Network

8 Fold - Cross Validation

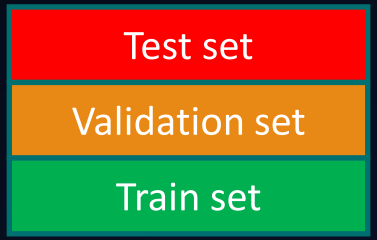
Test set
Validation set
Train set

Set 1
Set 2
Set 3
Set 4
Set 5
Set 6
Set 7
Set 8

33

Methods and Materials - Neural Network

8 Fold - Cross Validation



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Methods and Materials - Neural Network

8 Fold - Cross Validation

33

Methods and Materials - Neural Network

8 Fold - Cross Validation

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Methods and Materials - Neural Network

8 Fold - Cross Validation

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Methods and Materials - Neural Network

8 Fold - Cross Validation

33

Methods and Materials - Neural Network

8 Fold - Cross Validation

Test set

Validation set

Train set

Set 1

Set 2

Set 3

Set 4

Set 5

Set 6

Set 7

Set 8

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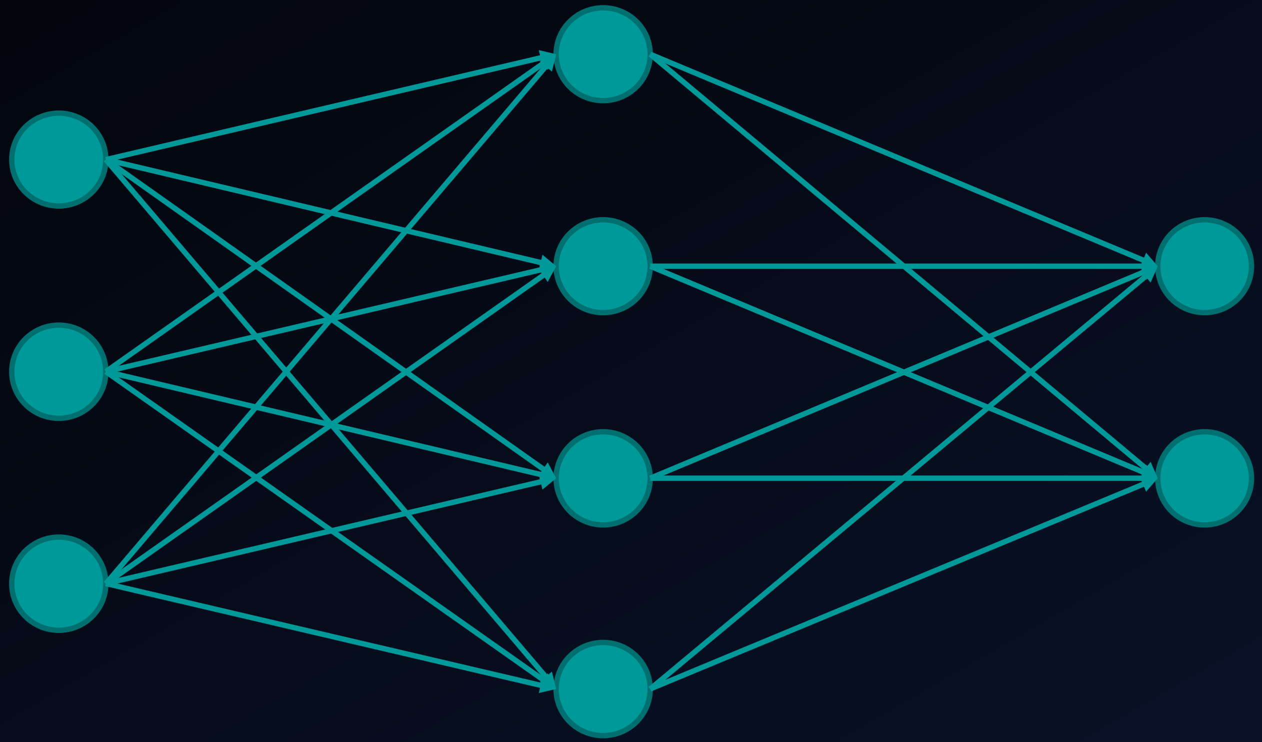
Methods and Materials - Neural Network



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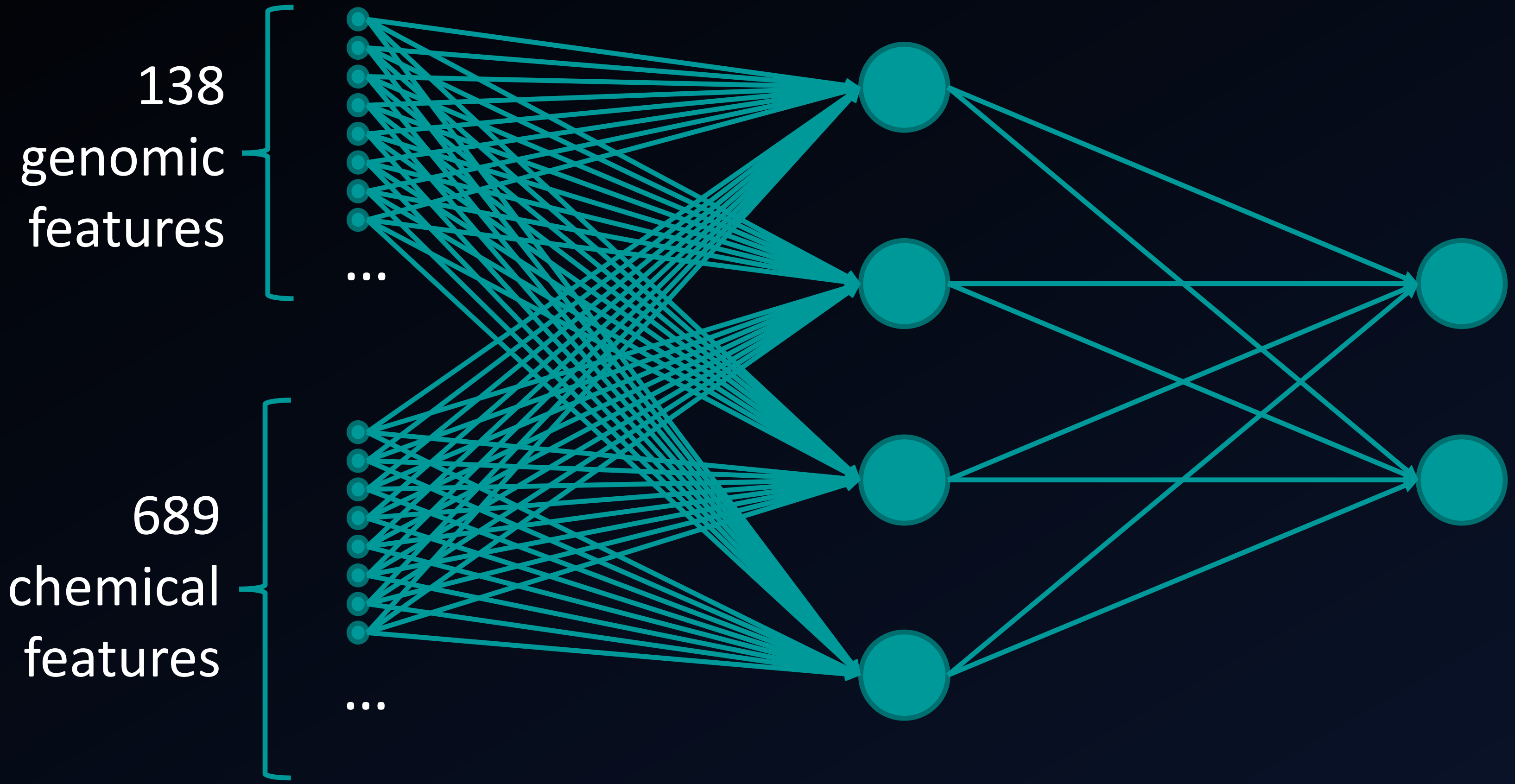
Methods and Materials - Neural Network



