



# Wet-TinyML

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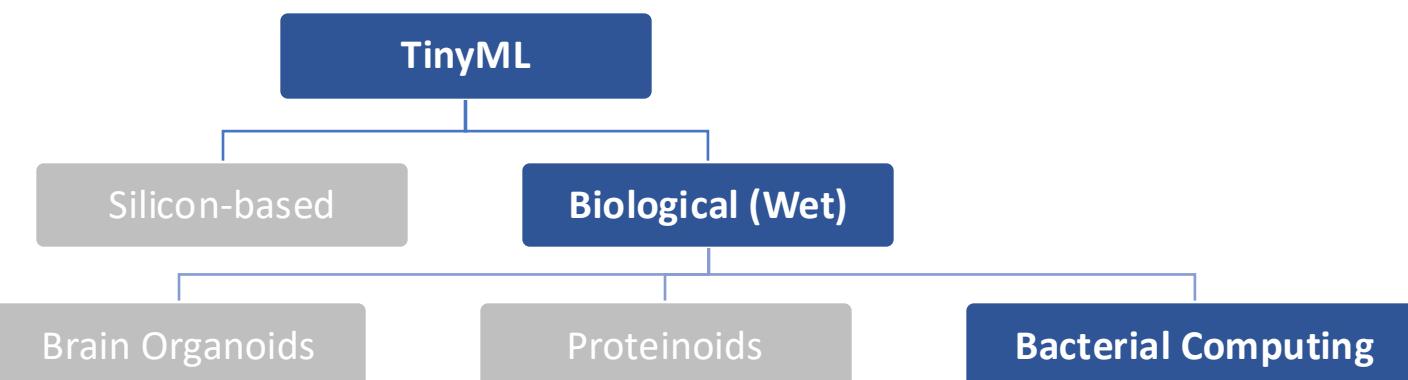
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# What is Wet-TinyML

- Wet-TinyML refers to the **integration** of TinyML concepts with **biological substrates or wetware**, such as living cells.
- It goes beyond simply mimicking ML in biology:
  - Exploiting conventional computing concepts (logics, memory) from biological systems.
  - Exploit native, substrate-specific computational features (e.g., **stochasticity, parallelism, adaptability**) that can outperform digital systems under certain constraints.



# Biological Substrates for Wet-TinyML

- **Brain Organoids**

- Miniaturized, 3D neural tissues grown from stem cells.
- Represent neural processors, capable of computation through biological dynamics.

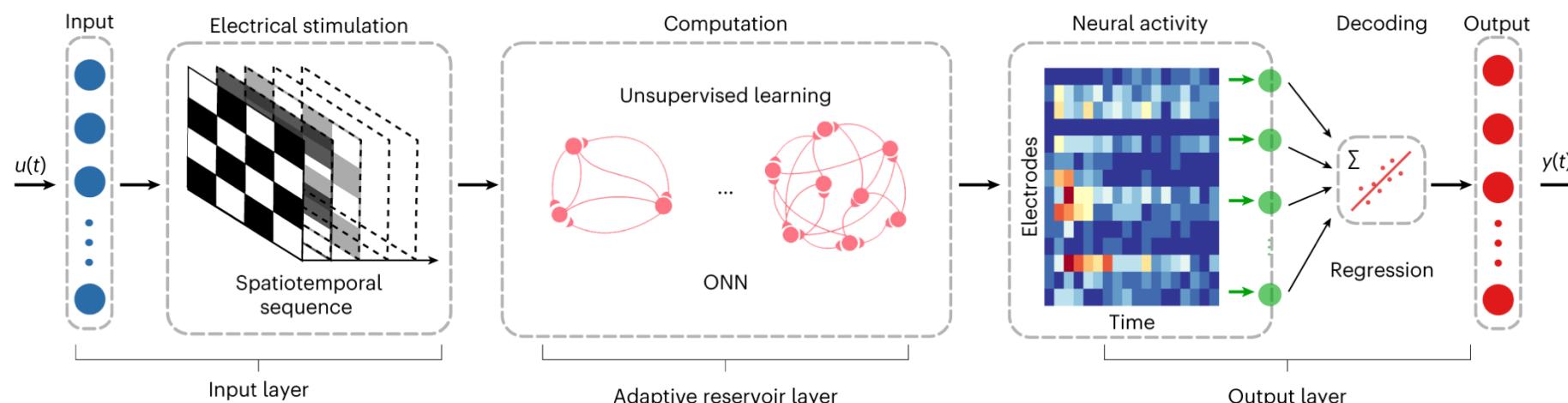


Figure: Brain organoid reservoir computing

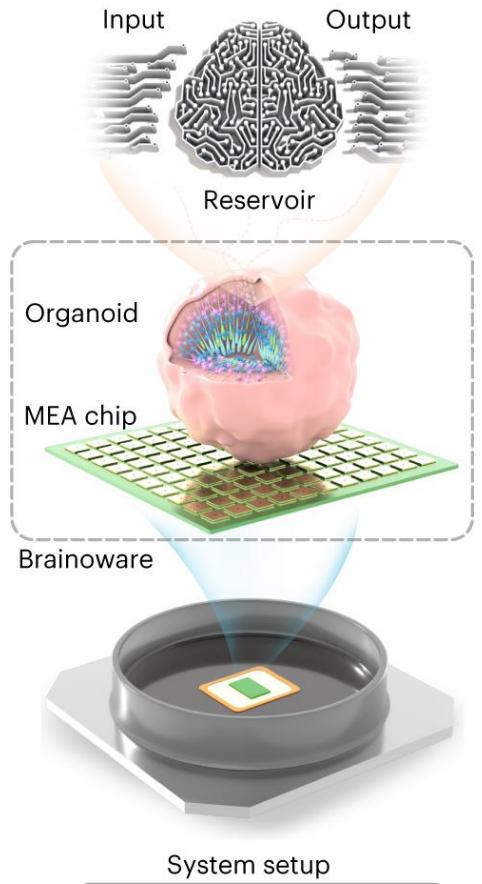


Figure: System Setup

Cai, H., Ao, Z., Tian, C. et al. Brain organoid reservoir computing for artificial intelligence. *Nature Electronics* **6**, 1032–1039 (2023).

# Biological Substrates for Wet-TinyML

Incredibly complex computing platform

Robustness

Learning/ adapting capabilities

Plasticity

Sustainability

Physical Scale

Energy efficiency

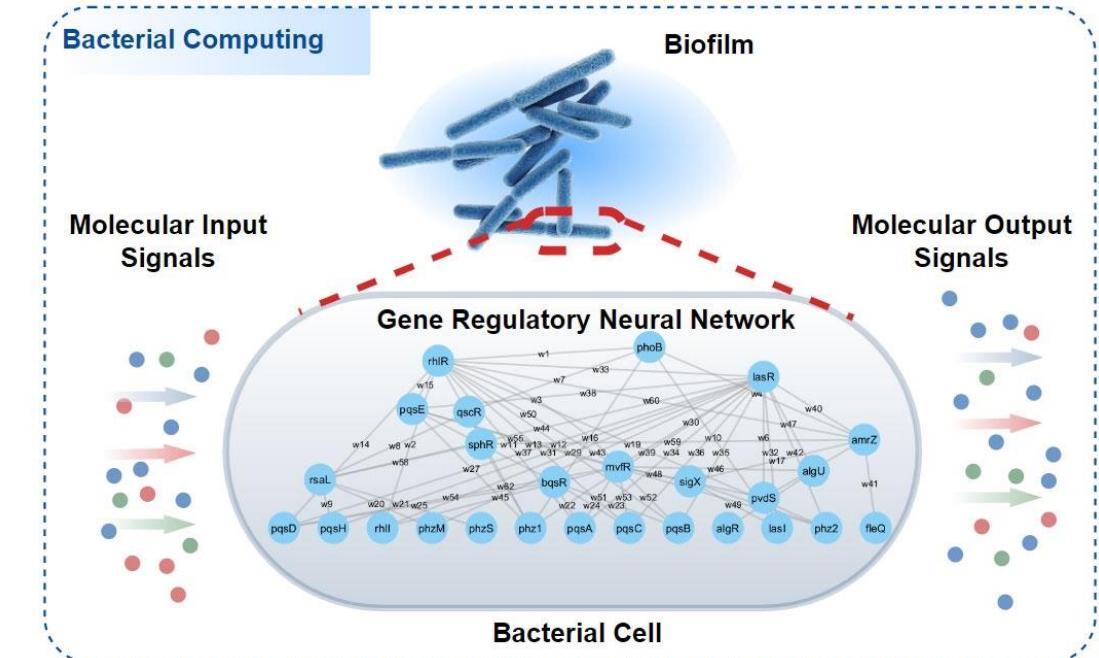
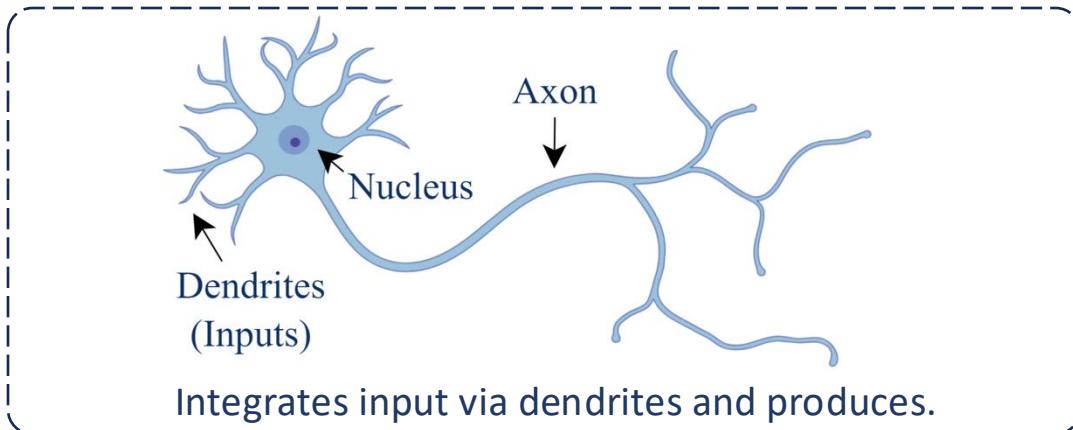
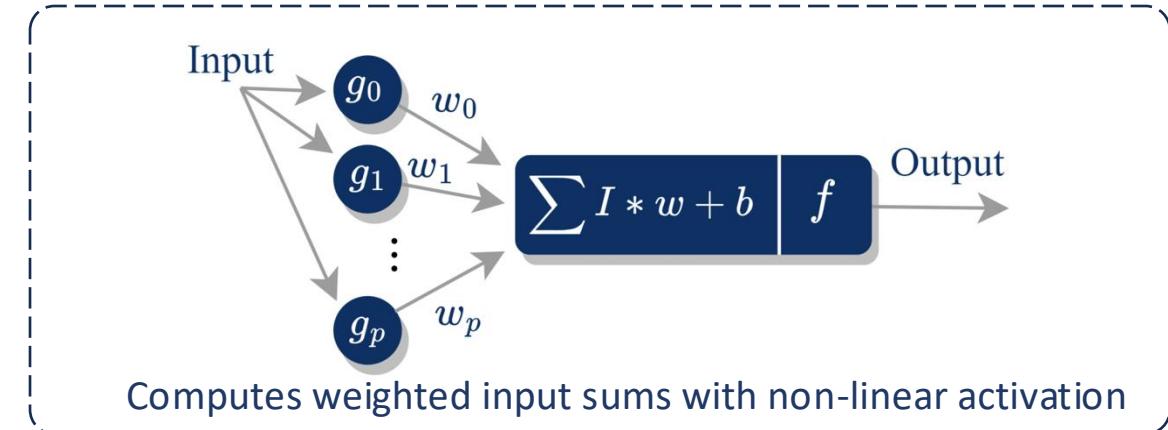


Figure: Bacterial computing paradigm with Gene Regulatory Neural networks.

