Wet TinyML: Chemical Neural Network Using Gene Regulation and Cell Plasticity

Samitha Somathilaka[1,2], Adrian Ratwatte[1], Sasitharan Balasubramaniam[1],
Mehmet Can Vuran[1], Witawas Srisa-an[1], Pietro Liò[3]

[1]University of Nebraska-Lincoln, USA, [2]Walton Institute, South East Technological University, Ireland, [3]University of Cambridge, UK.

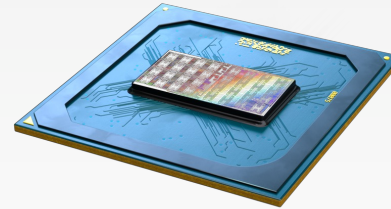*tinyML Research Simposium '24*, SanFrancisco
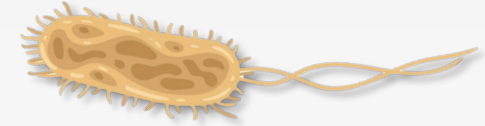April 22, 2024

Background & Motivation

	Human brain	Loihi 2	Bacteria
# Computing units	100 B neurons	1 M neurons	100-11000 genes
Storage	~2500 Tb	24 MB	~1.2 MB
Size	1300 cm^3	31 mm^2	~0.4 - 3 µm^3
Power consumption	20 W	100 mW	<0.1pW
Comp. unit density	7.7x10^4 mm^{-3}	3.2x10^4 mm^{-2}	**5 x10^{12} mm^{-3}**

Path to Creating AI

Brain

Neuronal Networks

Artificial Neural Networks

input layer

hidden layer 1

hidden layer 2

output layer

Deployment

S. Balasubramaniam, S. S. Somathilaka,, S. Sun, A. Ratwatte, M. Pierobon, **Realizing Molecular Machine Learning through Communications for Biological AI: Future Directions and Challenges**, *IEEE Nanotechnology Magazine*, " 2023.

S. S. Somathilaka, S. Balasubramaniam, D. P. Martins, X. Li, "**Revealing Gene Regulation-Based Neural Network Computing in Bacteria**", *Biophysical Reports*, vol. 3, 100118, 2023.
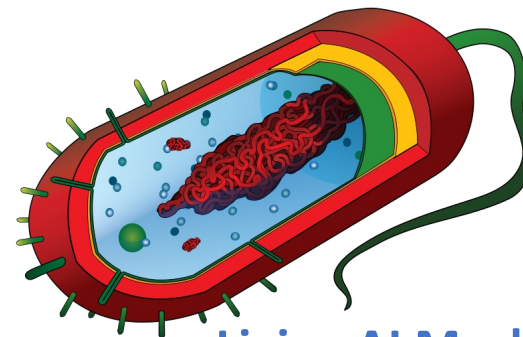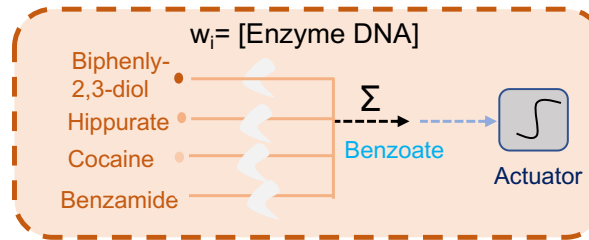
Living AI Machine

Silicon Technologies

Biological AI in Non-Neural Organisms
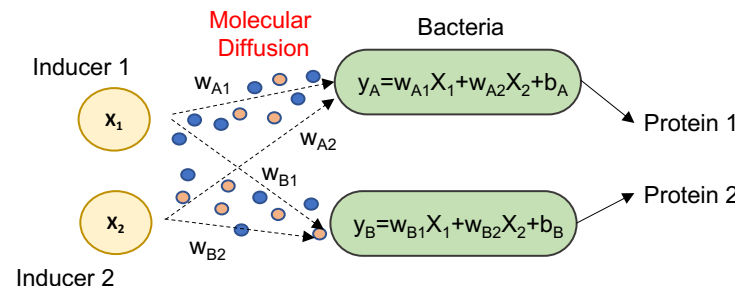
Metabolic Perceptron

- Cell-free system based on enzyme reaction of metabolic circuits.
- Offline design using Sensipath and Retropath computational tools.
- Binary classification application

w_i= [Enzyme DNA]

Biphenly-2,3-diol
Hippurate
Cocaine
Benzamide

Σ

Benzoate

Actuator

A. Pandi, M. Koch, P. L. Voyvodic, P. Soudier, J. Bonnet, M. Kushwaha, and J.-L. Faulon, "Metabolic perceptrons for neural computing in biological systems," Nature communications, vol. 10, no. 1, 2019.
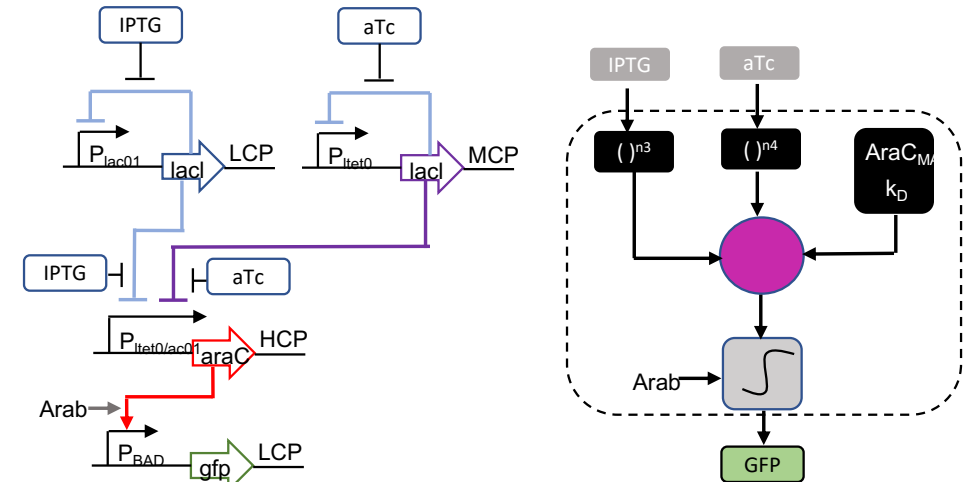
Bactoneuron

- Single layer ANN using engineered E.coli MC between cells.
- Cells are engineered to receive intercellular diffusing molecules.
- Internally each cell executes a log-sigmoid activation function.
- Offline design of the ANN.