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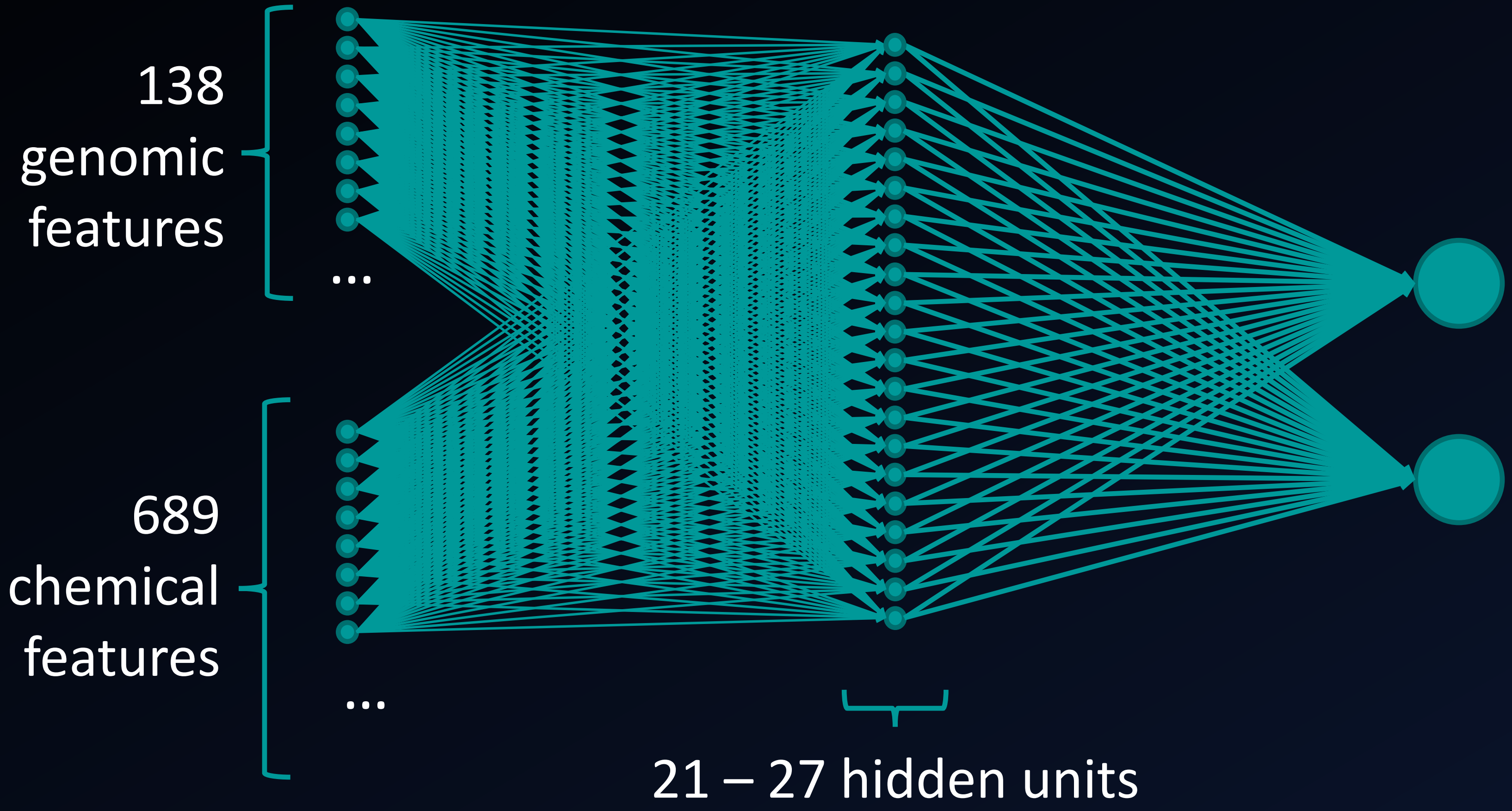
Methods and Materials - Neural Network



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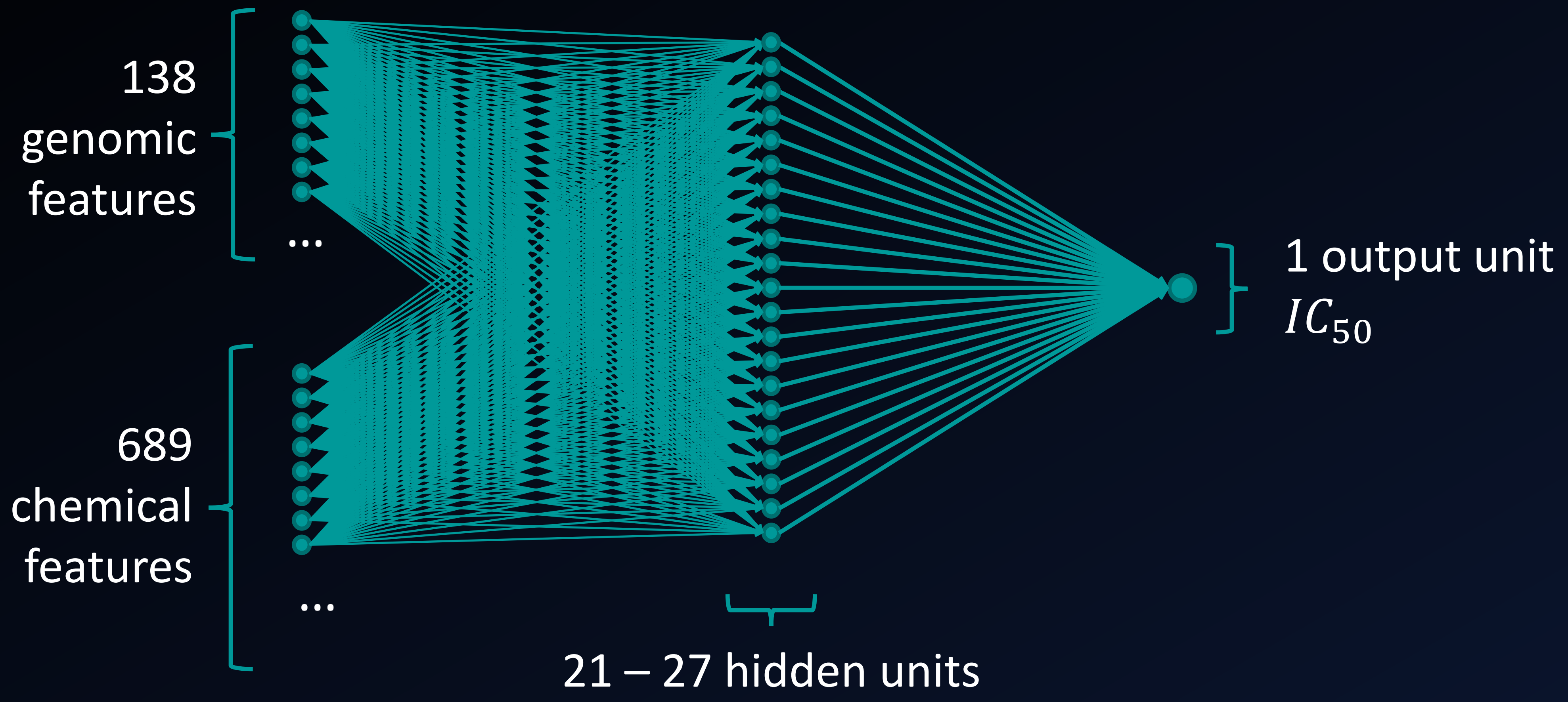
Methods and Materials - Neural Network



Structure

- Motivation
- Introduction
- Methods and Materials
  - Dataset
  - Feature Selection
  - Neural Network
  - Cross Validation
- **Results**
- Summary & Conclusion
- Discussion

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Results

Evaluation criteria

41

Results

Evaluation criteria

- Pearson correlation coefficient (R_p)

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Results

Evaluation criteria

- Pearson correlation coefficient (R_p) → [-1,1]

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Results

Evaluation criteria

- Pearson correlation coefficient (R_p) → [-1,1]

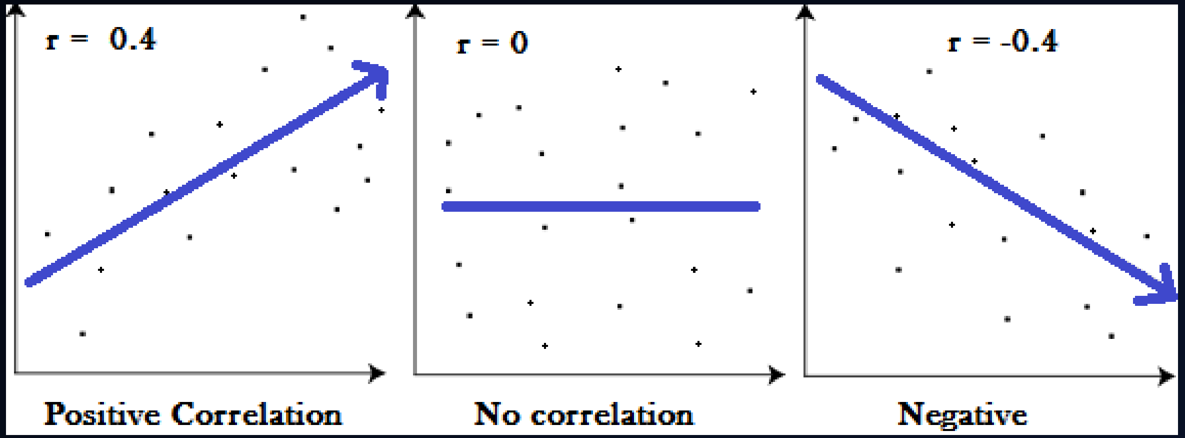

Fig. 6

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Results

Evaluation criteria

- Root Mean Squared Error (RMSE)