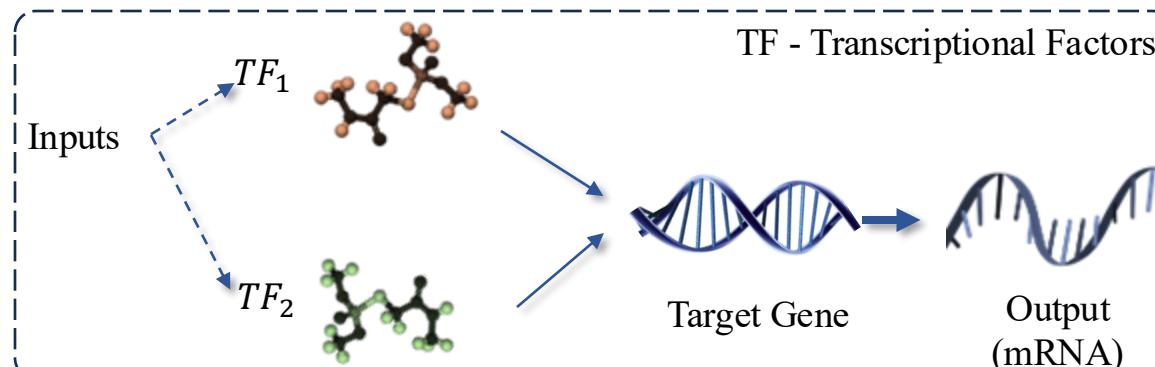
# Native Bacterial Computing



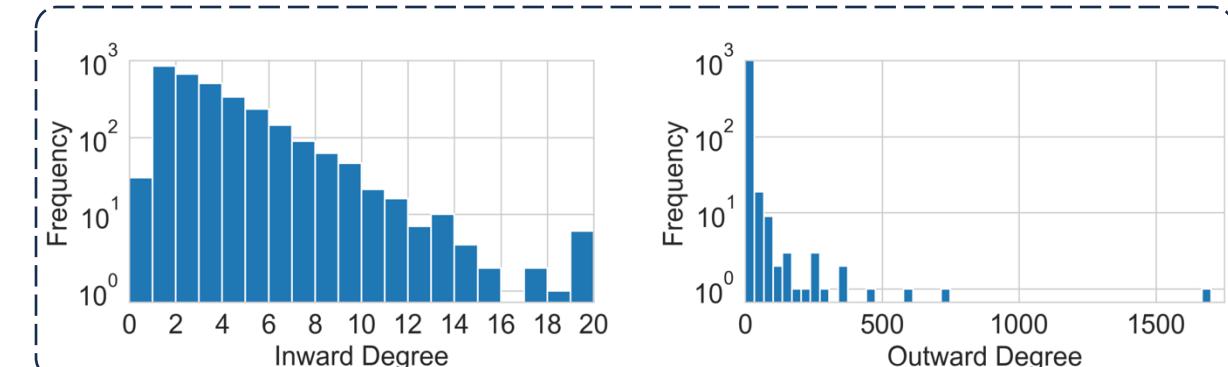
*Figure: Biological Neuron*



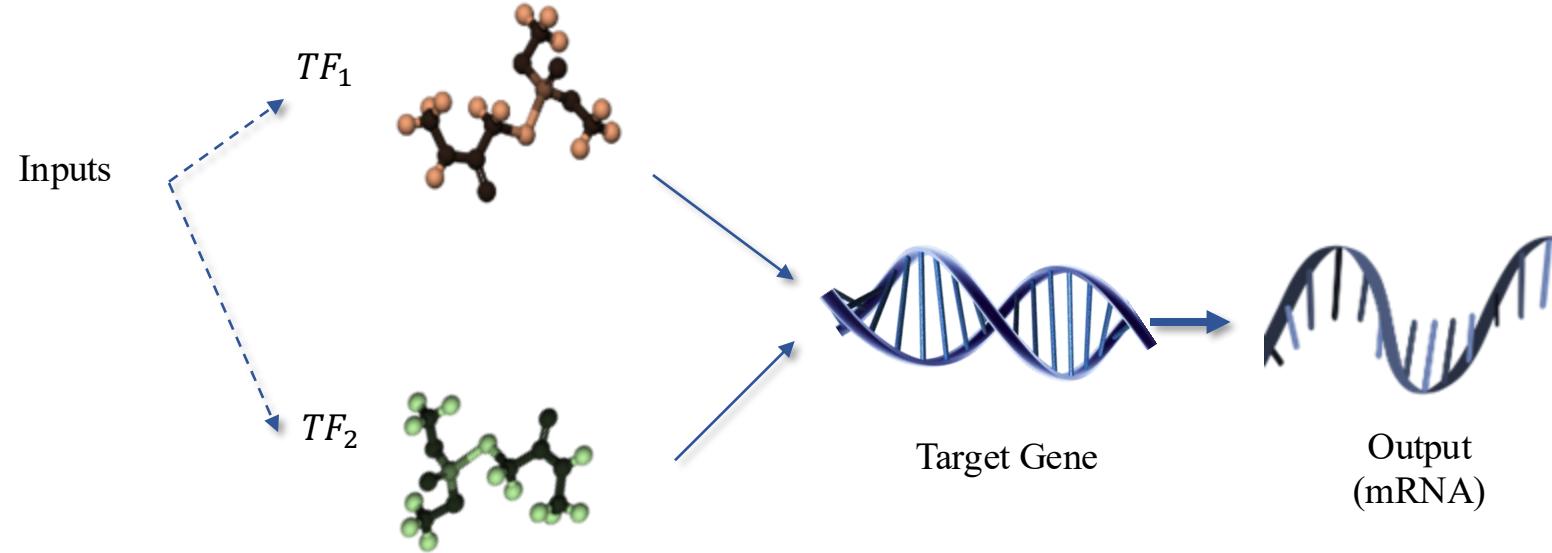
*Figure: Artificial Neuron*



*Figure: Gene Regulation*



*Figure: Degree Distribution of genes of *E. coli**



# Gene Regulatory Neural Networks

# Weighing Gene-Gene Interactions

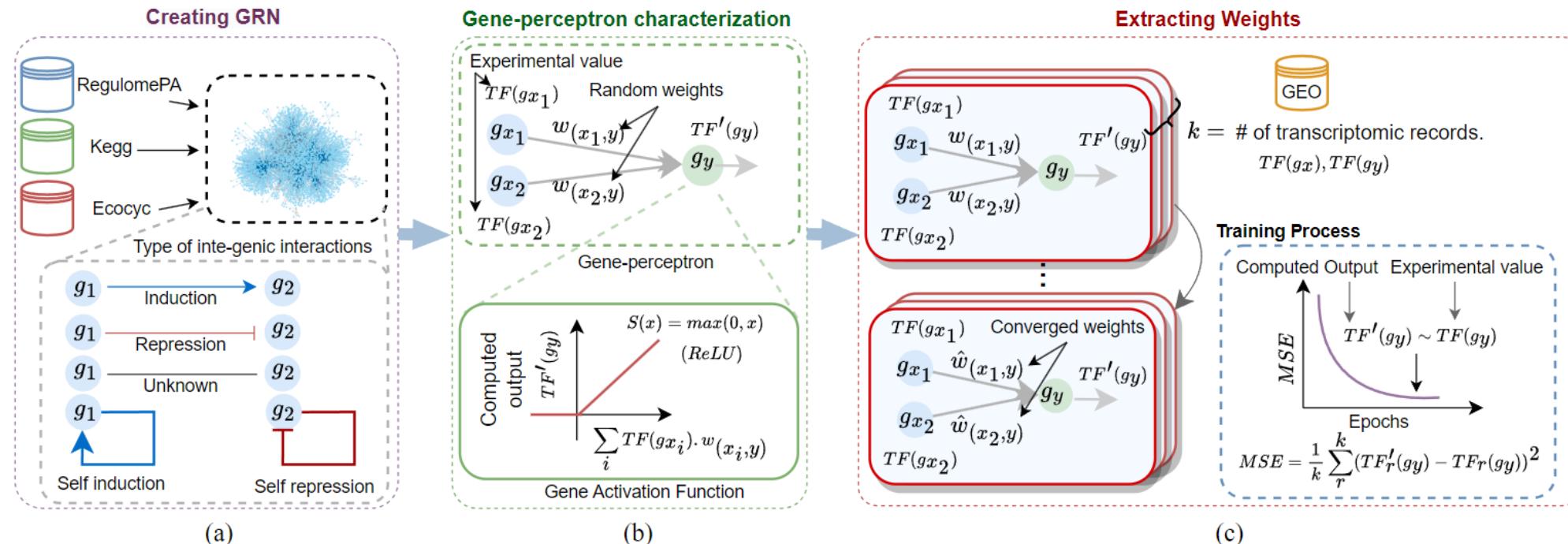


Figure: Illustration of a) diverse gene interaction types, b) single-layer gene-perceptrons, and c) weight extraction by fine-tuning edge weights to minimize the Mean Squared Error (MSE) between calculated, predicted and experimental gene expression levels.