Molecular Diffusion

Bacteria

Inducer 1

x_1

w_{A1}

w_{A2}

$y_A = w_{A1}X_1 + w_{A2}X_2 + b_A$ → Protein 1

w_{B1}

x_2

w_{B2}

$y_B = w_{B1}X_1 + w_{B2}X_2 + b_B$ → Protein 2

Inducer 2

K. Sarkar, D. Bonnerjee, R. Srivastava, and S. Bagh, "A single layer artificial neural network type architecture with molecular engineered bacteria for reversible and irreversible computing," Chemical science, vol. 12, no. 48, pp. 15821–15832, 2021.

Perceptgene

- Perceptron model of an ANN.
- Genetic circuit engineering of E.coli bacteria.
- Logarithmic input-output that fits to the non-linear biochemical reactions that occurs in the genetic circuit.
- Weights chemical inputs are established through power-law functions.
- Offline training.

IPTG

aTc

IPTG

aTc

P_{lac01} lacI LCP

P_{ltet0} lacI MCP

IPTG

aTc

$P_{ltet0/ac01}$ araC HCP

Arab →

P_{BAD} gfp LCP

IPTG

aTc

$()^{n3}$

$()^{n4}$

AraC$_{MA}$ k_D

Arab

GFP

L.Rizik, L.Danial, M.Habib, R.Weiss, and R.Daniel, "Synthetic neuromorphic computing in living cells," Nature communications, vol. 13, no. 1, 2022.

S. Balasubramaniam, S. S. Somathilaka,, S. Sun, A. Ratwatte, M. Pierobon, Realizing Molecular Machine Learning through Communications for Biological AI: Future Directions and Challenges,, IEEE Nanotechnology Magazine, " 2023.

Gene Regulatory Network

Similarity between gene expression and functionality of a neuron

Input Gene 1

Input Gene 2

**Gene perceptron**

TF_1

TF_2

Target Gene Output
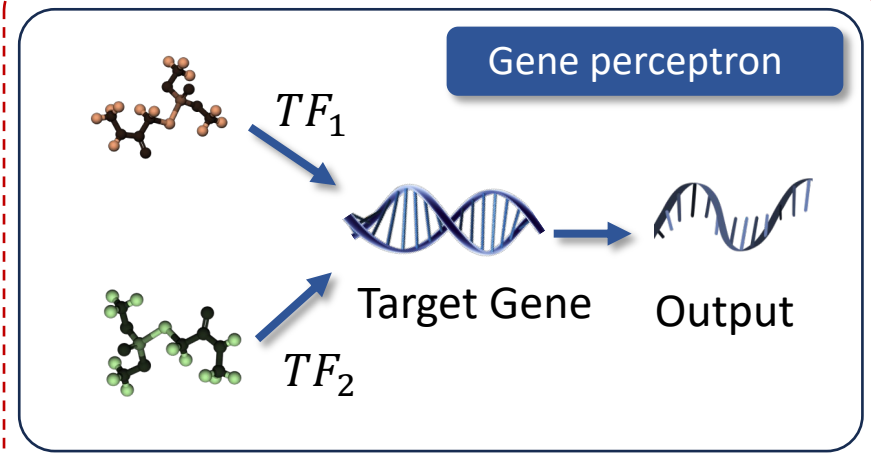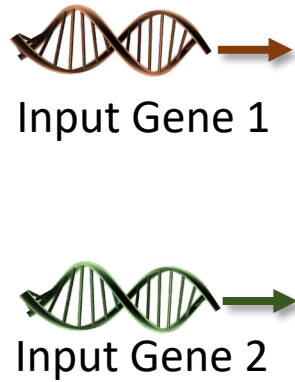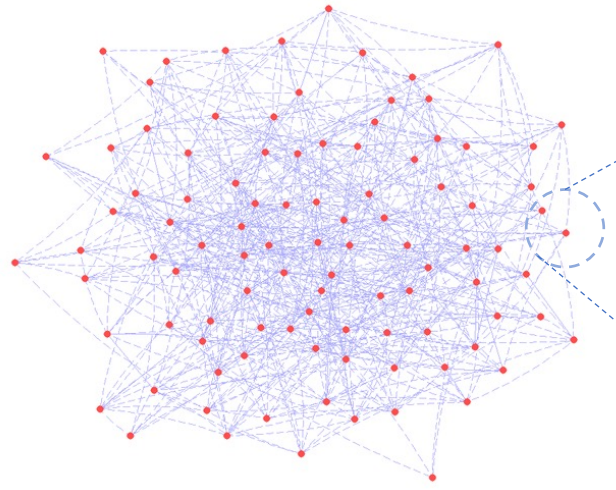
GRN properties
- **Nodes** represent **genes**, while **edges** represent **gene-gene interactions**.
- The network follows a **power-law** distribution.

GRN computing properties
- Gene-gene interactions are through **Transcriptional Factors (TF)**
- Gene regulation contains **feedback** and **feed-forward** loops.
- Gene expression rate can reach **2500+ counts/min**.

Perceptron model

I_1 w_1

I_2 w_2

$$\sum I * w + b \bigg| f$$

Output
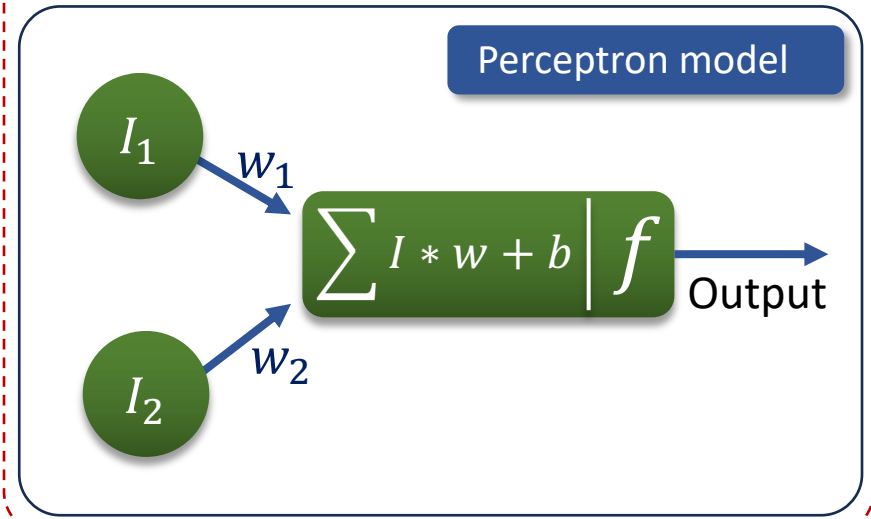
GRN TO GENE REGULATORY NEURAL NETWORK (GRNN)

GRNN is a computing model resembling **ANN**, developed by **quantifying** interaction strengths within the **GRN**.