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Results

Evaluation criteria

- Root Mean Squared Error (RMSE)

$$\mathrm{RMSE}(y, \hat{y}) = \sqrt{\frac{1}{n} \sum_{i=0}^{n} (y_i - \hat{y}_i)^2}$$

y : Observed values
$\hat{y}$: Predicted values
n : Number of values

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Results

Evaluation criteria

- Root Mean Squared Error (RMSE) → [0,∞[

$$\mathrm{RMSE}(y, \hat{y}) = \sqrt{\frac{1}{n} \sum_{i=0}^{n} (y_i - \hat{y}_i)^2}$$

y : Observed values
$\hat{y}$: Predicted values
n : Number of values

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Results

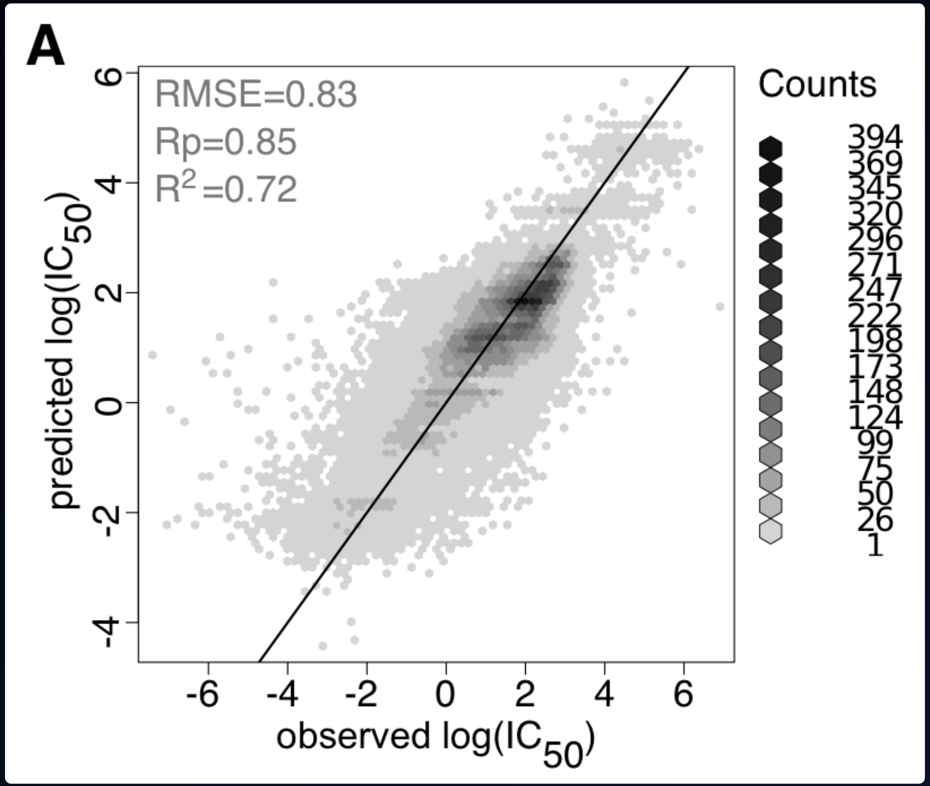

Fig. 7

$RMSE = 0.83$

$R_p = 0.85$

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Results

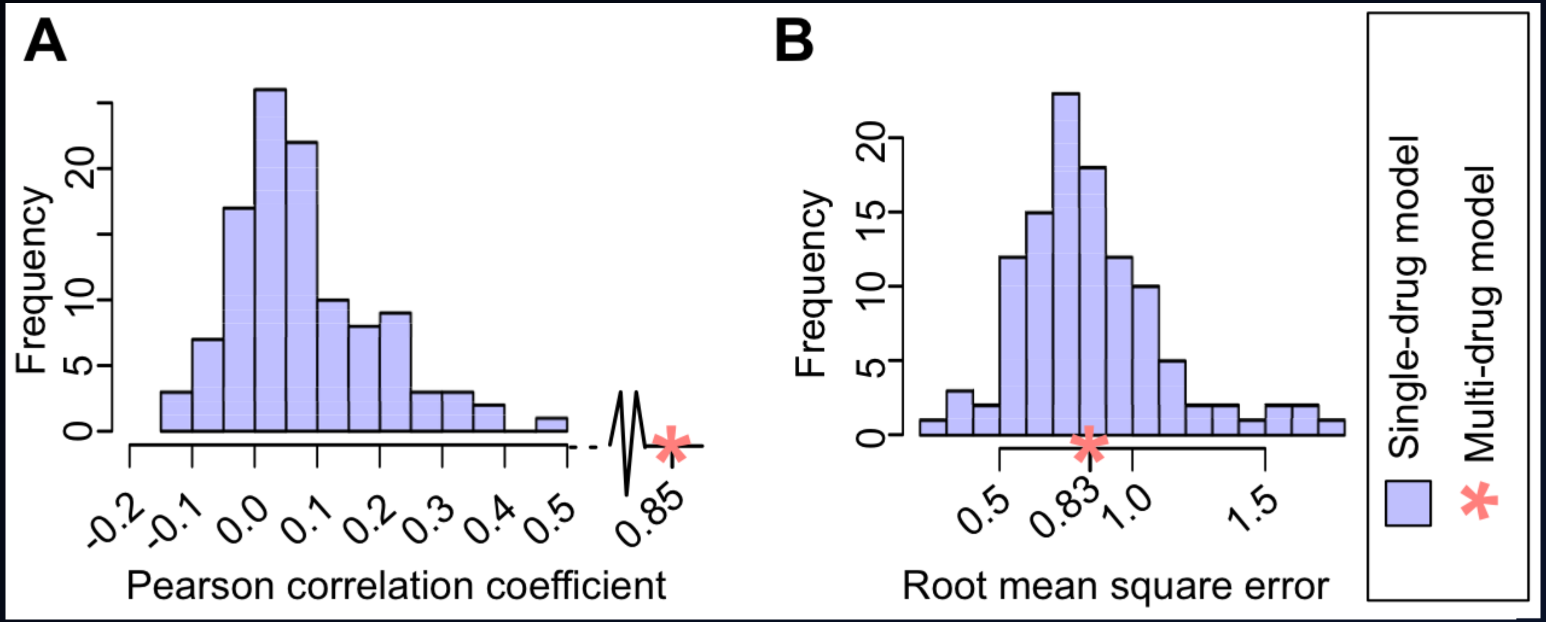

Fig. 8

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Structure

- Motivation
- Introduction
- Methods and Materials
  - Dataset
  - Feature Selection
  - Neural Network
  - Cross Validation
- Results
- **Summary & Conclusion**
- Discussion

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Summary and Conclusion

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Summary and Conclusion

- Multi-drug-models are more predictive

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Summary and Conclusion

- Multi-drug-models are more predictive
- Still not reliable

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Summary and Conclusion

- Multi-drug-models are more predictive
- Still not reliable
- Considering chemical features in machine learning seems to be a reasonable decision

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Structure

- Motivation
- Introduction
- Methods and Materials
  - Dataset
  - Feature Selection
  - Neural Network
  - Cross Validation
- Results
- Summary/Conclusion
- **Discussion**

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Discussion

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Discussion

- Fill experimental gaps

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Discussion

- Fill experimental gaps
- Drug discovery

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Discussion

- Fill experimental gaps
- Drug discovery
- Personalized treatment

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Thank you for your attention!