$TF_{gx_i}$  - TF concentration of  $i^{th}$  input gene

$w_{(x_i,y)}$  - weight between  $x_i$  and  $y$

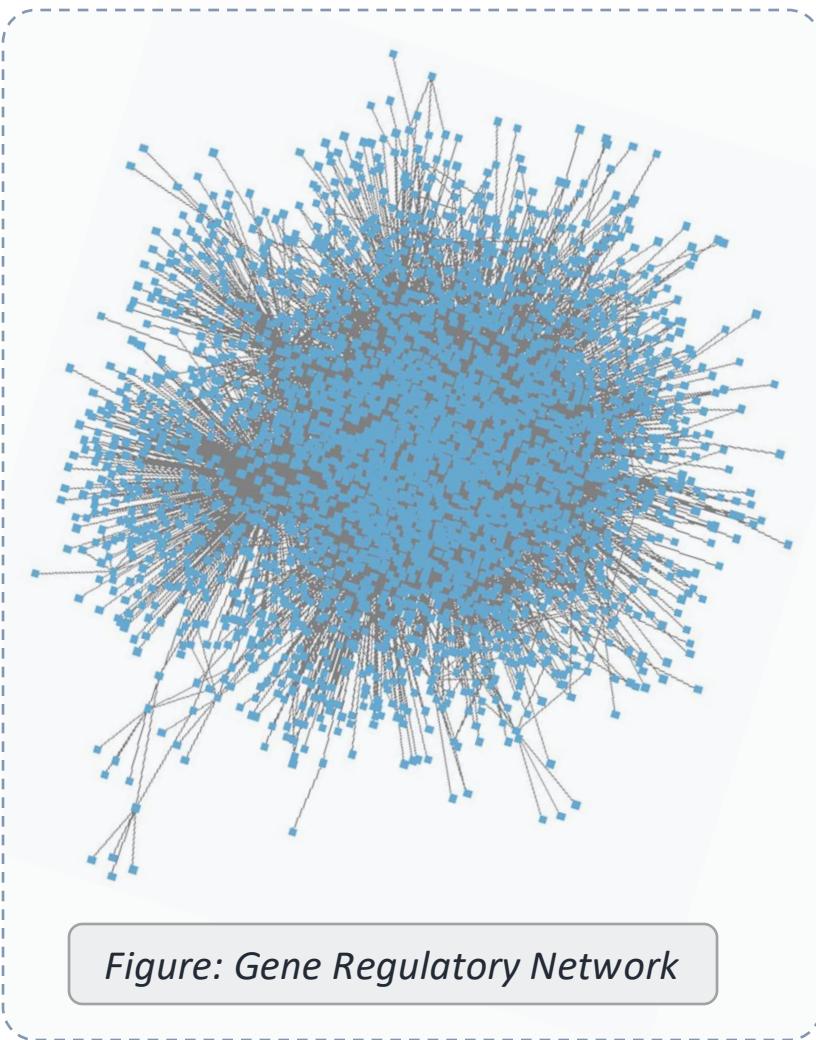
$TF'_{gy}$  - predicted TF concentration of output gene  $y$

$r$  -  $r^{th}$  transcriptomic record

Samitha S. Somathilaka, Sasitharan Balasubramaniam, Daniel P. Martins, and Xu Li. 2023. Revealing gene regulation-based neural network computing in bacteria. Biophysical Reports 3, 3 (2023), 100118. <https://doi.org/10.1016/j.bpr.2023.100118>



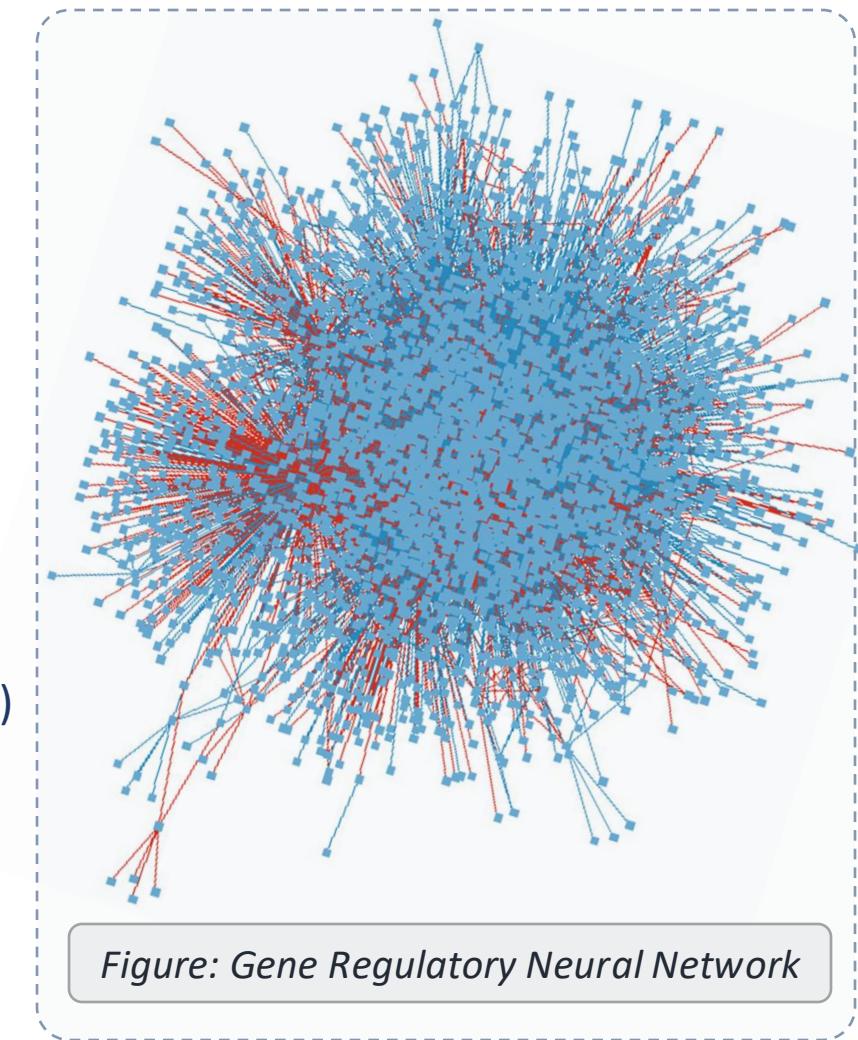
# Gene Regulatory Neural Network



Our algorithm determines weights  
of each edge

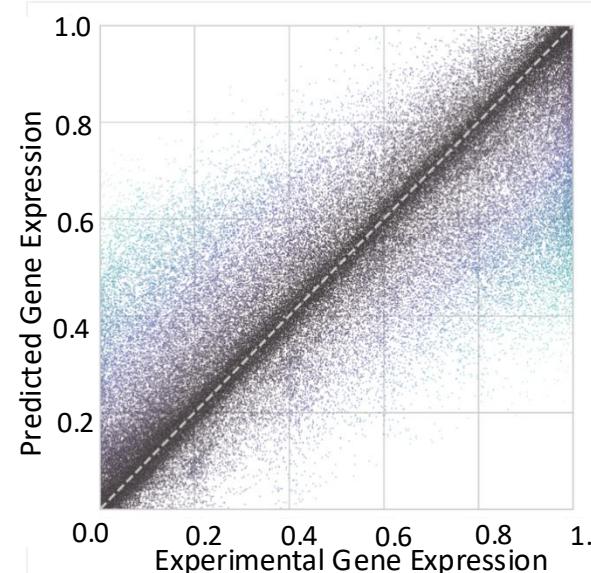


GRN is converted into GRNN  
(A random structure Neural Network)



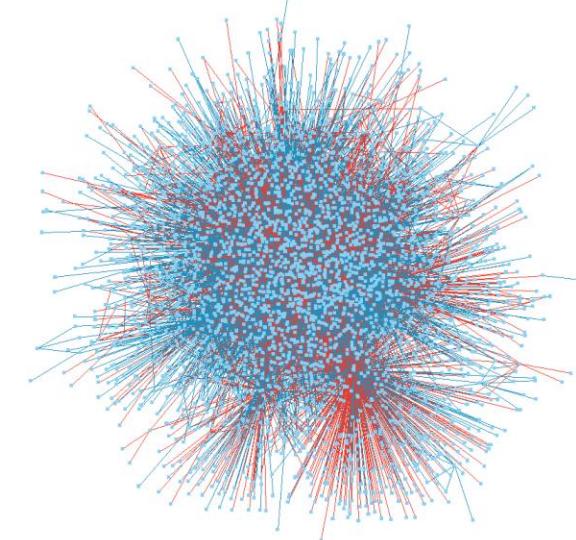
# E. Coli GRNN - (CSH50)

## E. Coli weight extraction accuracy



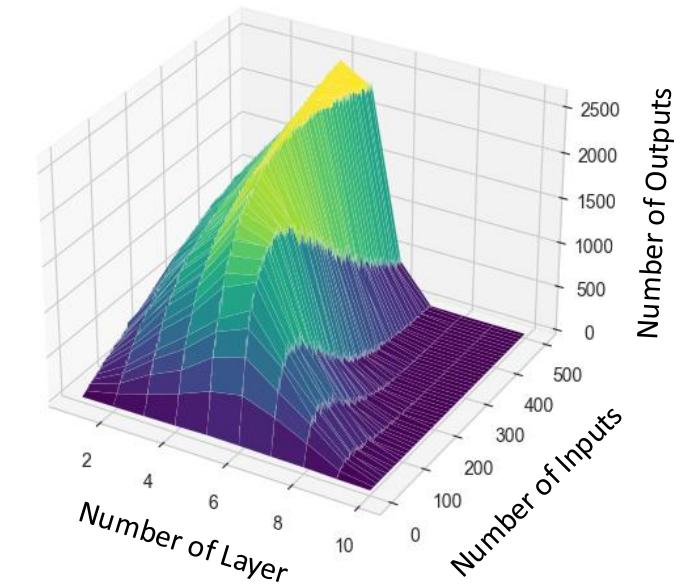
- The  $45^{\circ}$  line is where the predicted and experimental expressions are equal.
- Results show that the majority of the predictions are close to experimental values.

## E. Coli GRNN



- Contains 5000 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  $5.9 \times 10^{297}$ .

