Toward Self-Adapting Computation in Cells: Building Spiking Neural Network with Cell Signaling Pathways

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ABSTRACT

Following the realization that computation is an inherent attribute of evolving organisms, implementing desired computation in synthesized biochemical systems becomes an important pursuit for synthetic biology. Considering the stochastic nature of biochemical reactions, the always changing environment, and the infeasibility to analyze complete dynamics of designed systems over all probable conditions, autonomous self-adjustment is necessary for systems to be robust against internal and external variations. However, to date, the essential self-adapting capability remains missing from most synthetic designs. The deficiency hinders the robustness of designed systems, limiting applicable scenarios. To remedy the deficiency, we propose a cell-compatible way that exploits the similarities between two biological signal transmission media, i.e., cell signaling pathways and action potential of spiking neurons. Given the ubiquity and versatility of cell signaling pathways preserved across various cells and organisms, the proposed method can potentially embed self-adapting neuromorphic computation into biochemical reaction systems of a broader realm.

KEYWORDS

Cell signaling pathway, Neuromorphic, Adaptive system

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1 INTRODUCTION

As manifested in biological entities, nature's competence far surpasses existing artificial designs when it comes to solving a wide range of real world problems. Instead of always resorting to the long-dominant algorithmic approach on Von-Neumann architecture, directly adopting the structure and dynamics from natural designs presents a promising alternative to integrate nature's evolved strength into engineered systems. During accelerating advance in systems and synthetic biology, it was identified before long that the two crucial features—**adaptation** and **evolution**—that allow living organisms to achieve targeted goals **reliably** despite the always-changing environment, are in fact the biological analog of **spontaneous reconfiguration and optimization** capabilities of an engineered system. Inspired by the observation that many demanding tasks such as perception, association, and non-linear control, are elegantly solved by even the simplest living organisms, **neural system** has become the imitation target for artificial systems with high adaptability requirement.

The adaptability requirement is exactly one major challenge of synthesizing viable bio-computing systems. One important example in medical applications is to detect, and react to, certain patterns of physiological biomarkers [11, 13] with disease implications. Generally, the patterns are specified as non-trivial relations involving multiple biomarkers [6] that can be obscured by environmental noises and individual variations. **Self-adapting bio-computation** is an indispensable component for engineered system to not only decide the probability of certain disease [5, 7], but also to react appropriately to the disease given different hosting individuals.

As can be seen from the example, at least in two ways could bio-computing systems benefit from incorporating neural-network-like self-adaptability: **First**, because both the engineered system per se and the operating environment are of biochemical nature, unpredictable variations in system behavior and environmental conditions are the norm. Self-adaptability allows the system to maintain correct functionality under varying conditions, as well as to compensate for the system's own deviation from original design. Second, different scenarios may require different actions (ex. different therapies for different diseases detected on-site); if the system is capable of learning the decision rules, multiple functions targeted at different scenarios can be integrated into a single bio-computation system without ambiguity—as the appropriate one will be autonomously selected by the system [3, 4] based on encountered scenario.

Neural network is capable of **extracting** and **retaining** meanings from input history while maintaining reconfigurability to adapt. Each composing **neuron** integrates the input signals received to produce corresponding output voltage spikes. The voltage spikes are then interpreted and transmitted by connecting **synapses** to the next neurons. Each synapse plays dual roles of **self-adapting** information encoder and distributor. As a self-adapting **encoder**, the synapse spontaneously adjusts how its output depends on the strength and timing of incoming spikes; as a self-adapting **distributor**, the interconnects between two neurons can be dynamically

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established or removed—The capabilities are collectively known as **synaptic plasticity**.

To embed neural network's self-adapting ability into engineered systems, it is best to make use of the inherent mechanisms and materials of the *hosting system*. Take our case here as an example, **cells** are the *hosting systems*, so cell signaling pathway is chosen as the biochemical chassis for its **ubiquity** and **versatility**. The fact that cell signaling pathways exist naturally in various types of cells, and are involved in a wide range of cellular processes [1] make them an ideal substrate for implanting neuronal functionality to targeted cells with high compatibility. Furthermore, by identifying corresponding "modules" between different biological systems, it is possible to borrow the wisdom from one system and re-implement it using modules of similar roles in another system. The resulted system has higher probability to robustly reproduce the desired functions than if crafted manually from scratch.

To sum up, we propose in this paper a way to realize **cell-compatible** neuromorphic computing system, which can be implemented on existing cell signaling pathways. An FPGA-like, module-based architecture is adopted to promote instinctive migration of self-adapting and reconfiguration capabilities from neural system into **multiple types of cells in general.**

2 NEURON MODEL AND KEY CHARACTERISTICS

Model provides a means to represent complex dynamics of a system in a simpler form while retaining important characteristics of the original system; the goal is to make system analysis feasible and predictive of *concerned* system behaviors. Since abstraction is unavoidable in the process of modeling, whether the key contributors to concerned characteristics are correctly identified and included in the model determines the quality of the model. Thus, in this section, we first focus on identifying the crucial properties of spiking neurons that lead to **adaptability**; the way to realize adaptability with cell-signaling pathway motif by exploiting matching properties to the neurons will be presented in the next section.

Neurons transform complex dynamical inputs into trains of **action potential** in the form of abrupt voltage spikes. Apart from the amplitude of output action potential, the **temporal** profile of output spikes also holds a crucial role in encoding stimuli information. Furthermore, as demonstrated in [12], in order to realize useful sensory processing in nature, it is required to perform analog computations at a speed faster than that explainable by an averaging mechanism. As a result, the explicit **timing** of individual spikes is also indispensable with its unique share of information. Therefore, it is reasonable for our embedded neuromorphic computation to have plasticity also depend on the timing of spikes.