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Sources

- Paper: „Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties " By Menden et al. 2013 – https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0061318
- Genomics of Drug Sensitivity in Cancer: https://www.cancerrxgene.org/help#t_pubs
- PaDEL Descriptor: http://www.yapcwsoft.com/dd/padeldescriptor/
- Fig. 1: Screenshot - https://www.cancerrxgene.org/
- Fig. 2: https://www.pngkey.com/detail/u2r5o0u2y3t4i1r5_neuron-png/
- Fig. 3: MartinThoma, CC0, via Wikimedia Commons https://upload.wikimedia.org/wikipedia/commons/5/53/Sigmoid-function-2.svg
- Fig. 4: https://cdn-images-1.medium.com/max/800/1*NRCWfdXa7b-ak2nBtmwRvw.png
- Fig. 5, 7, 8, 9, 10: „Machine Learning Prediction of Cancer Cell Sensitivity to Drugs Based on Genomic and Chemical Properties " By Menden et al. 2013 – https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0061318
- Fig. 6: Statistics How To - https://www.statisticshowto.com/probability-and-statistics/correlation-coefficient-formula/

All links were opened the last time at 21:00 on 08.10.2021

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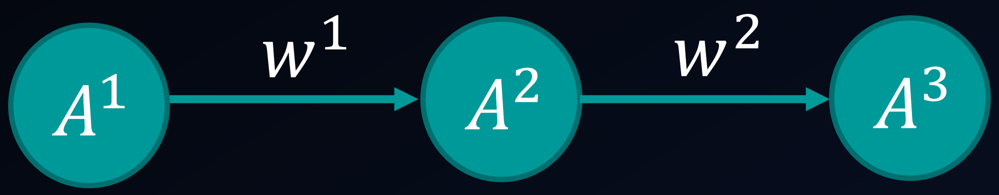
Appendix 1 - Neural Network

Backpropagation



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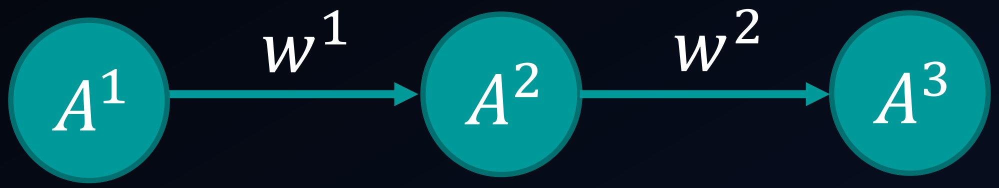
Appendix 1 - Neural Network

Backpropagation

C =



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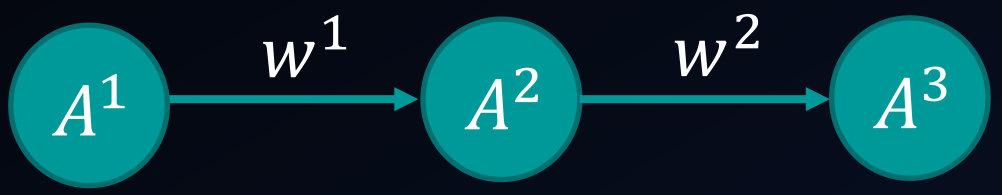
Appendix 1 - Neural Network

Backpropagation

$C = MSE(Y, \hat{Y})$



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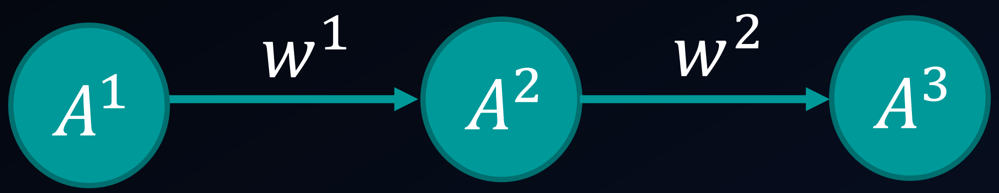
Appendix 1 - Neural Network

Backpropagation

C = MSE(Y, Ŷ)

C



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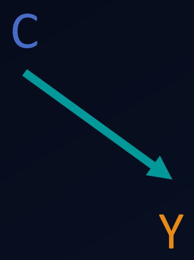
Appendix 1 - Neural Network

Backpropagation

$C = \text{MSE}(Y, \hat{Y})$



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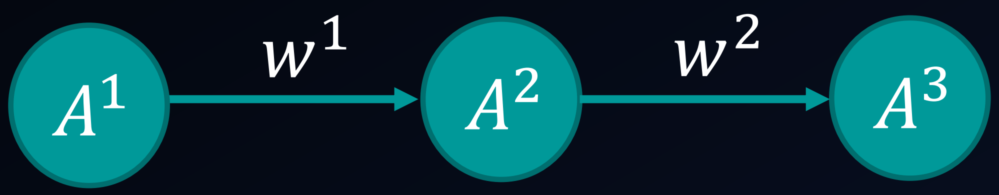
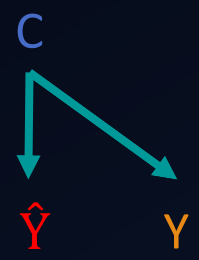
Appendix 1 - Neural Network

Backpropagation

$C = MSE(Y, \hat{Y})$





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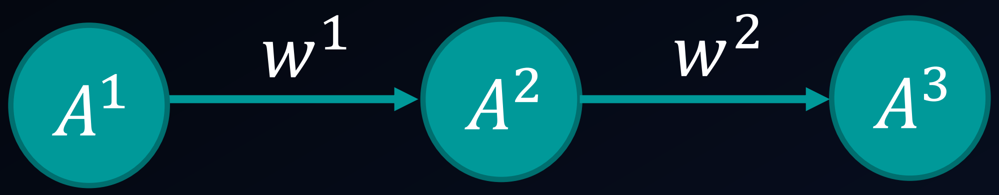
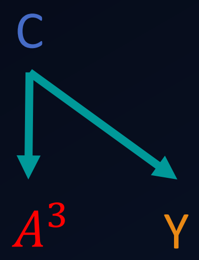
Appendix 1 - Neural Network

Backpropagation

$C = MSE(Y, A^3)$

$A^3 =$





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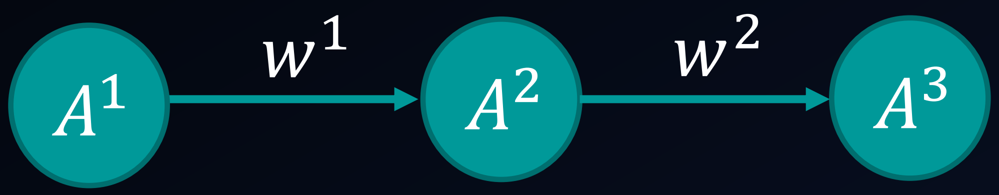
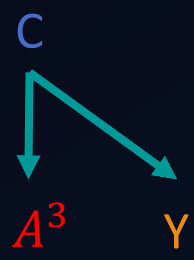
Appendix 1 - Neural Network

Backpropagation





$C = MSE(Y, A^3)$

$A^3 = \sigma(I^3)$

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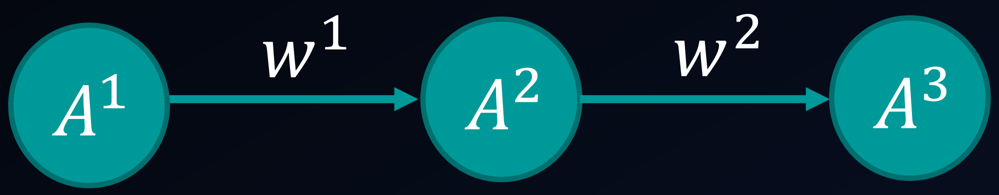
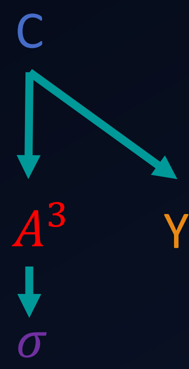
Appendix 1 - Neural Network

Backpropagation





C = MSE(Y, A^3)

A^3 = σ(I^3)

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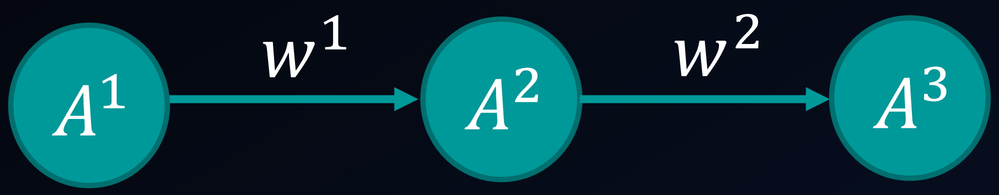
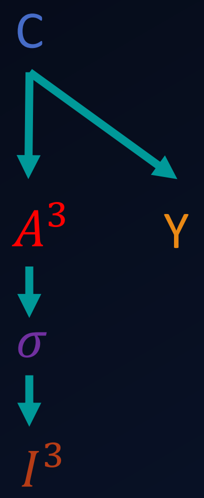
Appendix 1 - Neural Network