Weight extraction mechanism
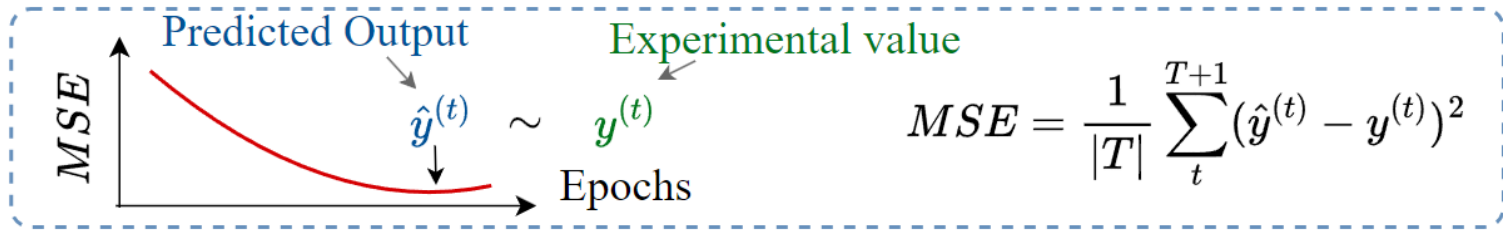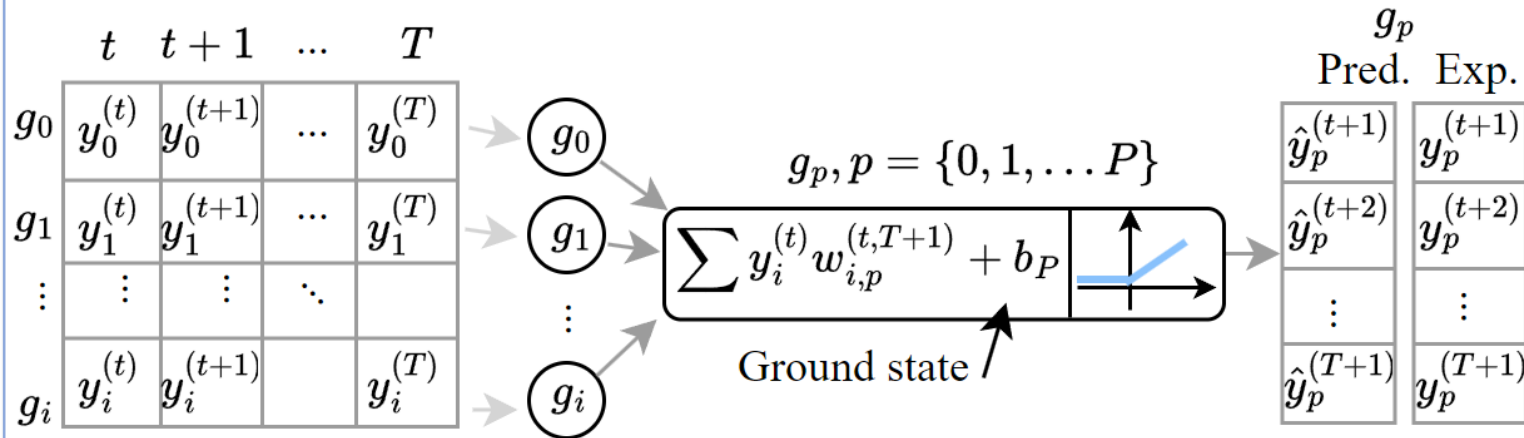
Transformation Method

1) Identification of GRN-sub networks similar to single layer-perceptrons, with source and target genes.

2) Pre-process temporal transcriptomic data.

3) Extract each gene-gene interaction weight following the method illustrated in the figure.
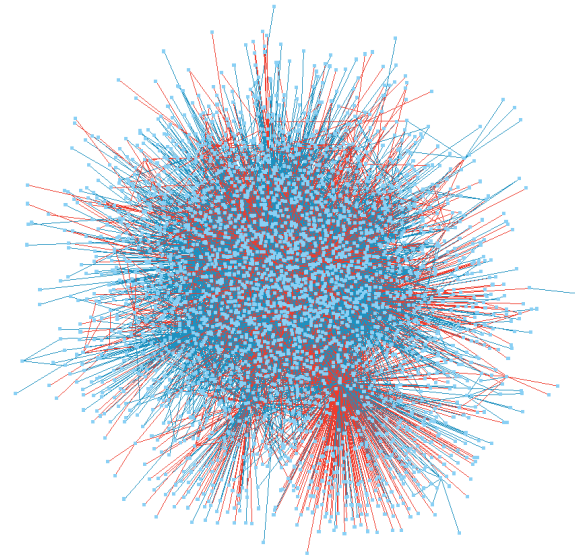
4) Repeat this for all the gene-perceptrons.