# More Properties of Bacterial Computing Systems

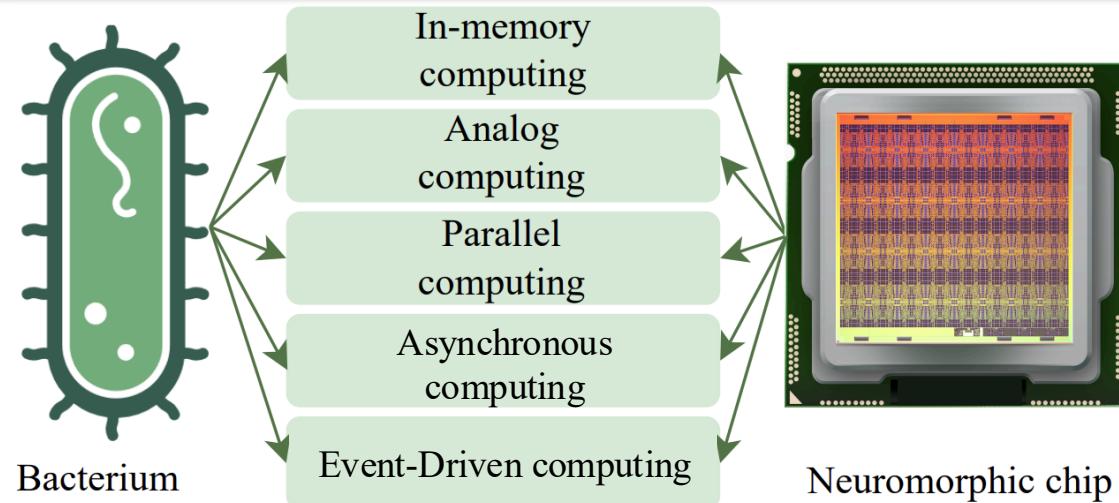


Figure: Neuromorphic Properties of Bacterial Computing Systems

**In-memory computing:** Gene regulatory processes store and process information simultaneously, reducing latency.

**Analog computing:** Continuous gene expression dynamics resemble analog signal processing.

**Parallel computing:** Multiple genetic pathways operate simultaneously without centralized control.

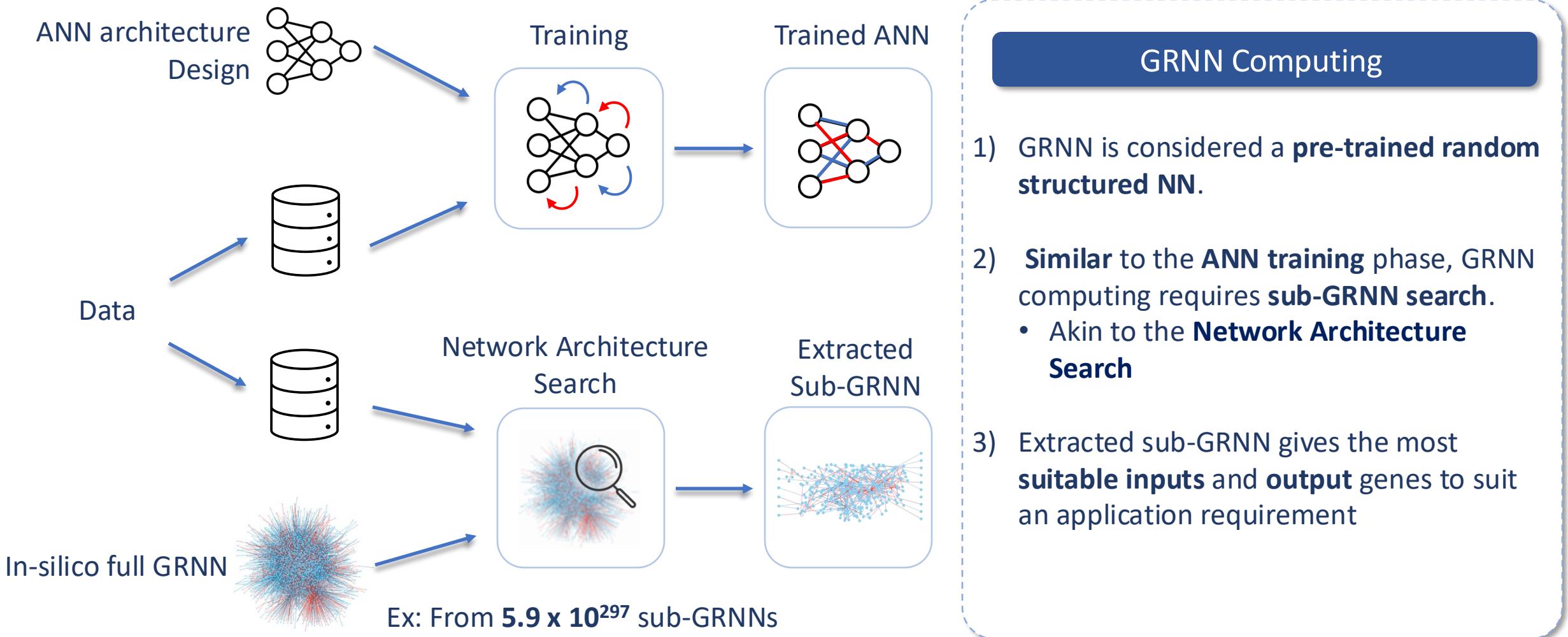
**Asynchronous computing:** Doesn't follow a global clock.

**event-driven computing :** Responses are triggered by molecular events occur.

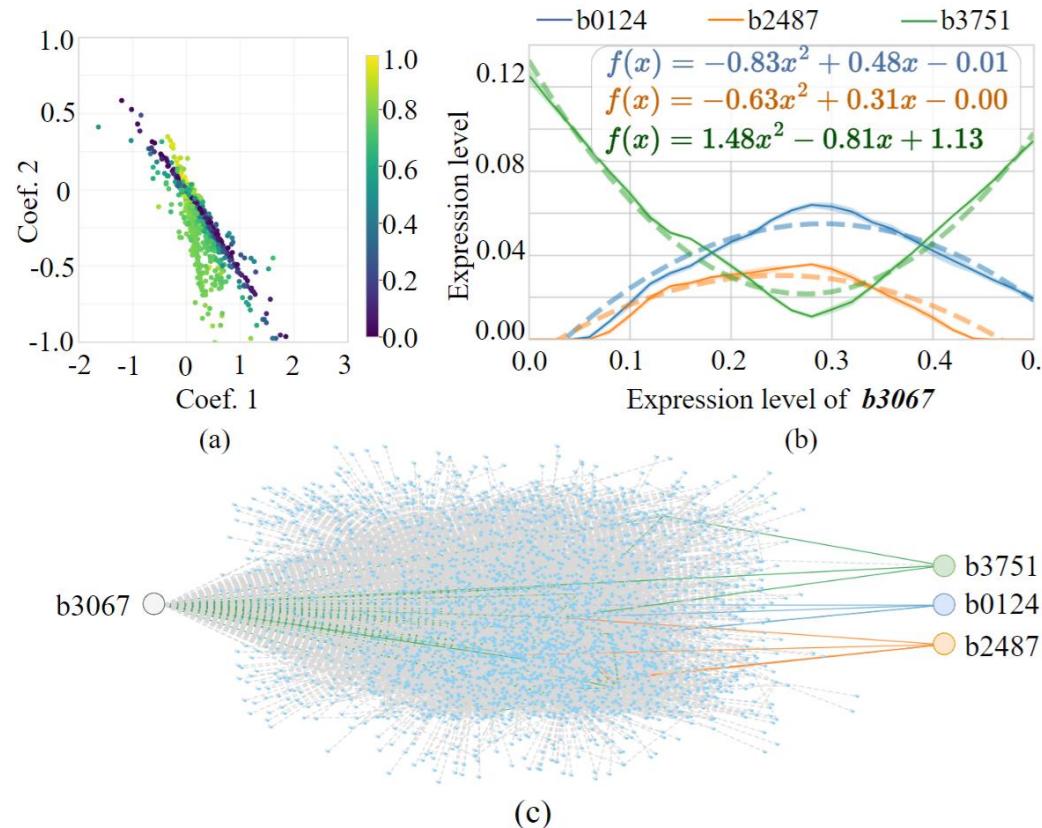
# Comparison Between Computing Platforms

	Human brain	Loihi 2	Bacteria
# Computing units	~86 B neurons	1 M neurons	100-11000 genes
Storage	~2500 Tb	24 MB	~1.2 MB
Size	1300 cm <sup>3</sup>	31 mm <sup>2</sup>	~0.4 - 3 μm <sup>3</sup>
Power consumption	20 W	100 mW	<0.1 pW
Comp. unit density	7.7x10 <sup>4</sup> mm <sup>-3</sup>	3.2x10 <sup>4</sup> mm <sup>-2</sup>	<b>5 x10<sup>12</sup> mm<sup>-3</sup></b>

# ANN vs GRNN Application



# GRNN Application in Regression (Single-cell Computing)



## Simple non-linear Regressions:

Gene expression dynamics exhibits non-linear trends with respect to inputs.

Fig. (a) shows coefficient behaviors of quadratic functions exhibiting regression diversity.

Fig. (b) exemplifies three curves with various coefficients.

Fig. (c) shows the extracted sub-network for corresponding regressions.

This proves the possibility of performing simple regression tasks using non-engineered bacterial cells.

Samitha Somathilaka, Sasitharan Balasubramaniam, and Daniel P Martins. 2023. Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks. <https://doi.org/10.36227/techrxiv.170327579.97407418/v1> (IEEE Transaction on Emerging Topics in Computing)

# GRNN Application in Regression (Single-cell Computing)

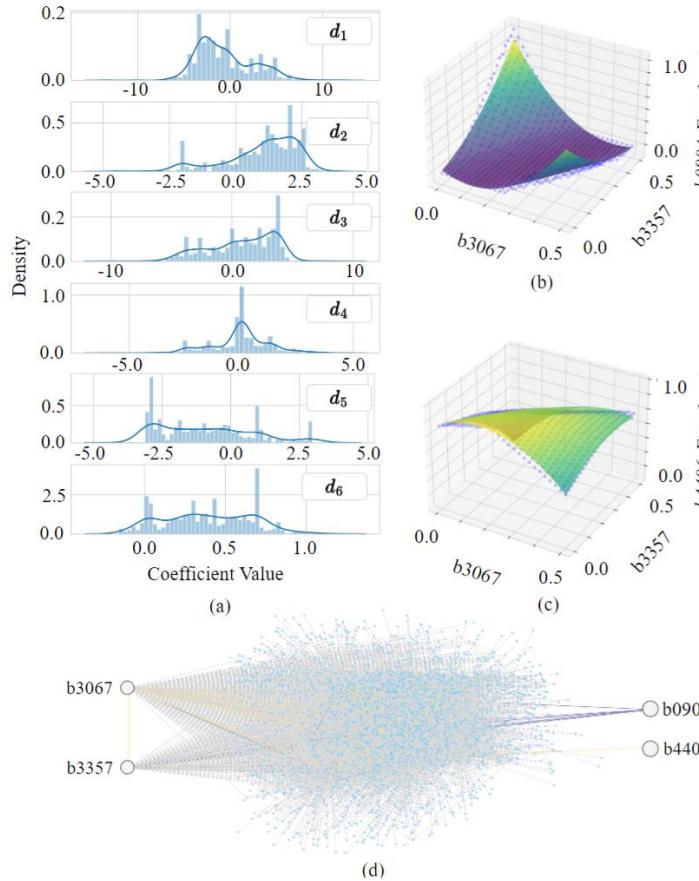


Fig: Multiple non-linear regression using *E.coli*

$$f(x_1, x_2) = d_1 x_1^2 + d_2 x_2^2 + d_3 x_1 x_2 + d_4 x_1 + d_5 x_2 + d_6$$

## Multiple non-linear regressions:

- This analysis explores the possibility of performing multiple non-linear regression.
- Fig. (a) illustrates the diversity of the coefficients of the above equation.
- Fig. (b) and (c) exemplify two multiple non-linear curves.
- Fig. (d) shows the extracted sub-network for corresponding regressions.
- These results elucidate the possibility of performing complex regression computing using non-engineered bacterial cells.