Backpropagation





$$C = \text{MSE}(Y, A^3)$$
$$A^3 = \sigma(I^3)$$

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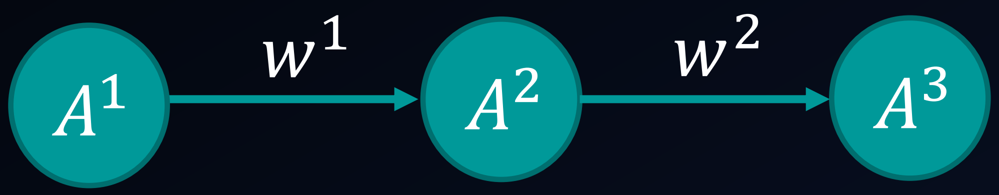
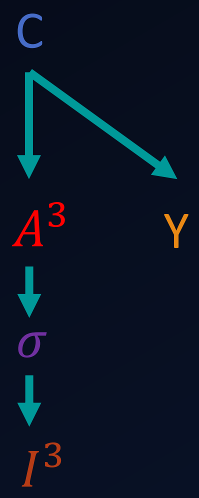
Appendix 1 - Neural Network

Backpropagation



$C = MSE(Y, A^3)$

$A^3 = \sigma(I^3)$



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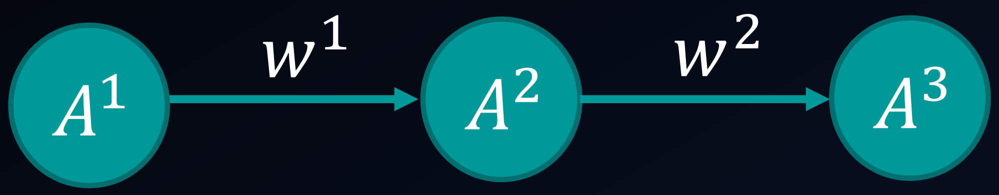
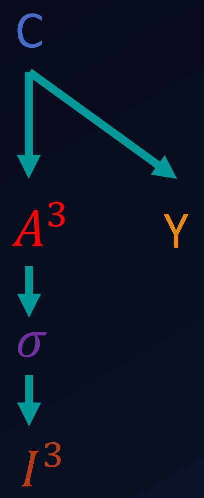
Appendix 1 - Neural Network

Backpropagation





$$C = MSE(Y, A^3)$$

$$A^3 = \sigma(I^3)$$

$$I^3 = A^2 w^2 + B^3$$

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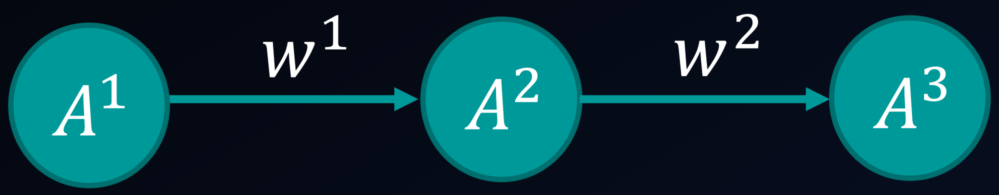
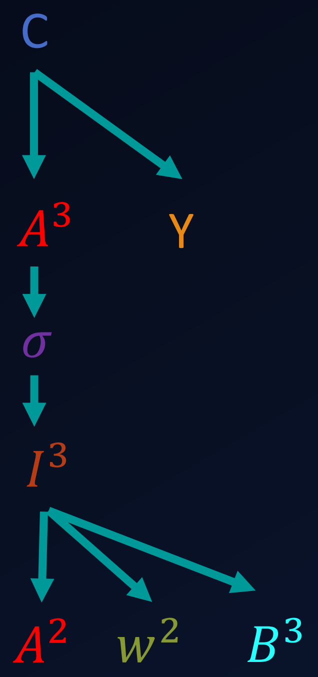
Appendix 1 - Neural Network

Backpropagation





$C = MSE(Y, A^3)$

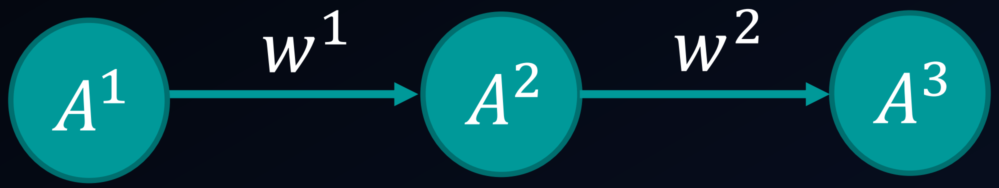
$A^3 = \sigma(I^3)$

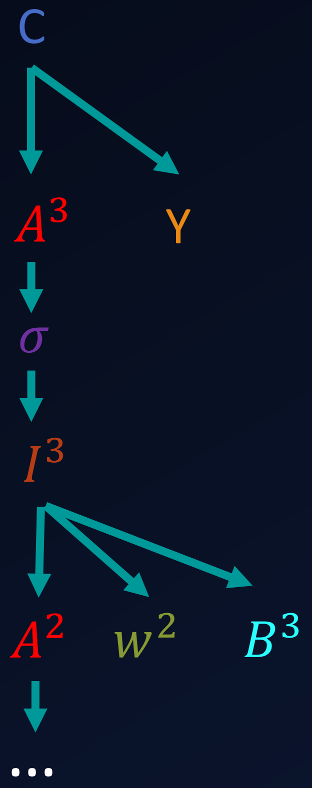
$I^3 = A^2 w^2 + B^3$

53

Appendix 1 - Neural Network

Backpropagation





$$C = MSE(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$

53

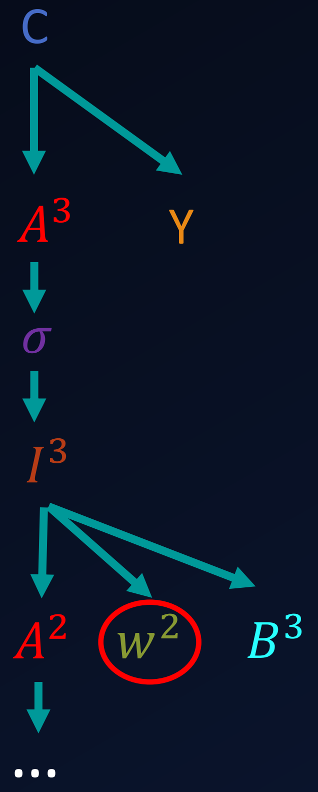
Appendix 1 - Neural Network

Backpropagation

$$C = MSE(Y, A^3)$$

$$A^3 = \sigma(I^3)$$

$$I^3 = A^2 w^2 + B^3$$



$$\frac{\partial C}{\partial w^2} =$$

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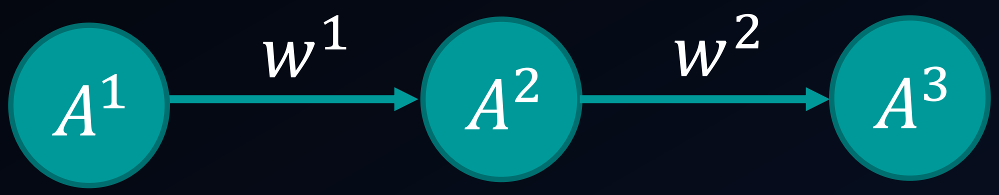
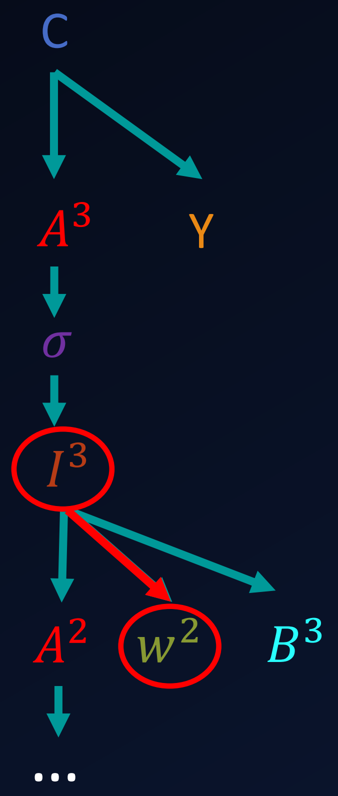
Appendix 1 - Neural Network

Backpropagation

$$C = \text{MSE}(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$





$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2}$$

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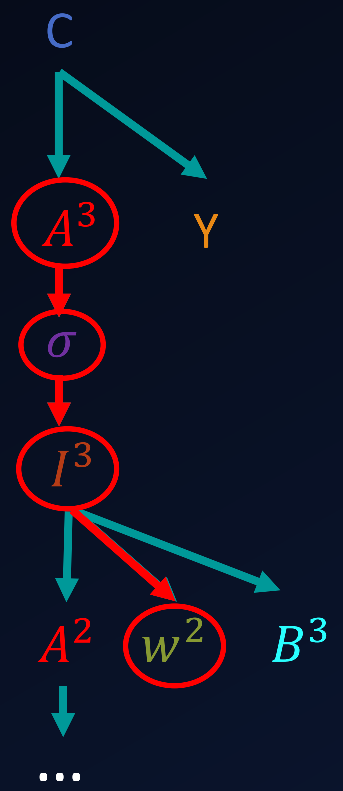
Appendix 1 - Neural Network