E. Coli GRNN - (CSH50)
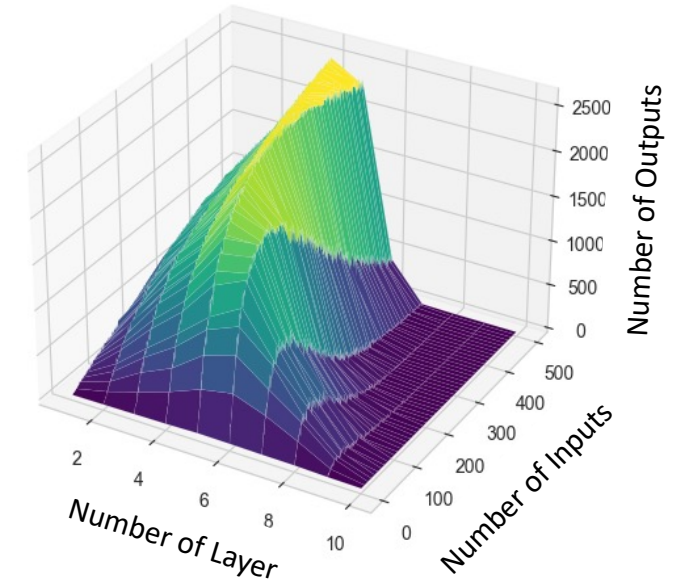
E. Coli weight extraction accuracy
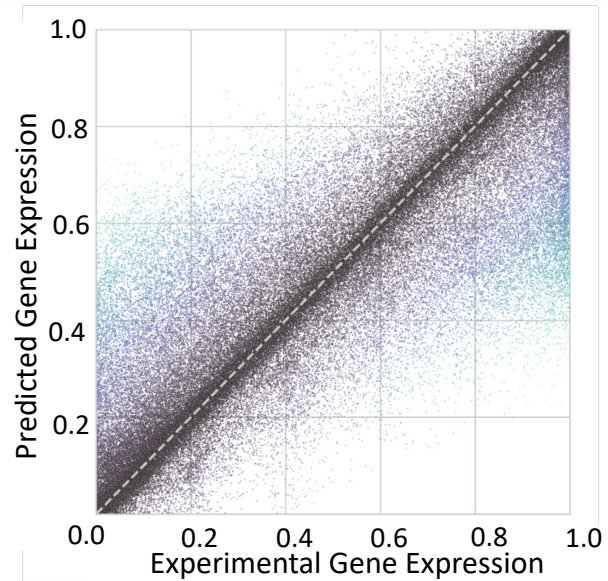
- The 45^0 line is where the predicted and experimental expressions are equal.

- Results show that the majority of the predictions are close to experimental values.

E. Coli GRNN

- Contains 4500+ nodes and 10,000+ edges.

- The feedback and feed-forward loops of gene expressions results in non-linear computing.
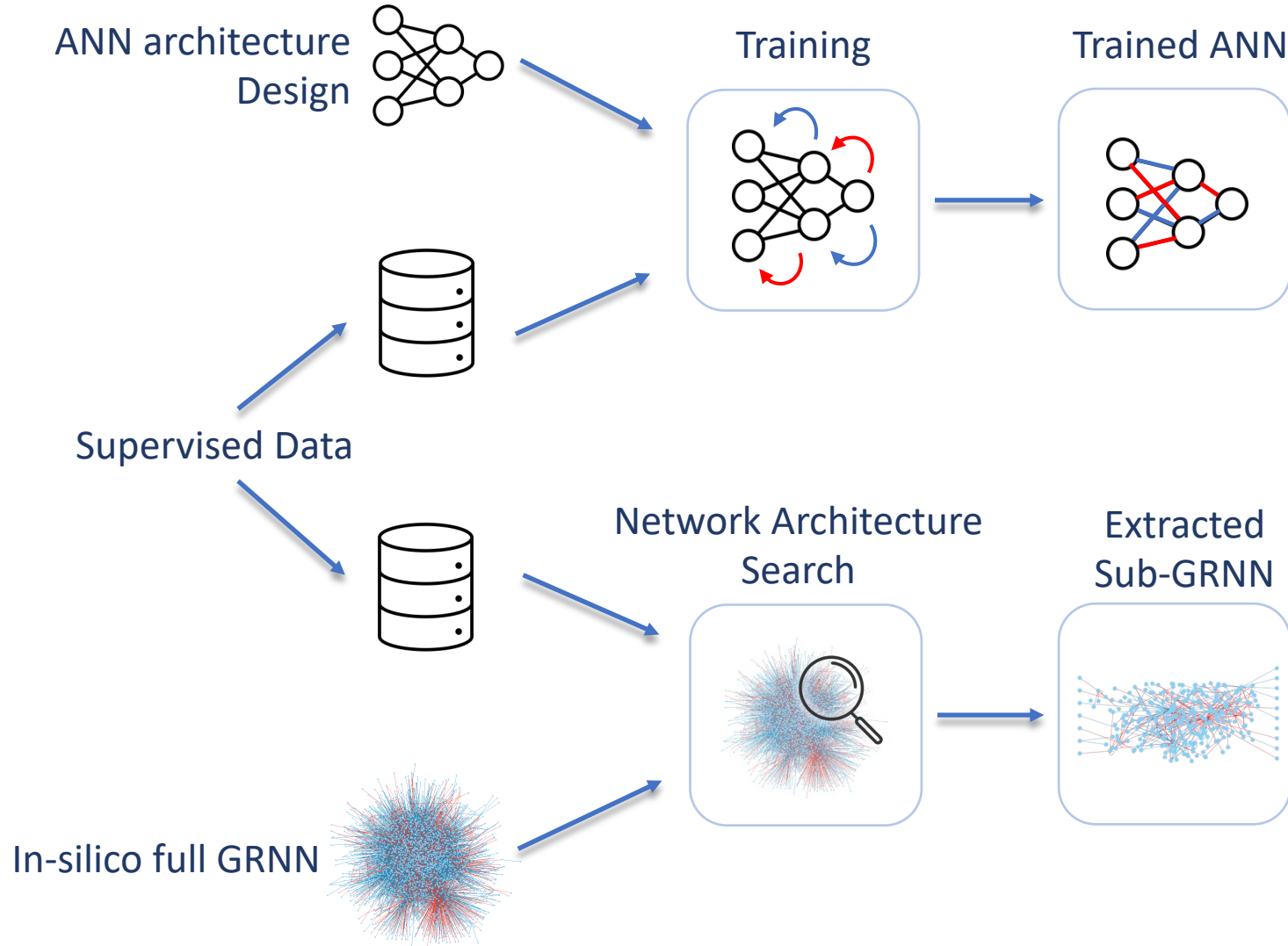
Sub-GRNN diversity

The diversity of GRNN shows:
- With 100 nodes as inputs, GRNN gives networks with a maximum 500 outputs.