Samitha Somathilaka, Sasitharan Balasubramaniam, and Daniel P Martins. 2023. Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks. *IEEE Transaction on Emerging Topics in Computing*

# GRNN Application in Classification (Single-cell Computing)

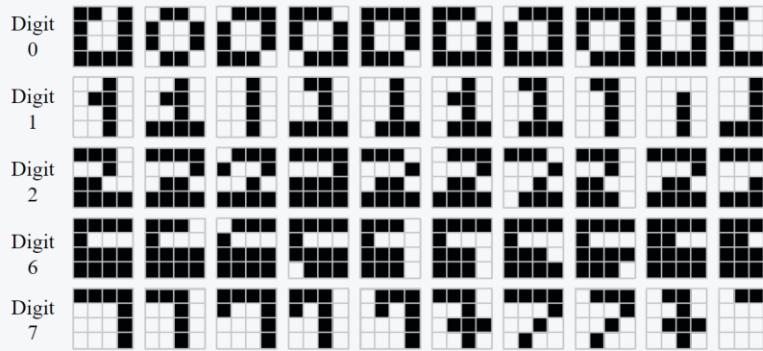


Figure:  $4 \times 4$  images under the five classes of digits and the associated augmentations.

## Search Data set:

- Five digits
- 16 pixels
- 10 augments

## Differentiability analysis

- Extracting genes with the highest differentiability.
- The first 5 plots show expression differentiability in each digit pool.
- The last plot shows the differentiability of all the selected output genes.

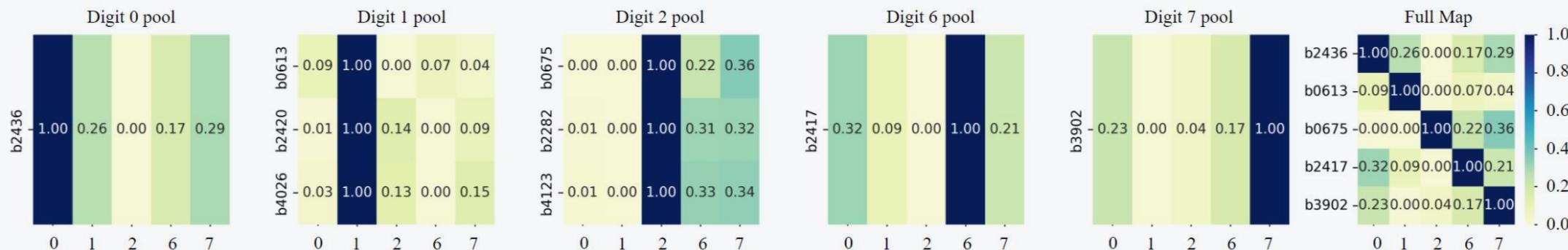


Fig. Differentiation capability of each gene assigned for each digit

# GRNN Application in Classification (Single-cell Computing)

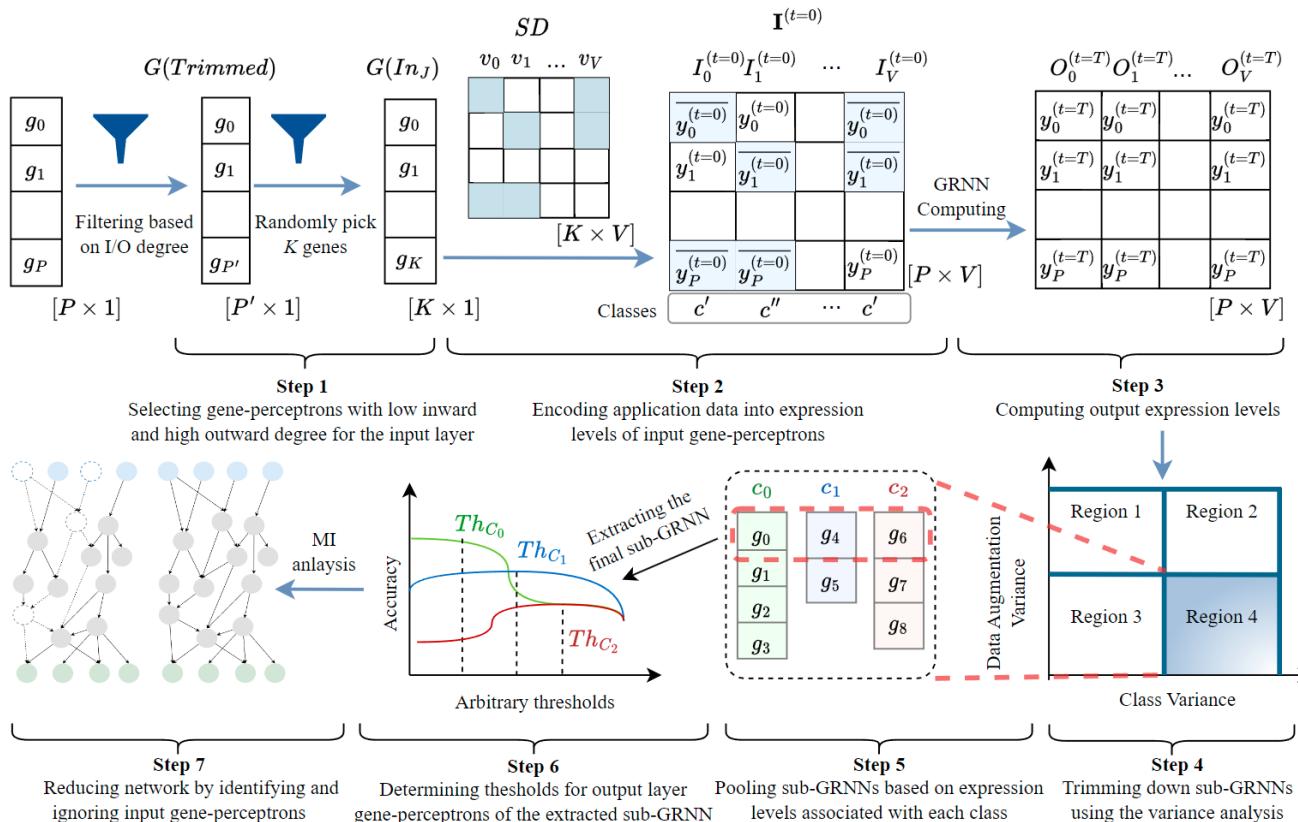


Fig. Steps of the application-specific search algorithm.

Samitha Somathilaka, Sasitharan Balasubramaniam, and Daniel P Martins. 2023. Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks. *IEEE Transaction on Emerging Topics in Computing*

## Random permutation-based search algorithm:

1. Suitable input genes are identified based on inward/outward degrees.
2. Encode search data into expression levels.
3. Output expression levels are computed using the *in-silico* GRNN.
4. Variance analysis identifies genes that can represent each class.
5. Filters genes in each class with the highest differentiability.
6. Determines thresholds for each gene.
7. Reduce network using MI analysis.

# GRNN Application in Classification (Single-cell Computing)

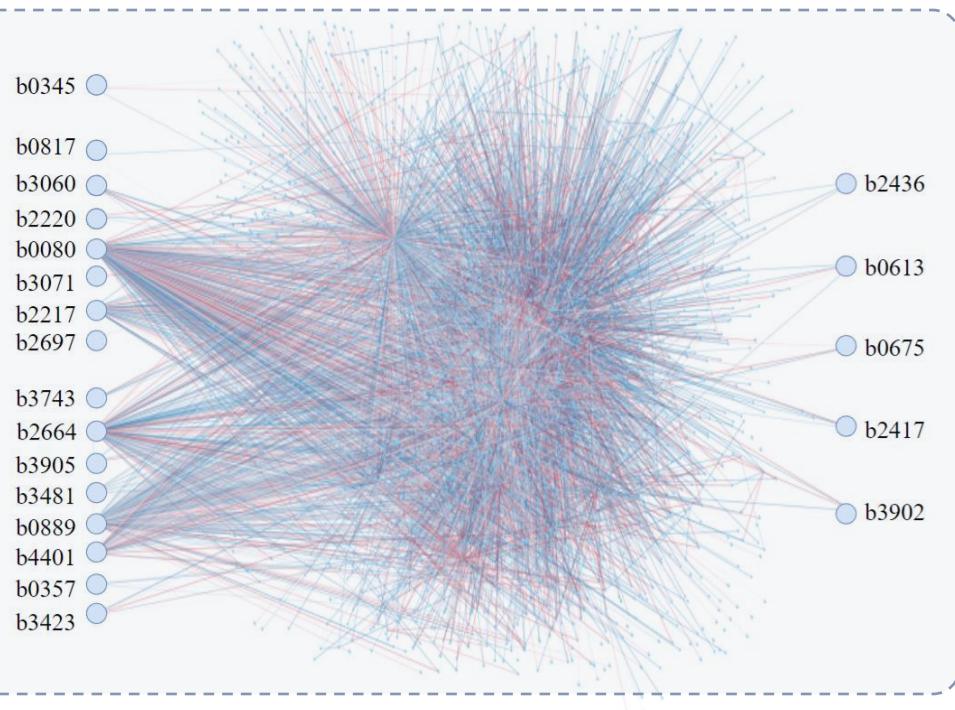
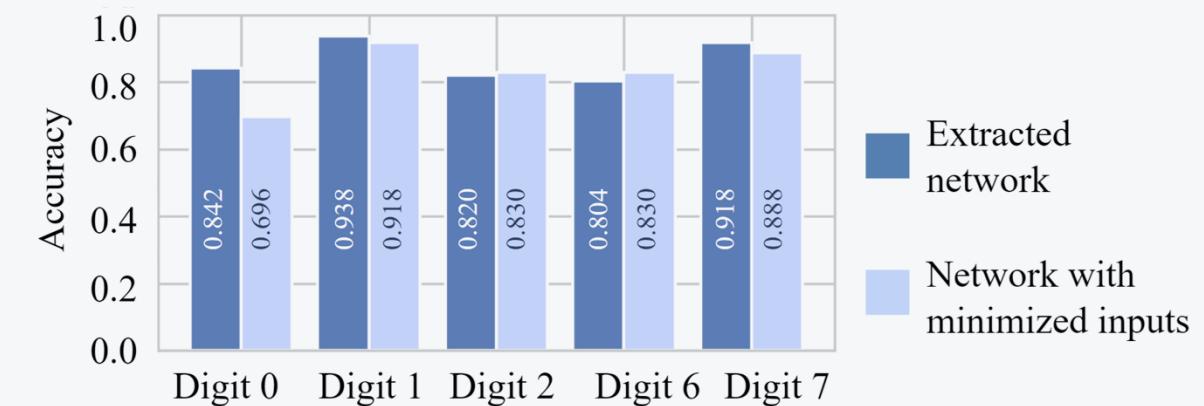