Backpropagation

$$C = MSE(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$



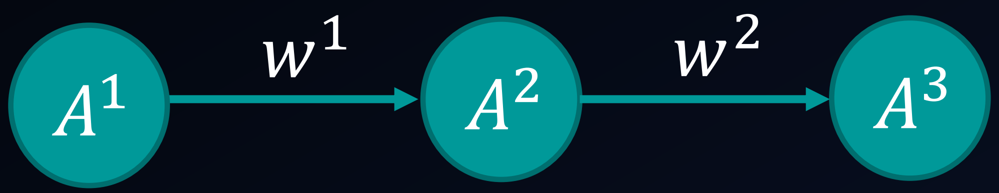
$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2} \frac{\partial A^3}{\partial I^3}$$

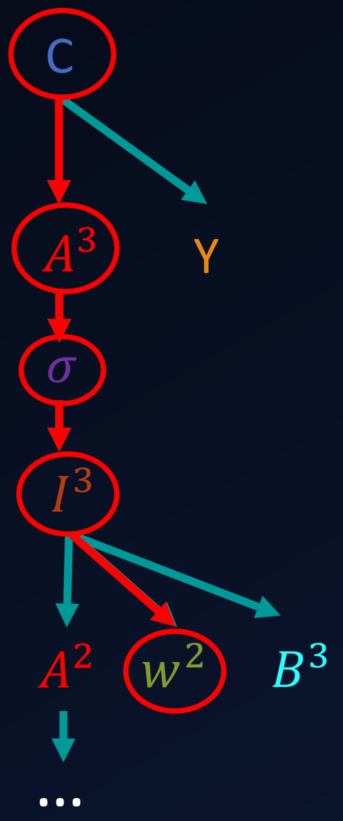
53

Appendix 1 - Neural Network

Backpropagation

$$C = MSE(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$





$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2} \frac{\partial A^3}{\partial I^3} \frac{\partial C}{\partial A^3}$$

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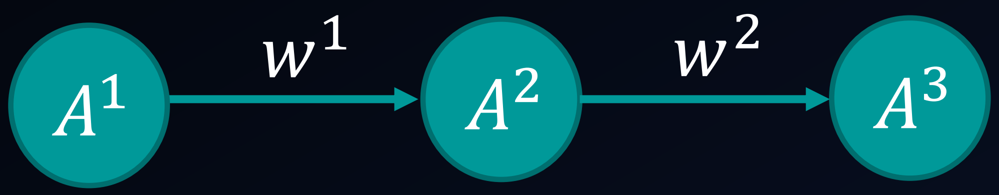
Appendix 1 - Neural Network

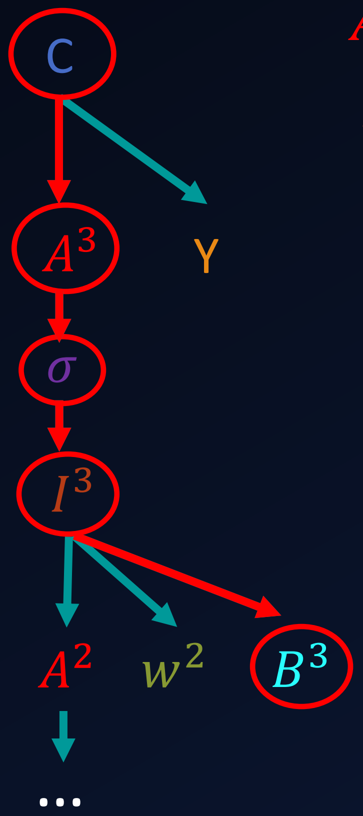
Backpropagation

$$C = \text{MSE}(Y, A^3)$$

$$A^3 = \sigma(I^3)$$

$$I^3 = A^2 w^2 + B^3$$



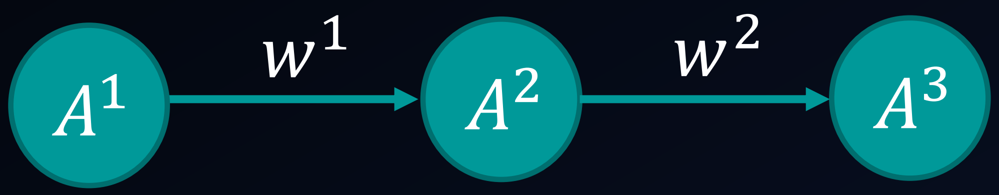


$$\frac{\partial C}{\partial B^3} = \frac{\partial I^3}{\partial B^3} \frac{\partial A^3}{\partial I^3} \frac{\partial C}{\partial A^3}$$

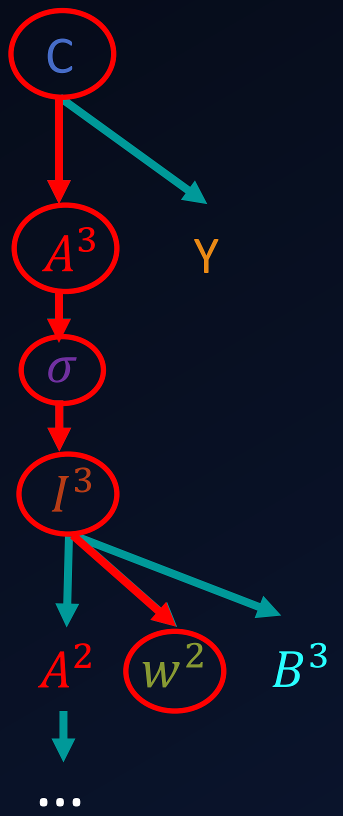
55

Appendix 1 - Neural Network

Backpropagation



$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2}\frac{\partial A^3}{\partial I^3}\frac{\partial C}{\partial A^3}$$



$$C = MSE(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$

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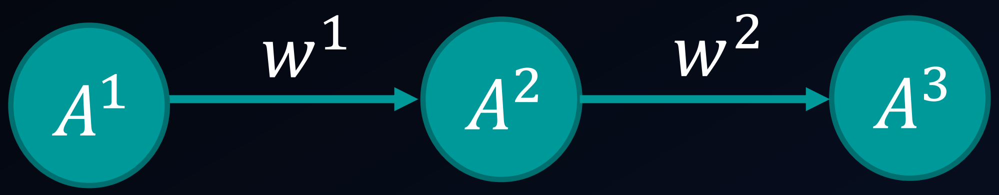
Appendix 1 - Neural Network

Backpropagation

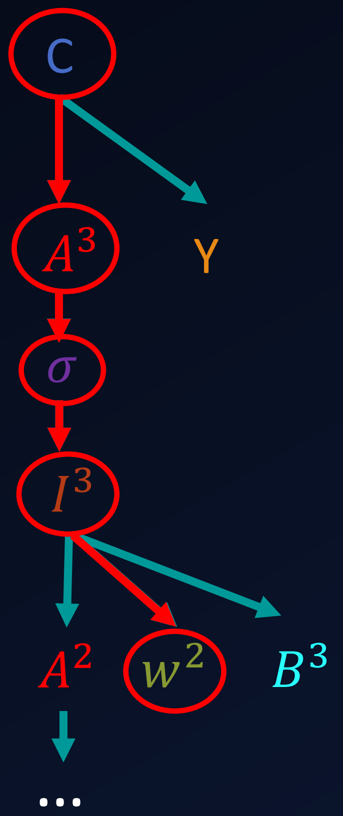
$C = MSE(Y, A^3)$

$A^3 = \sigma(I^3)$

$I^3 = A^2 w^2 + B^3$



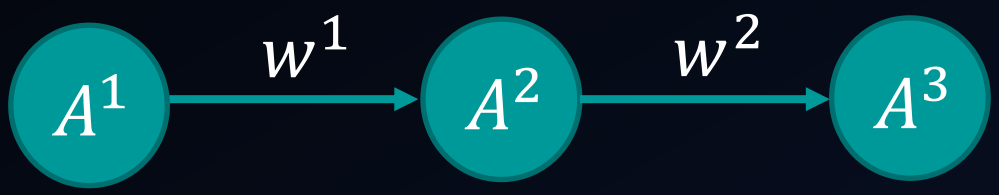
$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2} \frac{\partial A^3}{\partial I^3} \frac{\partial C}{\partial A^3}$$