- No. of sub-GRNNs exceeds 5.9×10^{297}.

ANN vs GRNN Application

ANN architecture Design

Training

Trained ANN

Supervised Data

Network Architecture Search
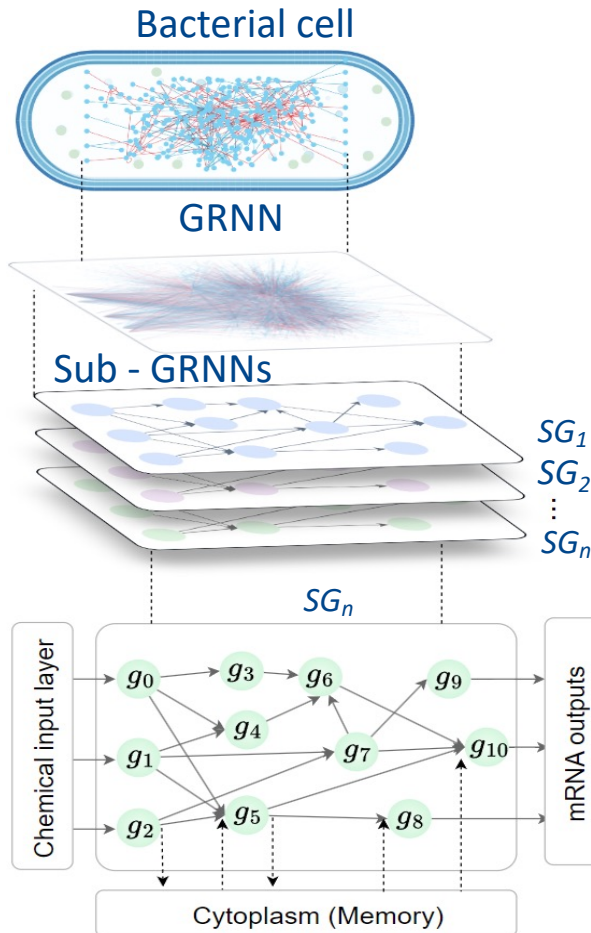
Extracted Sub-GRNN

In-silico full GRNN

GRNN Computing

1) GRNN is considered a **pre-trained random structured NN**.

2) **Similar** to the **ANN training** phase, GRNN computing requires **sub-GRNN search**.
   - Akin to the **Network Architecture Search**

3) Extracted sub-GRNN gives the most **suitable inputs** and **output** genes to suit an application requirement

GRNN PLASTICITY FOR COMPUTING

Cell as a repository of sub-GRNNs

Bacterial cell

GRNN

Sub - GRNNs

SG_1
SG_2
SG_n

SG_n

Chemical input layer

g_0 g_3 g_6 g_9
g_4
g_1 g_7 g_{10}
g_2 g_5 g_8
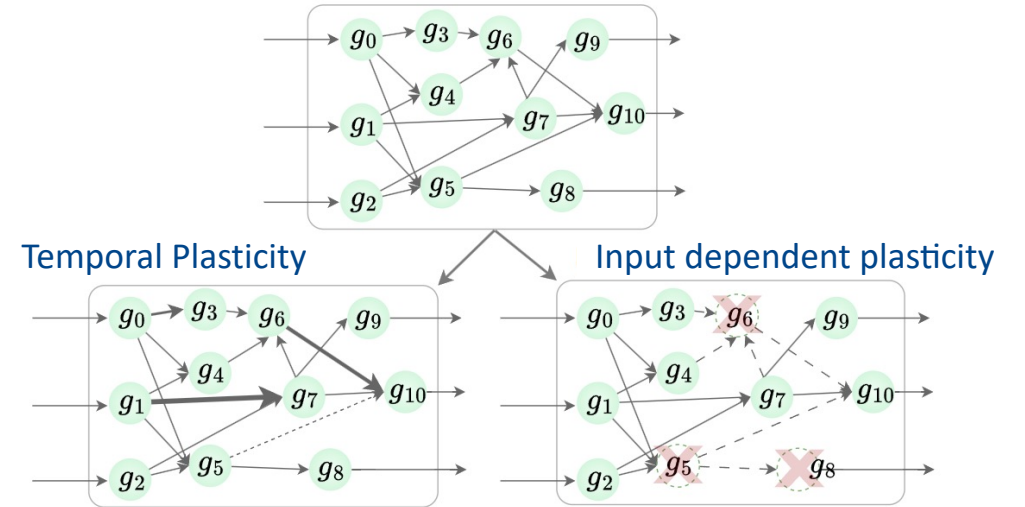
mRNA outputs

Cytoplasm (Memory)

GRNN

- Contains redundant paths.

- Gene Expressions are highly selective.

- Gene Expression pathways depend on the inputs.

- Cytoplasm acts as a memory.

Neuromorphic properties

- Gene expressions are highly parallel and event-driven.

- Genes exhibit in-memory computing.

g_0 g_3 g_6 g_9
g_4
g_1 g_7 g_{10}
g_2 g_5 g_8

Temporal Plasticity

g_0 g_3 g_6 g_9
g_4
g_1 g_7 g_{10}
g_2 g_5 g_8

Input dependent plasticity

g_0 g_3 g_6 g_9
g_4
g_1 g_7 g_{10}
g_2 g_5 g_8

Temporal Plasticity

- Alterations in the influence of one gene on another over time.

- Optimizes the behavior for a given environment.

Input dependent plasticity

- Input sensitivity leads to the expression of a specific subset of genes (can be from chemical or other environmental influence).

- This results in keeping the irrelevant genes largely idle.

TEMPORAL WEIGHT PLASTICITY

Deviation of weight correlation
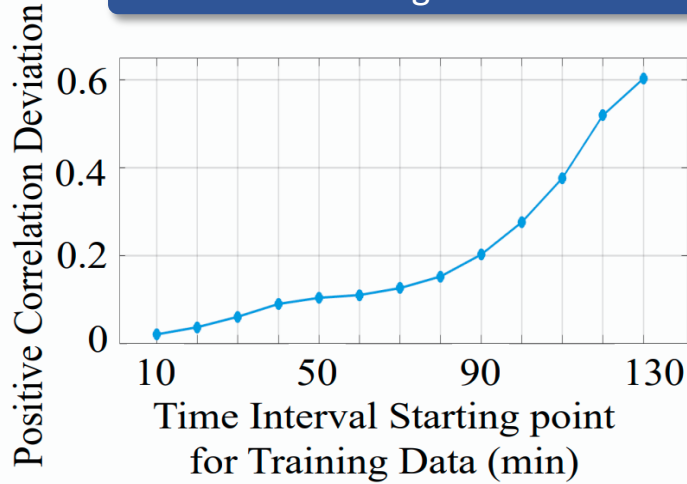
- Weight deviation gradually rises to 0.1 between the time period 10-300 and 60-350 minutes at a gradual pace, before increasing rapidly.