Figure: Extracted application-specific sub-GRNN

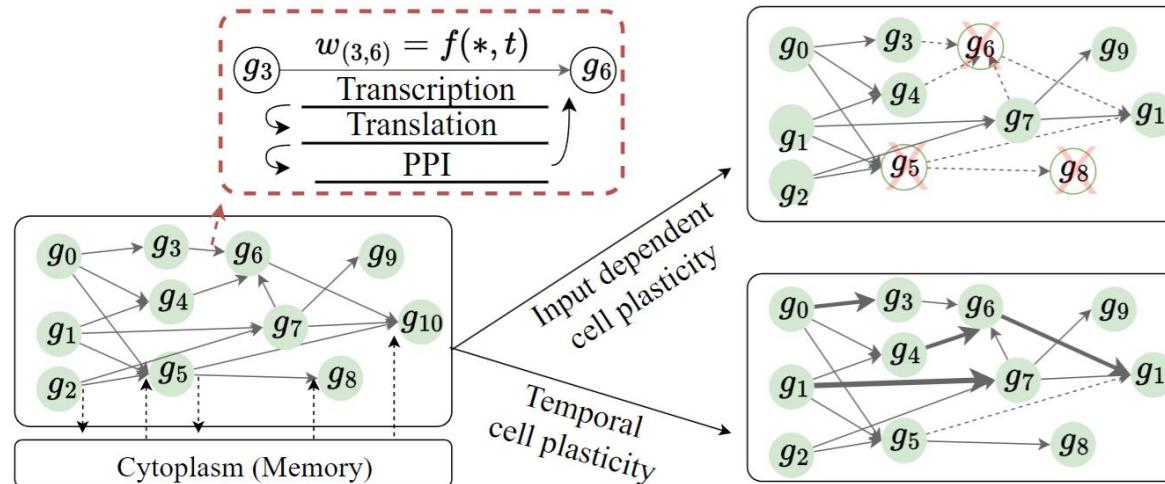


*Fig. Class-based accuracies before and after network reduction.*

1. Extracted sub-network shows significant accuracy.
2. Reduction of the network has a minimal impact on the accuracy.
3. The class-based accuracies suggest that the non-engineered bacterial cells can be used for classification tasks.

Samitha Somathilaka, Sasitharan Balasubramaniam, and Daniel P Martins. 2023. Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks. *IEEE Transaction on Emerging Topics in Computing*

# GRNN Plasticity – Dynamic weights



*Fig: Two types of plasticities of the GRNN.*

## Cell Plasticity:

Cellular plasticity makes cells adaptable to many environments.

This allows the cells to have a vast spectrum of GRNN weight configurations.

## Input Dependent Plasticity:

This is driven by the selective responsiveness of genes to specific input chemicals

GRNN selectively channels information flow, activating only the relevant expression pathways.

## Temporal Plasticity

Over the environmental dynamics, it is observed that the weights of the edges change.

This leads the GRNN to have various weight configurations over time.

# GRNN Applications in Regression with Plasticity

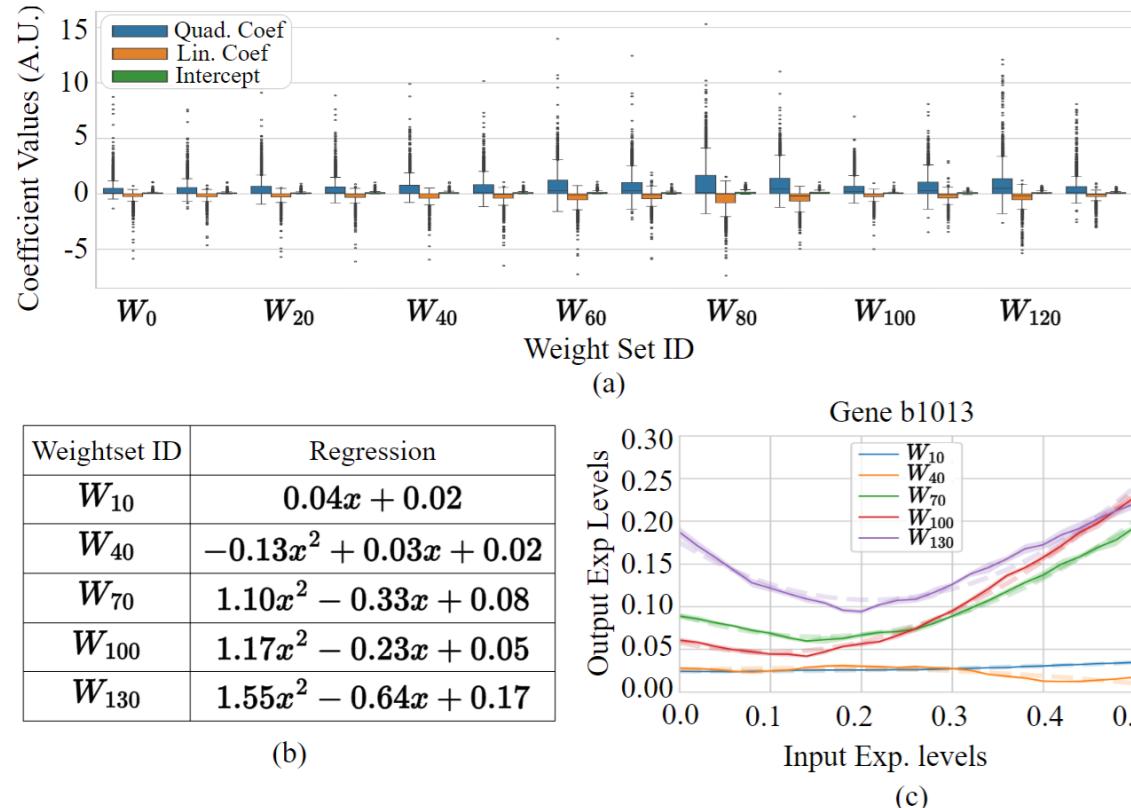


Figure: Expansion of regression space using cell plasticity.

## Expanding the search space with plasticity

- Fig. (a) illustrates the coefficient diversity of extracted.
- Fig. (b) and (c) is a table of five quadratic regressions of the example gene  $b1013$  in five weight configurations over time.
- This study proved the possibility of expanding the computing diversity using plasticity.**
- This dynamic behavior can be used in the future for dynamic computing.**

Samitha Somathilaka, Sasitharan Balasubramaniam, and Daniel P Martins. 2023. Analyzing Wet-Neuromorphic Computing Using Bacterial Gene Regulatory Neural Networks. *IEEE Transaction on Emerging Topics in Computing*

# Energy Profile Comparison

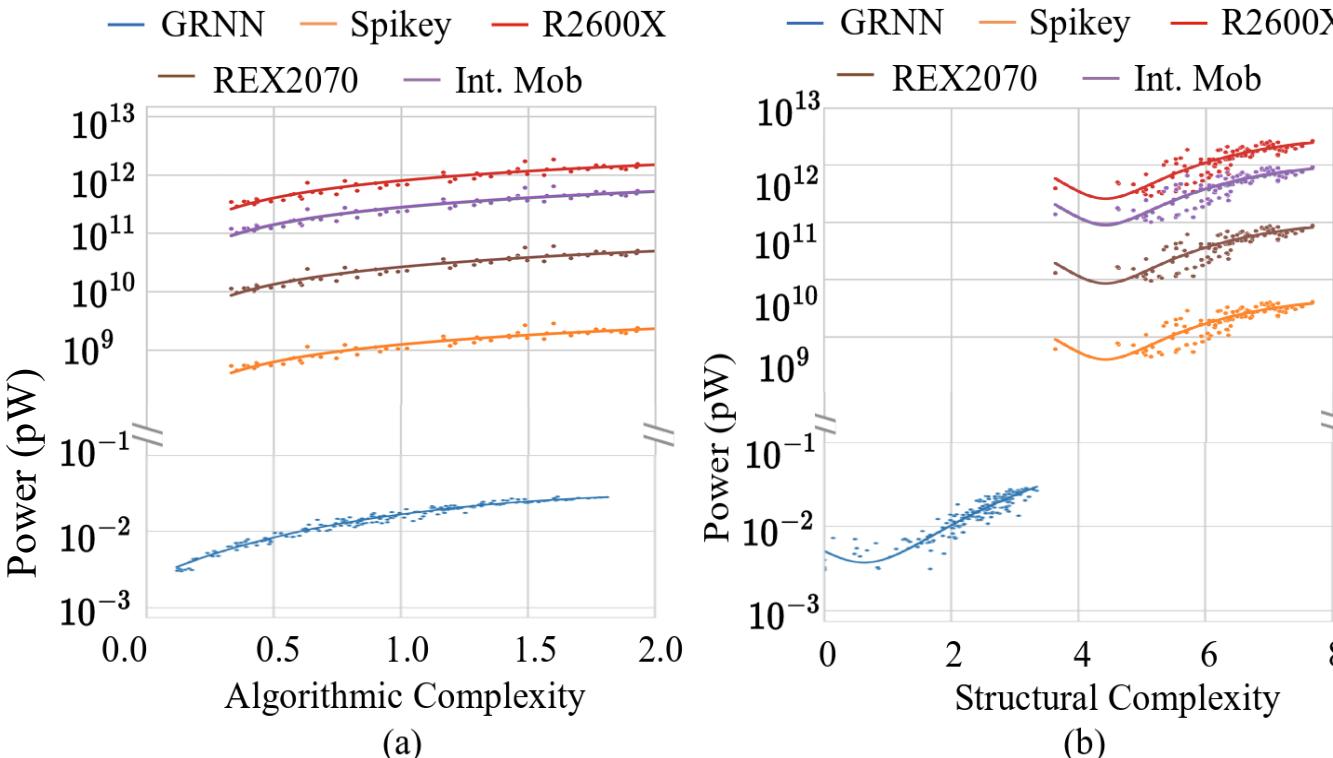


Figure: a) Algorithmic complexity and b) structural complexity.

- GRNN operates in the **femto-to-picowatt range** ( $\sim 10^{-3}\text{--}10^{-2}$  pW), **much lower** than all others.
- All silicon-based systems operate in the **milliwatt to watt range** ( $\sim 10^9\text{--}10^{13}$  pW)
- All systems show **increasing power** with algorithmic complexity.
- GRNN's increase is **sublinear**, suggesting efficient scaling.
- Digital systems (R2600X, Int. Mob, etc.) scale much more steeply.