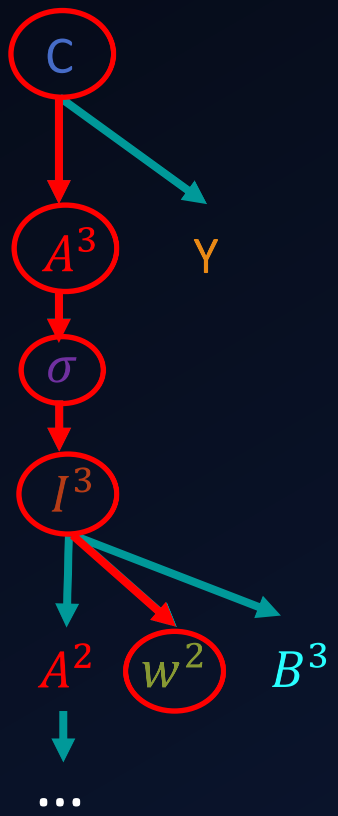
55

Appendix 1 - Neural Network

Backpropagation



$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2}\frac{\partial A^3}{\partial I^3}\frac{\partial C}{\partial A^3}$$



$C = MSE(Y, A^3)$

$A^3 = \sigma(I^3)$

$I^3 = A^2 w^2 + B^3$

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Appendix 1 - Neural Network

Backpropagation

$C = \mathrm{MSE}(Y, A^3)$

$A^3 = \sigma(I^3)$

$I^3 = A^2 w^2 + B^3$

$$\frac{\partial C}{\partial w^2} = \frac{\partial I^3}{\partial w^2}\frac{\partial A^3}{\partial I^3}\frac{\partial C}{\partial A^3}$$

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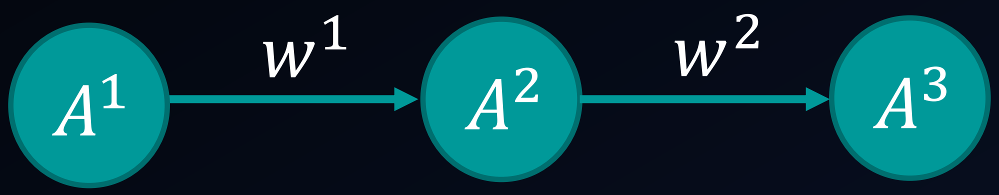
Appendix 1 - Neural Network

Backpropagation

$$C = \mathrm{MSE}(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$



$$\frac{\partial C}{\partial w^2} = A^2 \frac{\partial A^3}{\partial I^3} \frac{\partial C}{\partial A^3}$$

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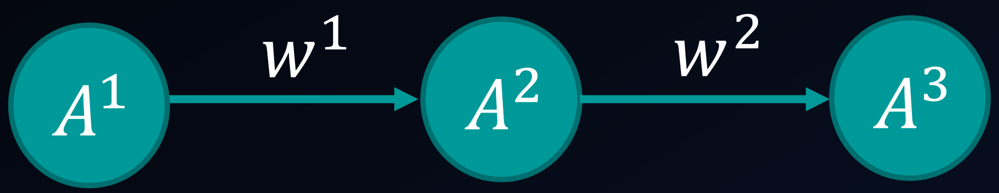
Appendix 1 - Neural Network

Backpropagation

$$C = MSE(Y, A^3)$$
$$A^3 = \sigma(I^3)$$
$$I^3 = A^2 w^2 + B^3$$



$$\frac{\partial C}{\partial w^2} = A^2 \sigma'(I^3) \frac{\partial C}{\partial A^3}$$

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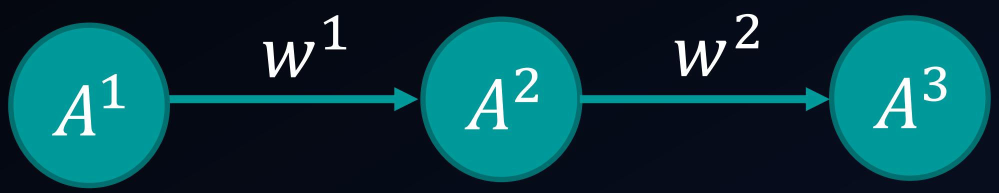
Appendix 1 - Neural Network

Backpropagation

$C = MSE(Y, A^3)$

$A^3 = \sigma(I^3)$

$I^3 = A^2 w^2 + B^3$



$$\frac{\partial C}{\partial w^2} = A^2 \sigma'(I^3)\, 2(A^3 - Y)$$

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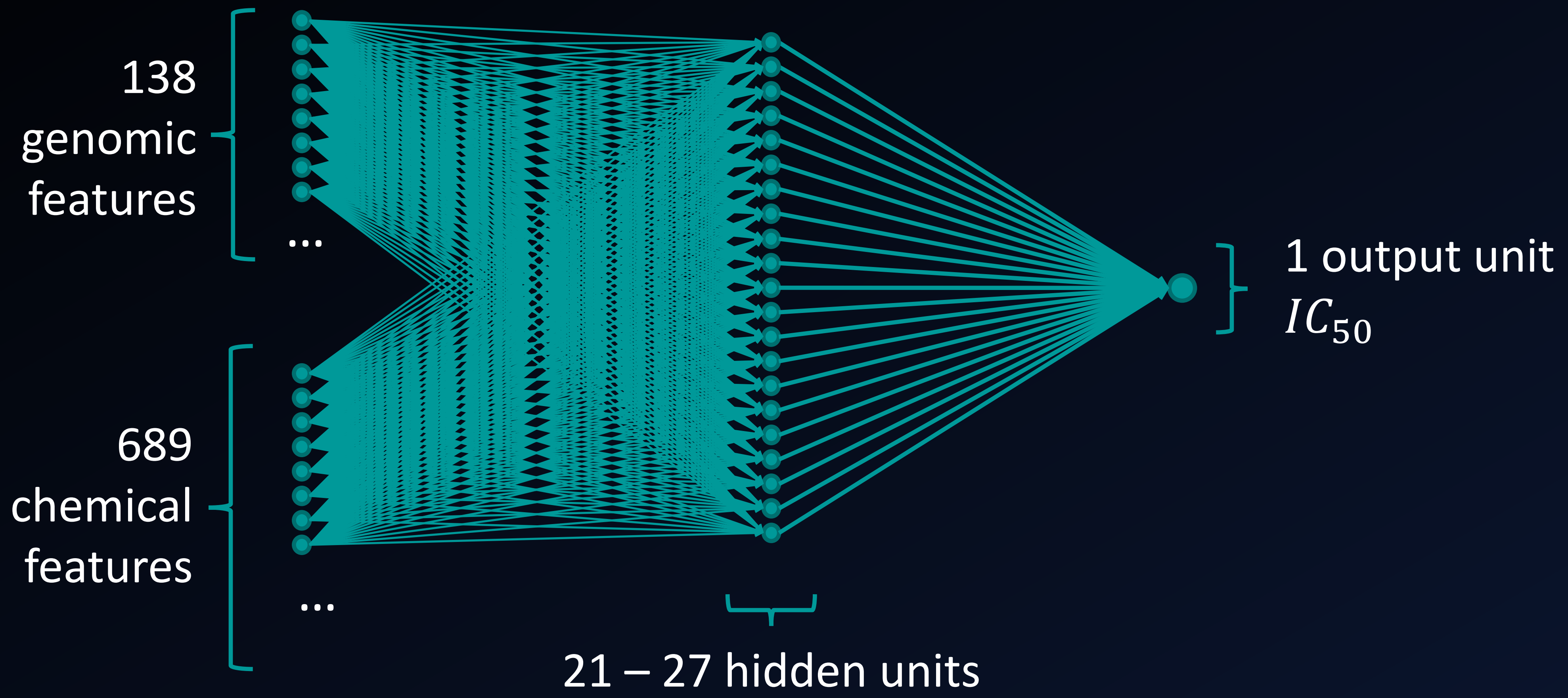
Appendix 2 – IC50 Normalisation