- Results demonstrate that overtime GRNN update its weights, contributing to the cell's survival as part of its plasticity process.

Correlation of gene expression
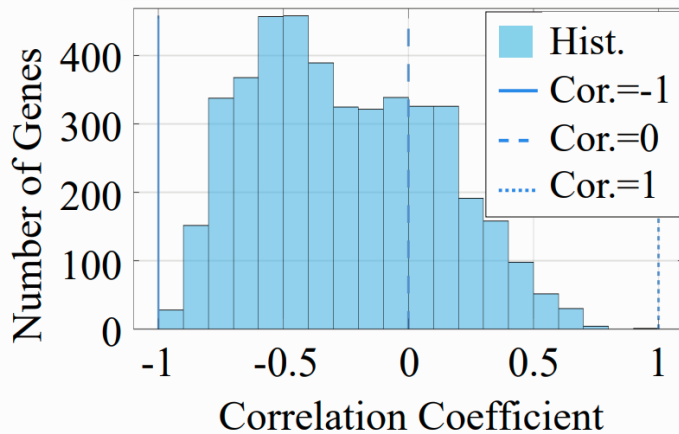
- 80% of genes within the GRNN display negative correlation, while 20% of the total genes exhibit positive correlation.

- These results show the majority of weights updates over time exhibiting temporal plasticity.

GRNN APPLICATION FOR REGRESSION

GRNN can be applied to a wide range of computing tasks, such as **classification** and specially **regression**.

S. S. Somathilaka, S. Balasubramaniam, D. P. Martins, X. Li, "**Revealing Gene Regulation-Based Neural Network Computing in Bacteria**", *Biophysical Reports*, vol. 3, 100118, 2023.
S. S. Somathilaka, S. Balasubramaniam, D. P. Martins. "**Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks**" *Authorea Preprints* (2023).

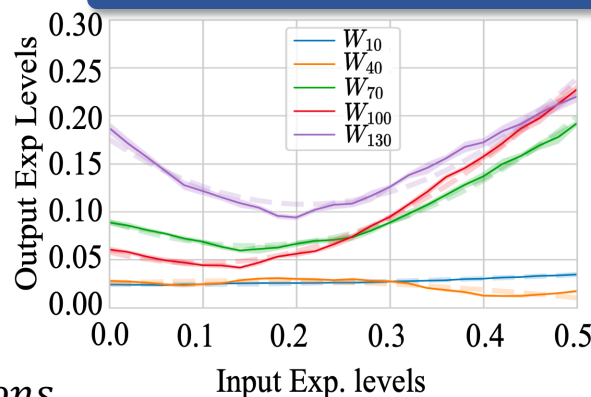## (a) Quadratic, linear coefficients, and intercepts across weight configurations
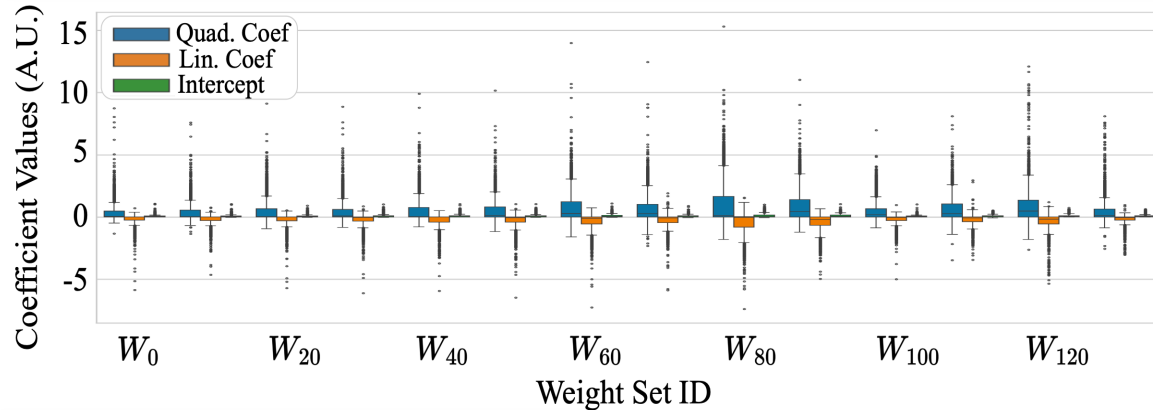
(b) Regression coefficients of b1013