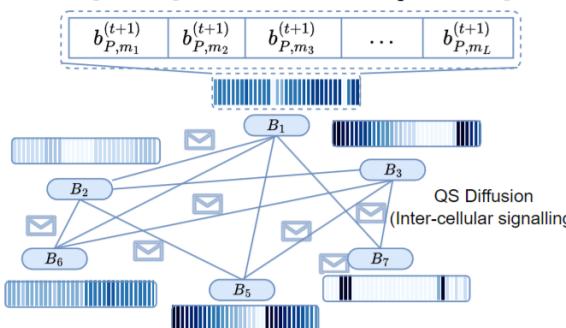
# GRNN Distributed Computing (Multi-cellular Computing)

Introduced a **Graph Neural Network (GNN)** Model that integrates the **MC** of population and **GRNN** computing.

$FV_P^{(t+1)}$  - Feature vector of  $P^{th}$  cell

$b_{P,m_L}^{(t+1)}$  - Concentration of the molecular species  $m_L$  cell

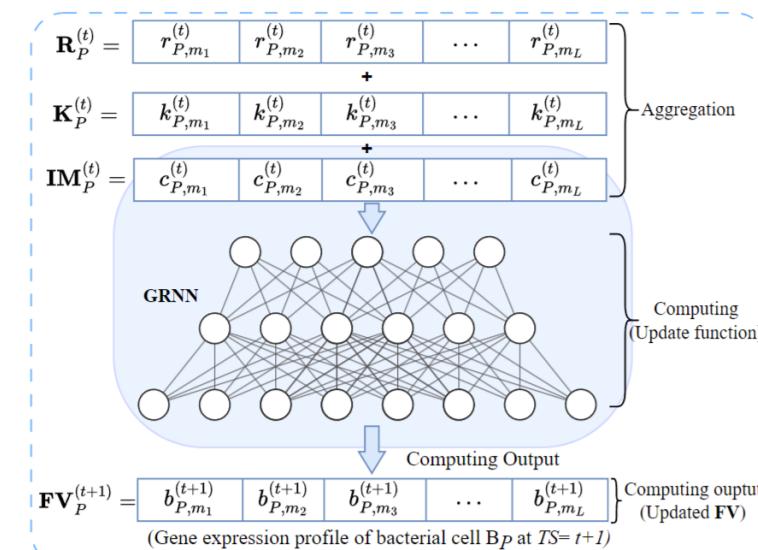
$\mathbf{FV}_P^{(t+1)}$   
(Gene expression profile of bacterial cell  $B_1$  at time step  $t+1$ )



(a)

Figure: Illustration of a) the GNN model of the MC and b) GRNN to GRNN messaging.

$$FV_P^{(t+1)} = GRNN(S_P^t)$$



(b)

$S_P^t$  - Input molecular vector of  $P^{th}$  cell

GRNN - GRNN of the cell as the update function

## Single Cell GRNN Model

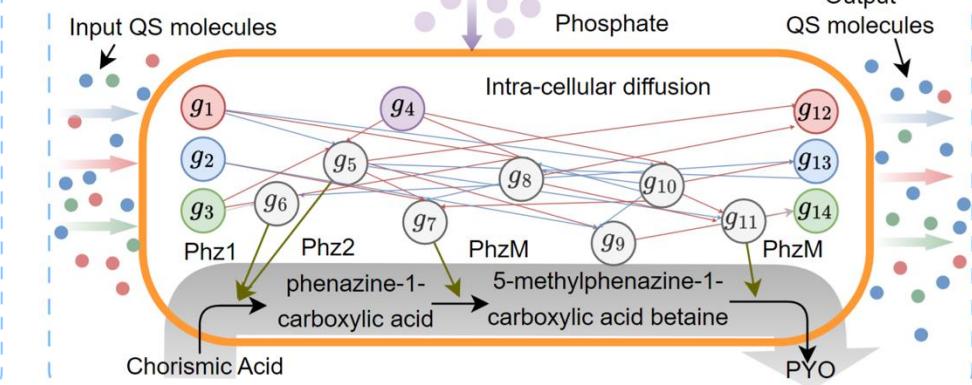
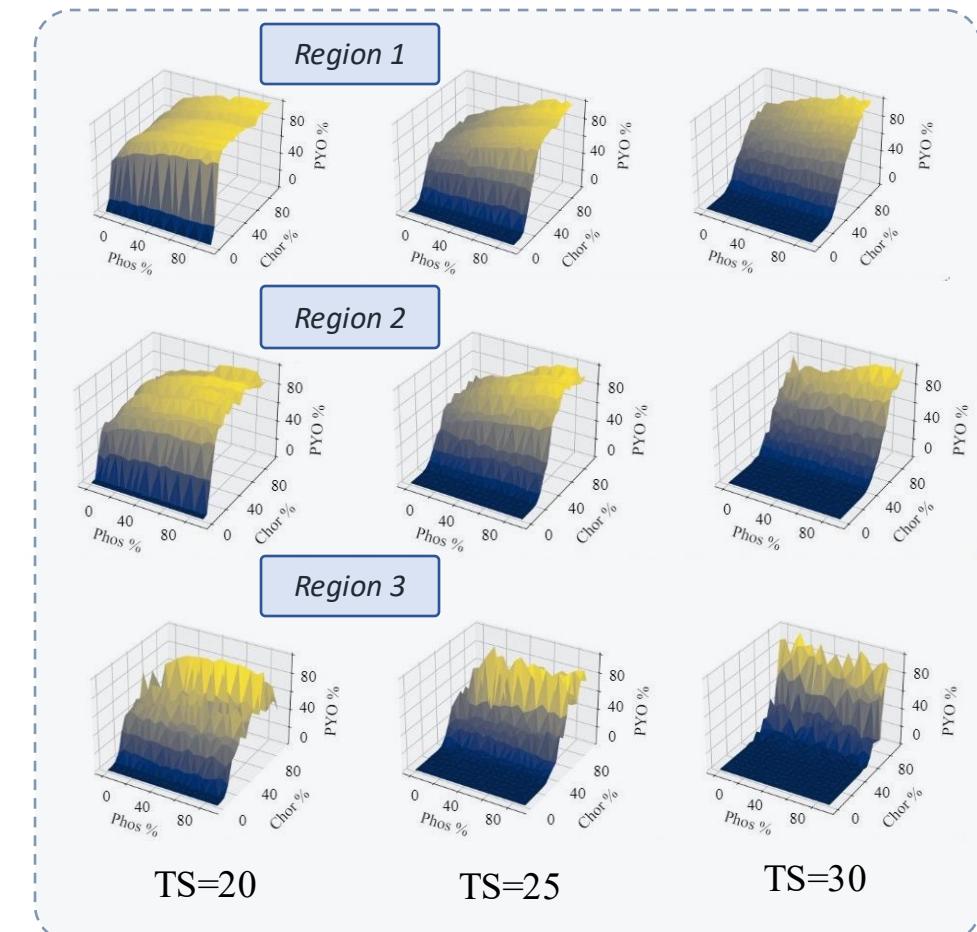
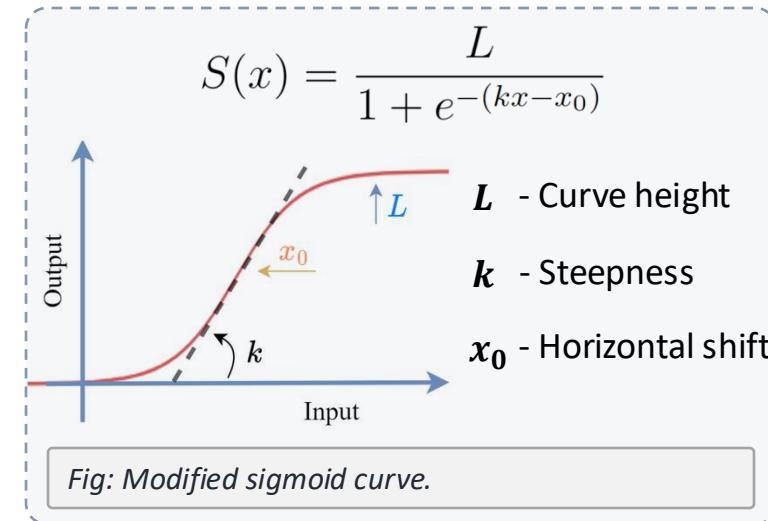
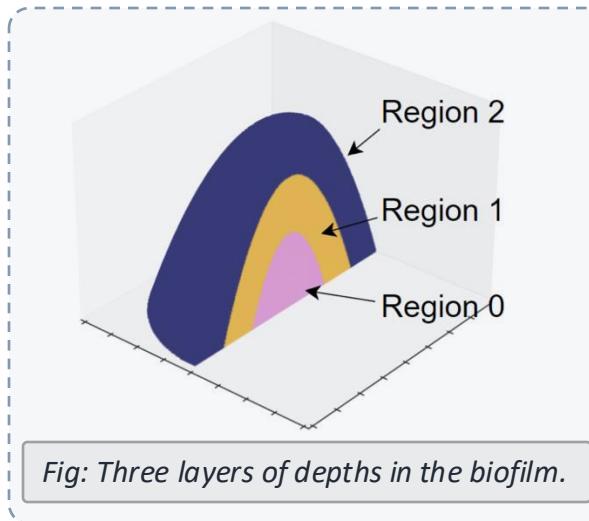


Figure: Computational process for incoming cell-cell communication molecules and the transformation of chorismic acid into PYO.