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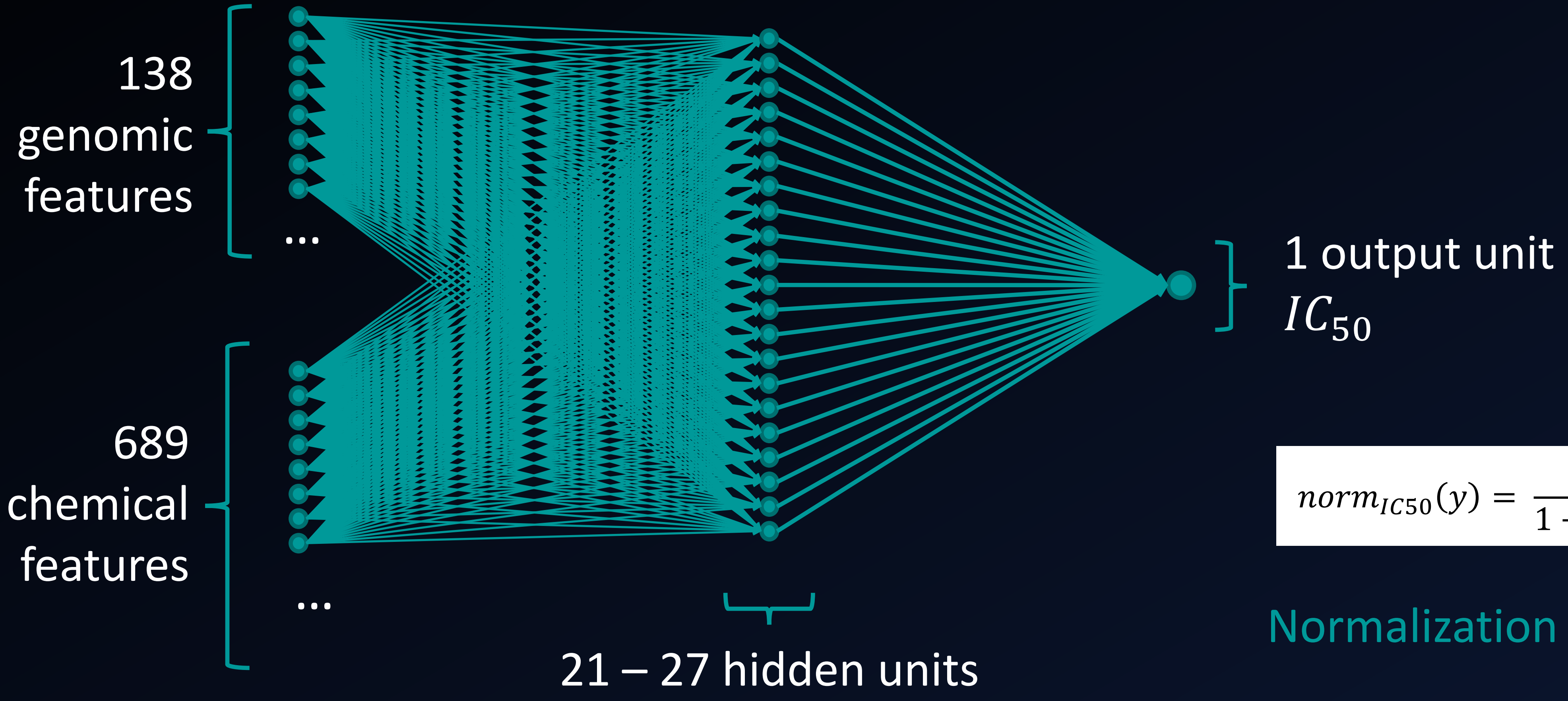
Appendix 2 – IC50 Normalisation



$$norm_{IC50}(y) = \frac{1}{1 + y^{-0,1}}$$

Fig. 5
Normalization function

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Appendix 3

Pearson correlation coefficient:

x : Observed values
y : Predicted values
n : Number of values

$$R_p = \frac{n(\sum_{i=1}^{n} x_i y_i) - (\sum_{i=1}^{n} x_i)(\sum_{i=1}^{n} y_i)}{\sqrt{[n\sum_{i=1}^{n} {x_i}^2 - (\sum_{i=1}^{n} x_i)^2][n\sum_{i=1}^{n} {y_i}^2 - (\sum_{i=1}^{n} y_i)^2]}}$$

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Appendix 4

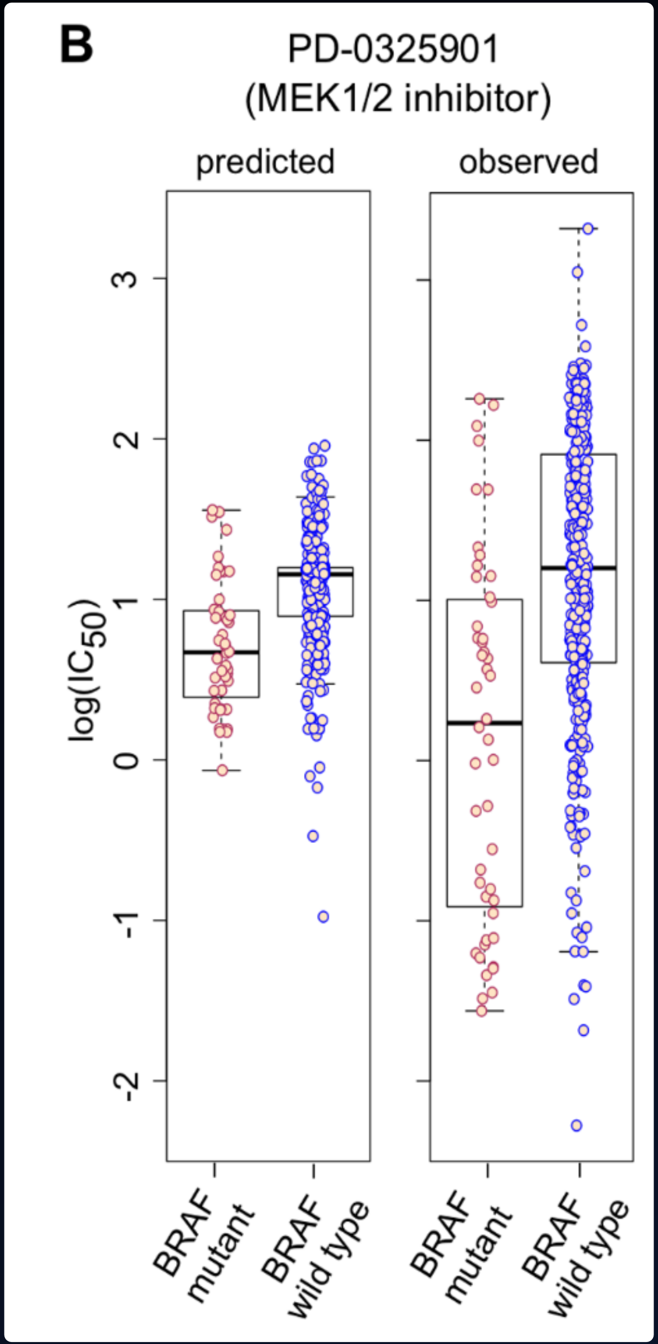

Fig. 9

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Appendix 5

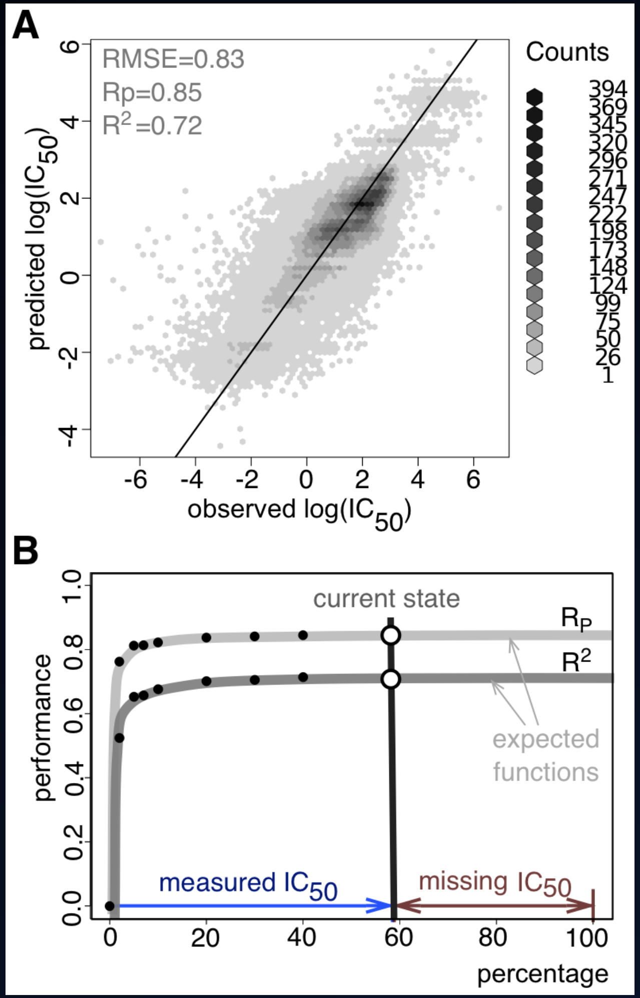

Fig. 10