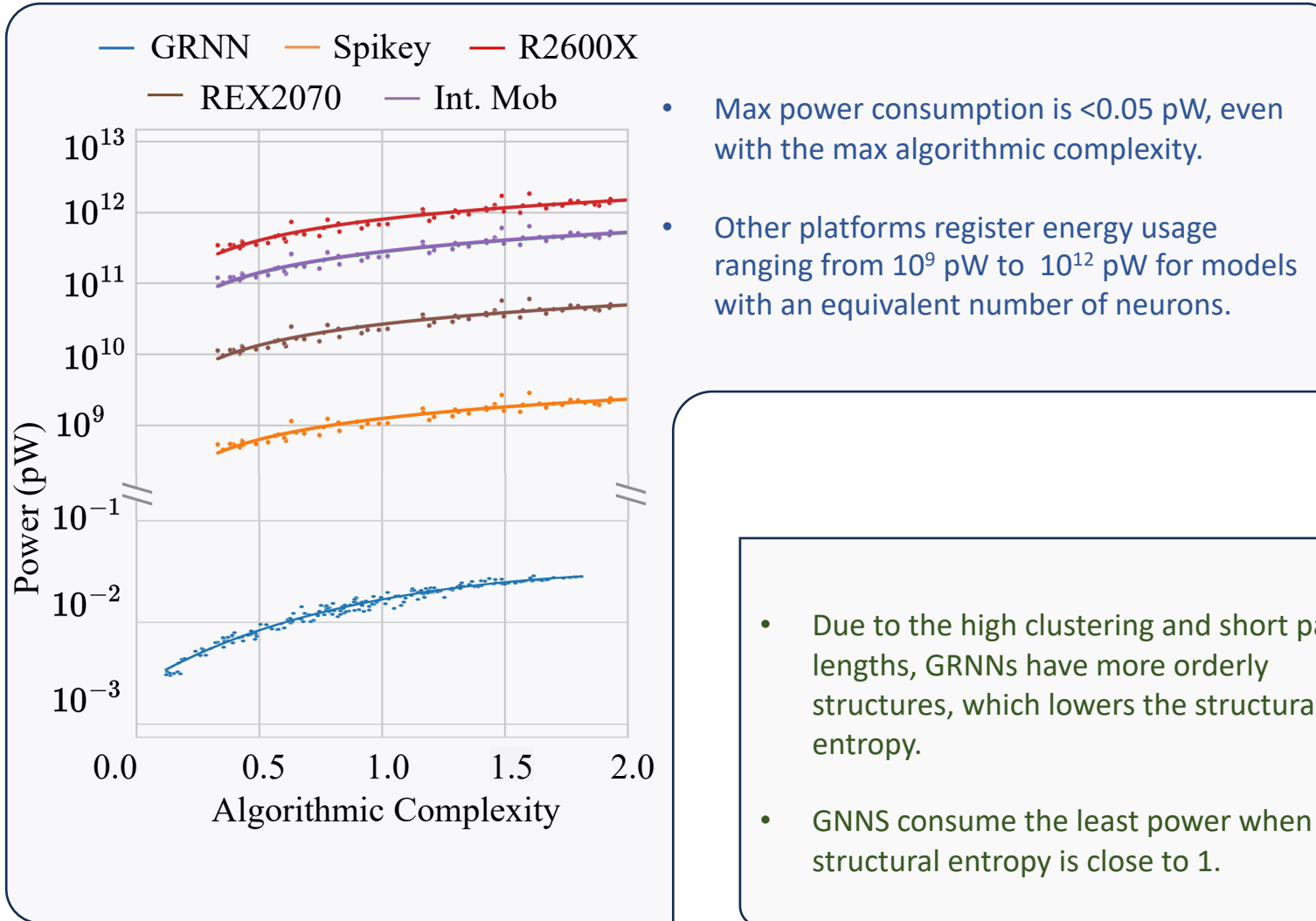| Weightset ID	Regression
W_{10}	$0.04x + 0.02$
W_{40}	$-0.13x^2 + 0.03x + 0.02$
W_{70}	$1.10x^2 - 0.33x + 0.08$
W_{100}	$1.17x^2 - 0.23x + 0.05$
W_{130}	$1.55x^2 - 0.64x + 0.17$

(c) Regression curves of b1013
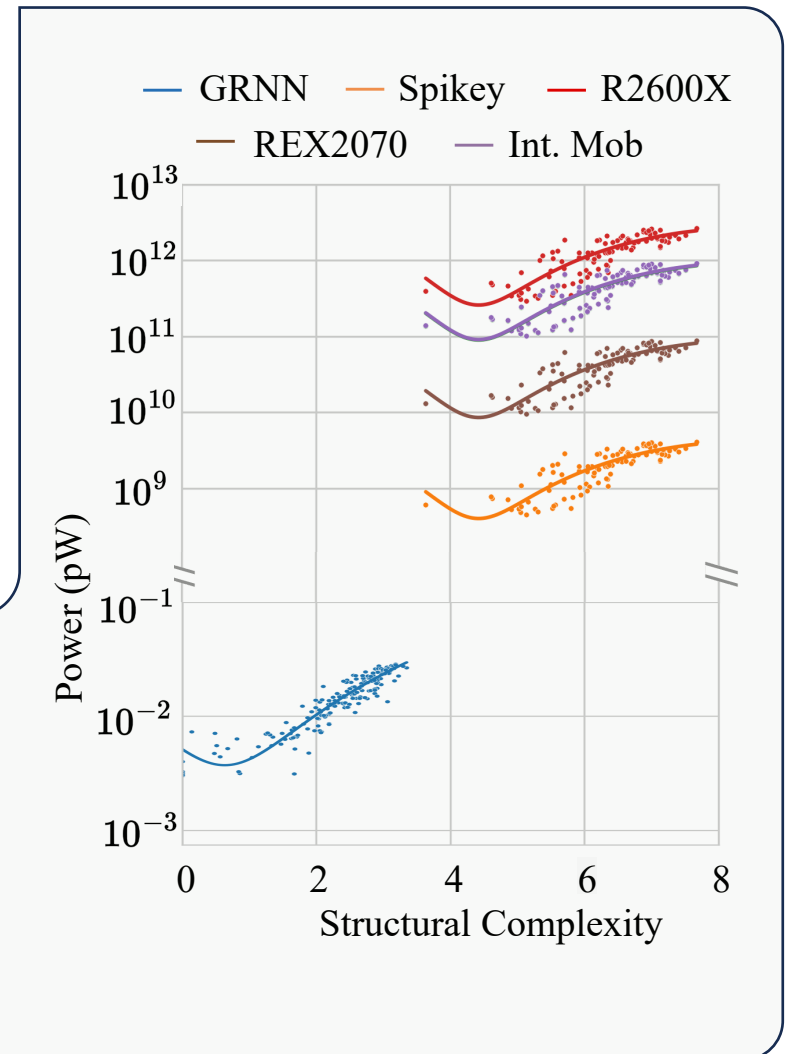

$W_i = i^{th} \ weight \ Configurations$

Analysis on impact of weight plasticity on regression diversity

1) Utilized the E. coli GRNN.

2) Chose Gene b3067 as input, that can directly impact 1702 output gene-perceptrons.

3) Each box in (a) shows coefficients for 2,875 gene-perceptrons, highlighting varied quadratic coefficients

4) Selected b1013 as output gene-perceptrons.

5) (b) and (c) illustrate five regression curves and their plots for b1013 **due to temporal plasticity.**

ENERGY CONSUMPTION

- Max power consumption is <0.05 pW, even with the max algorithmic complexity.