*Fig: Illustration of a sigmoid function-based solution space found in biofilms.*

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# The Internet of Biofilm Living AI Devices (BLAID)

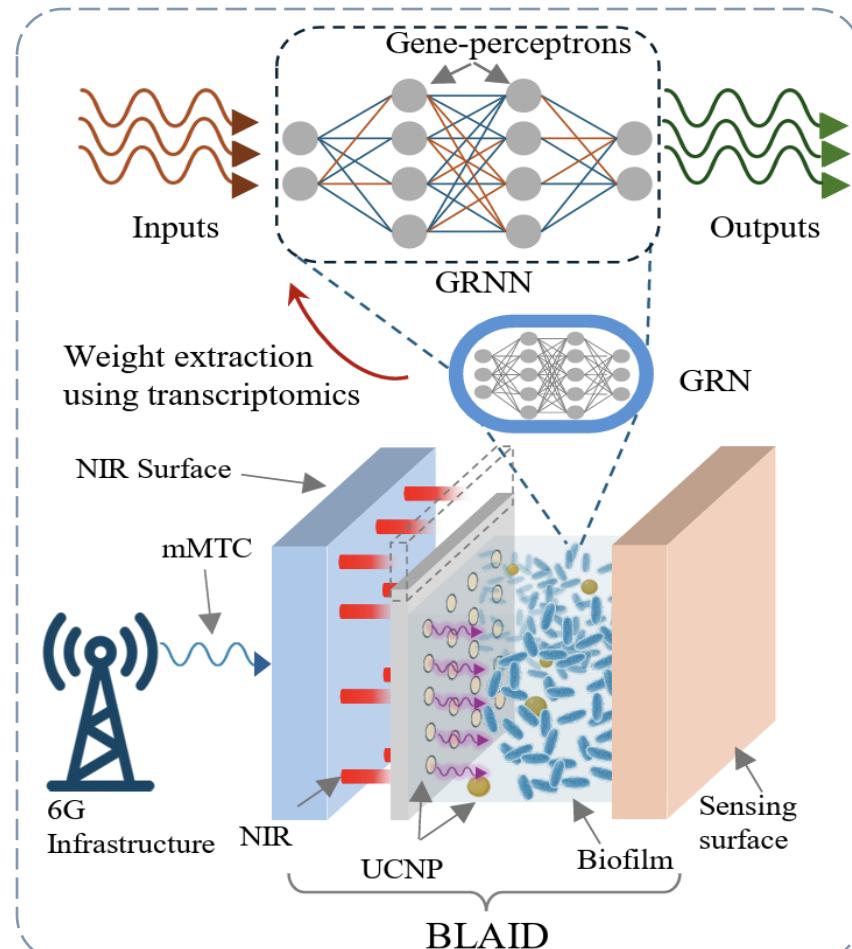


Figure: BLAID Concept

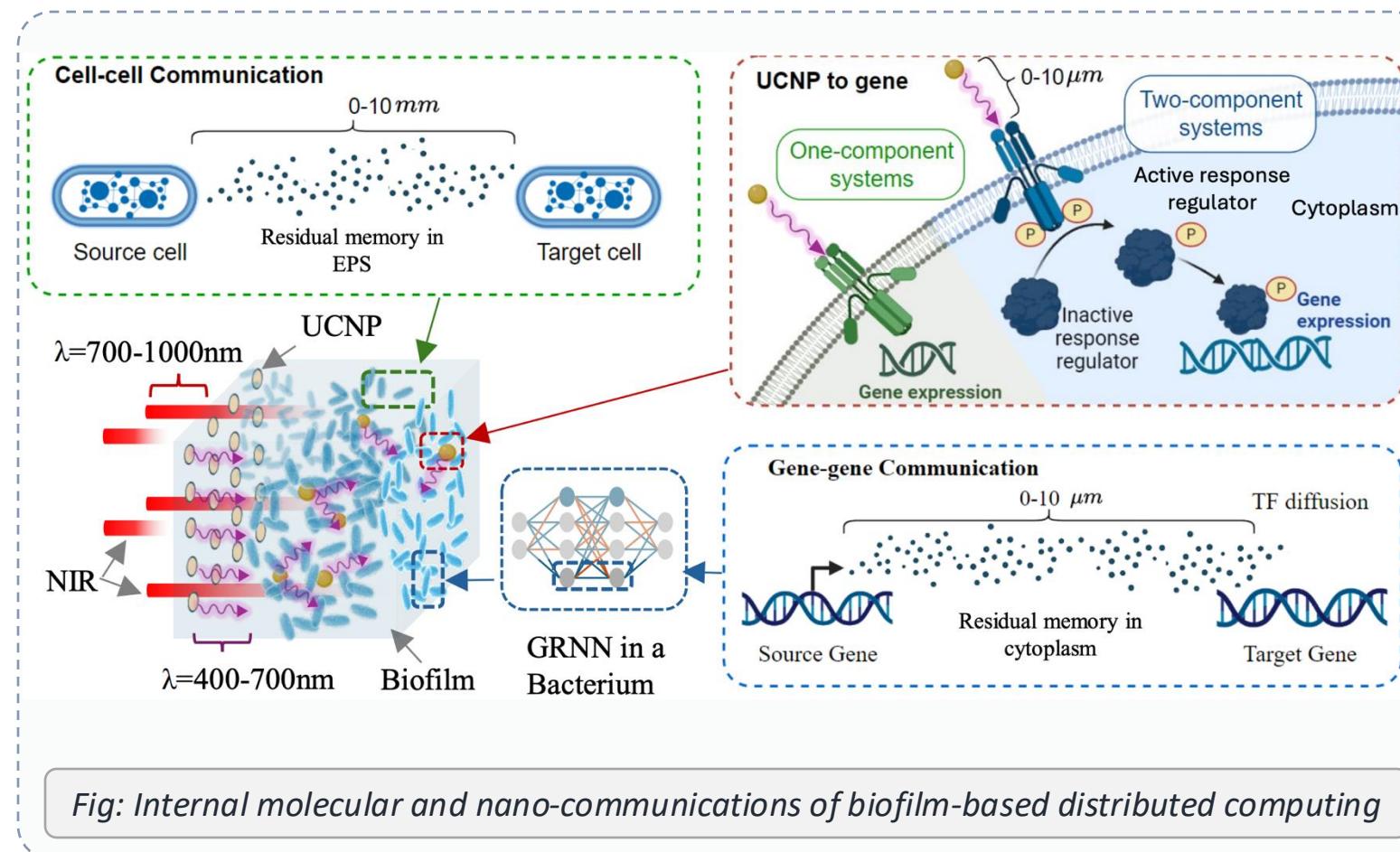
## Biofilm Living AI Devices (BLAID)

- **BLAID** integrates **biofilm-based GRNs** with wireless communication infrastructure for ultra-low-power, distributed intelligence.
- **Upconversion nanoparticles (UCNPs)** convert **near-infrared (NIR)** signals to biologically active wavelengths.
- Integration with **6G Infrastructure**

## Potential Applications

- **Environmental monitoring** – detect pollutants, or pathogens.
- **Smart biomedical implants** – continuous health monitoring and local decision-making.
- **Industrial bioprocess control** – real-time adaptive optimization.

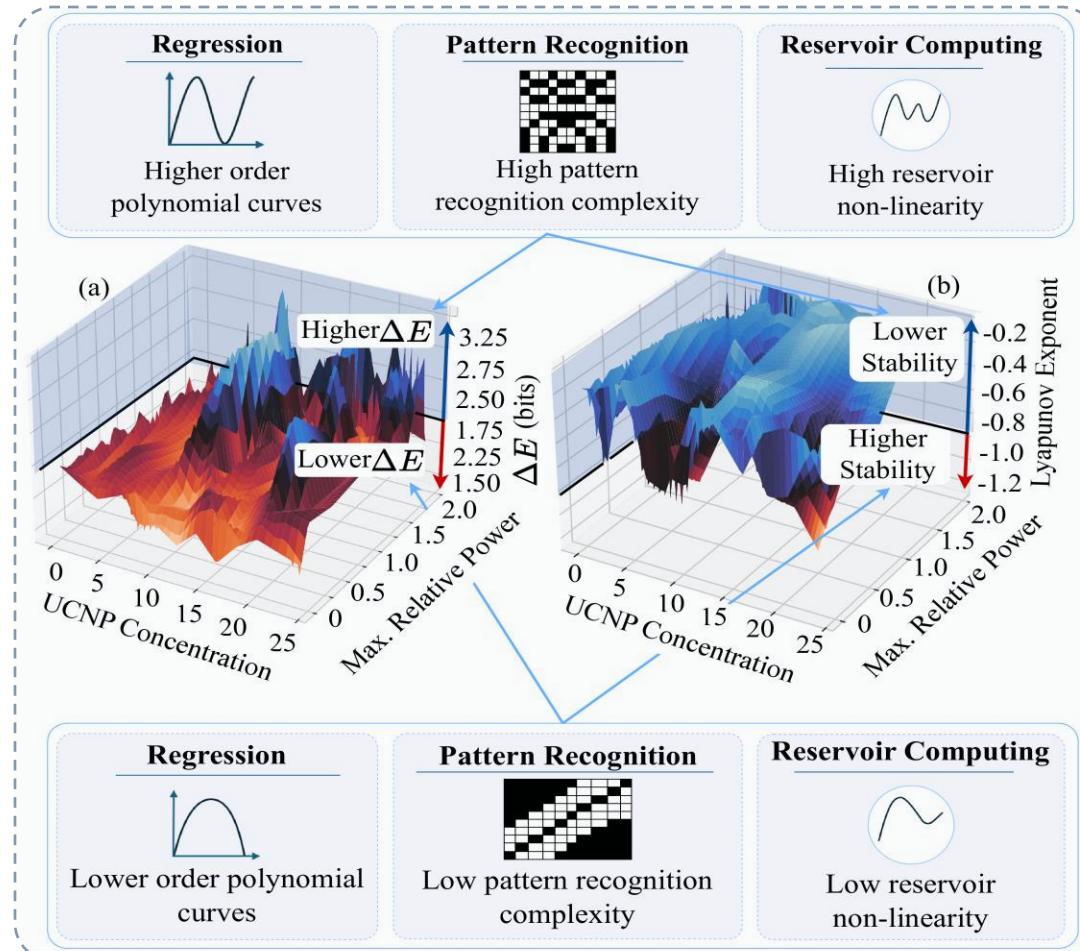
# The Internet of Biofilm Living AI Devices (BLAID)



- **Cell-cell communication** enables distributed decision
- **UCNP-to-gene phototransduction** allows remote, wavelength-specific control of gene expression using one- and two-component signaling systems.
- **Gene–gene communication via TF diffusion** supports intracellular coordination and complex genetic computations.

S. Somathilaka, H. Elayan, J. T. Atkinson, J. M. Jornet and S. Balasubramaniam, "The Internet of Biofilm Living AI Devices," in *IEEE Communications Magazine*.

# Applications of GRNN (Multicellular computing)



- Entropy Difference ( $\Delta E$ ):**  
Higher  $\Delta E$  values indicate greater information-processing for complex computing.
- Lyapunov Exponent:**  
Lower values indicate more stability.
- UCNP Concentration & Power:**  
Together, these parameters modulate  $\Delta E$  and Lyapunov exponent, allowing tuning between low-complexity and high-complexity computational regimes.

Figure: Entropy difference ( $\Delta E$ ) and b) Lyapunov Exponent between output and input signals

# CONCLUSION

## Wet-TinyML bridges biology and ML

- Leverages living substrates (e.g., bacteria, organoids) to perform computation.
- Exploits native biological properties—stochasticity, parallelism, plasticity, and energy efficiency.

## GRNN as a natural computing framework

- Bacterial Gene Regulatory Neural Networks act as repositories of pre-trained networks.
- Ultra-low-power (~femto–picowatt) operation with scalable complexity.
- Dynamic adaptation via cell plasticity supports real-time, environment-driven computation.

## Future impact

- Distributed biofilm-based AI devices for environmental monitoring, biomedical implants, and industrial control.
- Pathway to new bio-compatible, adaptive, and sustainable computing paradigms.



# IEEE –TMBMC has an ongoing special issue

**IEEE Transactions on Molecular, Biological, and Multi-Scale Communications**

has an ongoing special issue on

**Exploring Intelligence in Living Organisms for Designing Novel Computing Paradigms**

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# Thank You!

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