- Other platforms register energy usage ranging from 10^9 pW to 10^{12} pW for models with an equivalent number of neurons.
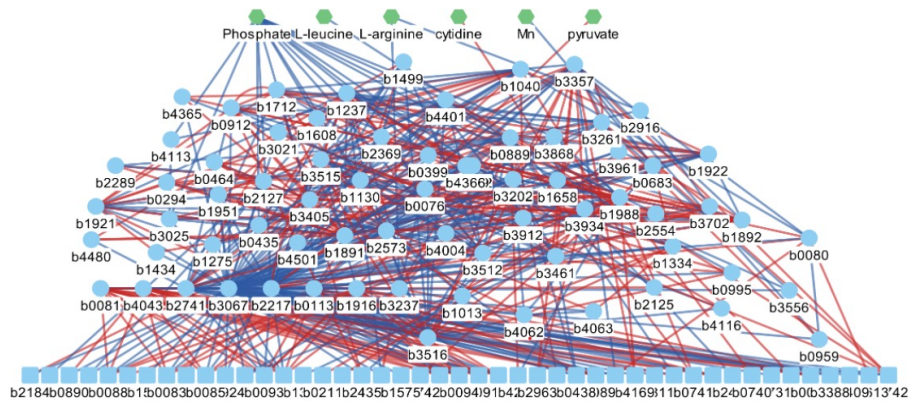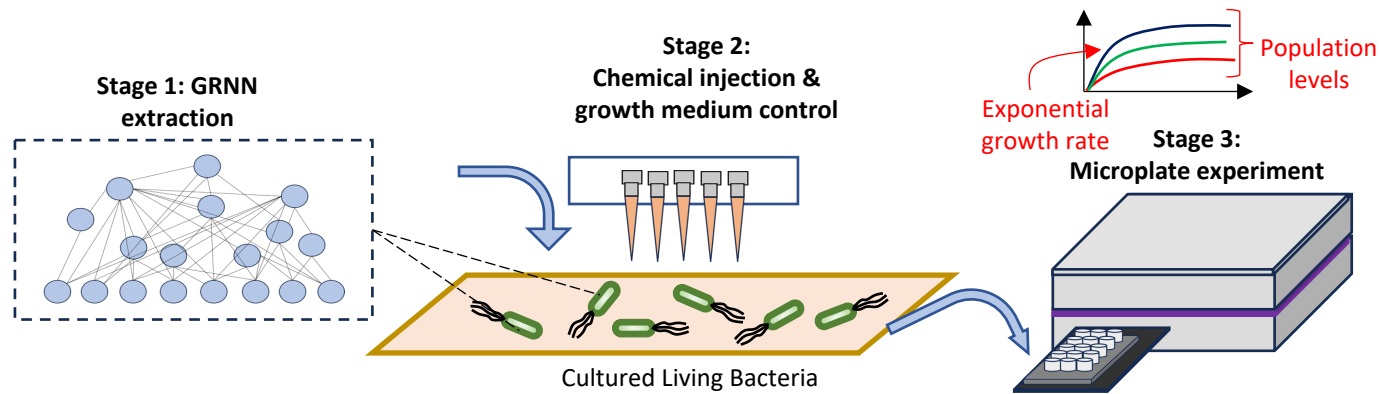
- Due to the high clustering and short path lengths, GRNNs have more orderly structures, which lowers the structural entropy.

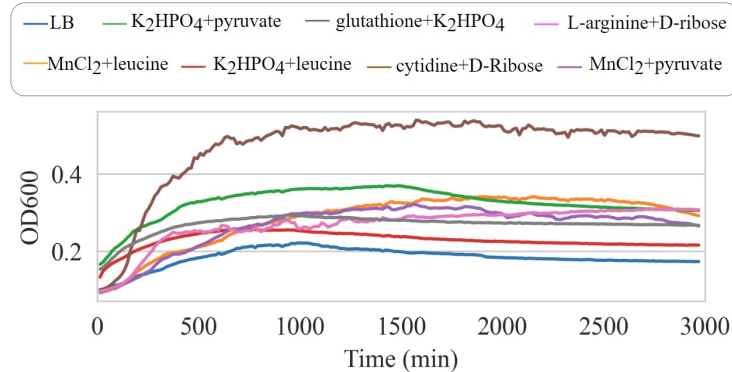- GNNS consume the least power when the structural entropy is close to 1.

ONGOING EXPERIMENTS

Wet Lab Experiment

Stage 1: GRNN extraction

Stage 2: Chemical injection & growth medium control

Stage 3: Microplate experiment

Exponential growth rate

Population levels

Cultured Living Bacteria

Sub-GRNN associated with cell growth.

- LB
- K$_2$HPO$_4$+pyruvate
- glutathione+K$_2$HPO$_4$
- L-arginine+D-ribose
- MnCl$_2$+leucine
- K$_2$HPO$_4$+leucine
- cytidine+D-Ribose
- MnCl$_2$+pyruvate

Various inputs are computed from the sub-GRNN, resulting in diverse growth curves.

Computing reliability analysis

Objectives :

- Investigate parallel computing properties.
- Conduct noise and weight plasticity analyses during computing.

Method :

- Transcriptomic analysis with multiple input sets.
- Temporal transcription level-based cross-talk & information theoretical analysis.

Collaborators :

Prof. Xu Li
Civil & Environmental Engineering, University of Nebraska

CONCLUSION

Bacterial decision-making

- Despite being non-neuronal organisms, bacterial cells exhibit an incredibly complex decision-making process.

- **GRN** drives this **decision-making** process resembling a **neural network**.

Gene Regulatory Neural Networks (GRNN)

- **GRNN** reveals the natural computing capabilities of bacteria based on a network of gene expressions.

- **GRNN** can be considered a repository of pre-trained neural networks, which can be searched to match computing applications.

Wet-Neuromorphic computing

- Aim is to use the **bio-compatibility**, **physical size** of chemical neural networks and **energy efficiency** of bacteria for new bio-computing.

- Cell **plasticity** enhances the **computing diversity** and makes cells suitable for **dynamic system computing**.

Thank you!

Samitha Somathilaka

Email: ssomathilaka2@unl.edu

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