2.1 Voltage-gated ion channels on action potential dynamics

In the **Hodgkin-Huxley** neuron model[8], the behavior of a neuron depends on the coordination of two main types of **voltage-gated** ion channels: the sodium channel Na_v, and the potassium channel K_v. "Voltage-gated" here is used to indicate that the channel's conductance is dependent on the **membrane potential** V_m

Figure 1: The equivalent circuit of Hodgkin-Huxley model. Note that as implied in the opposite polarities of V_{Na^+} and V_{K^+}, the flow of Na^+ increases membrane potential while K^+ flow causes decrease in membrane potential.

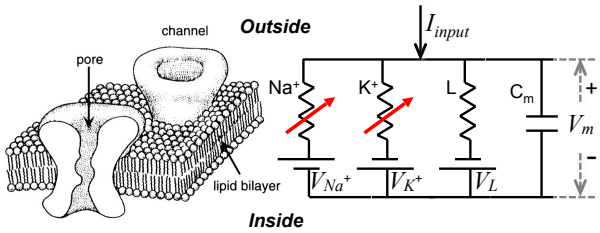
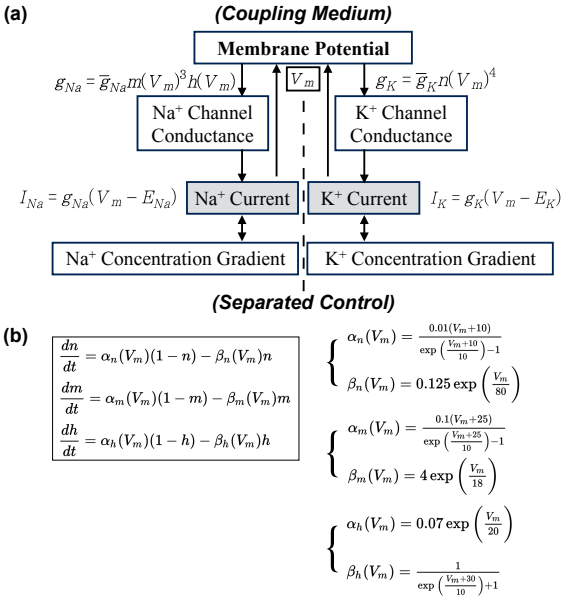
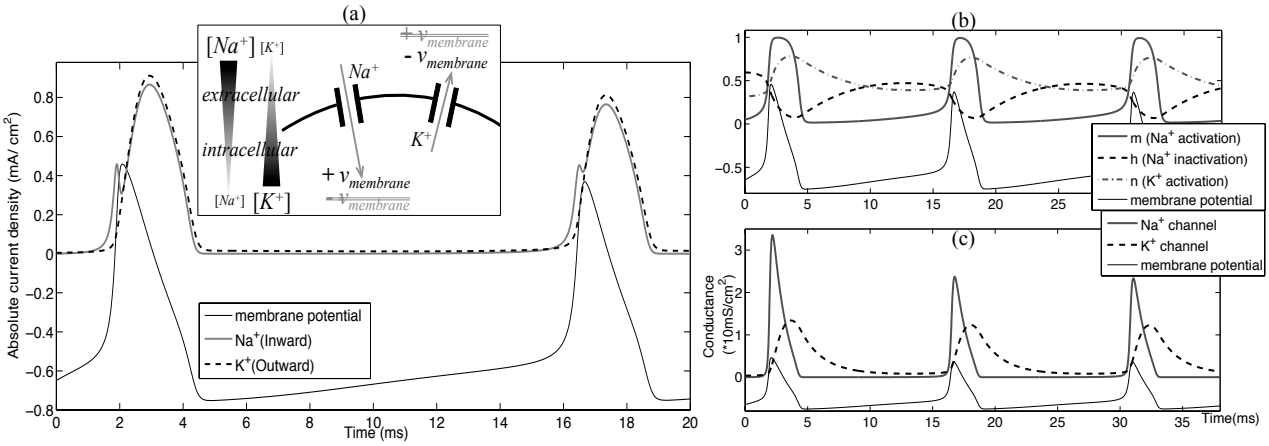


Figure 2: (a) Influence diagram of membrane potential in neurons. Membrane potential couples the dynamics of otherwise independent ion flows through its different influences on channel conductance g_{Na} and g_K. (b) m, h, n as functions of V_m are gating variables representing the probability, or the degree, of corresponding gate's opening.



(i.e. the **voltage** difference across membrane due to ion concentration gradient). An unspecified leaking channel is also included in the model for completeness, however, since its **constant** conductance is **significant lower** than others, it is of small influence on the dynamics of membrane potential. An equivalent circuit model of electrical properties across and in immediate vicinity to the membrane is given in Figure 1. The voltage-gated ion channels are modeled as **variable resistors** to describe their V_m-dependent conductance; the electrochemical gradient resulted from concentration difference of each ion is modeled as corresponding voltage source. While both Na^+ and K^+ are positively charged, the opposite concentration gradient across the membrane makes the two types

Figure 3: The dynamics of Hodgkin-Huxley neuron with equivalent circuit abstraction given in Fig. 1. (a) The *absolute* values of current density through ion channels and corresponding membrane potential. *Subfigure:* opposite concentration gradient of Na^+ and K^+, and their respective one-way ion flow. (b) Ion activation and deactivation variables' evolution with membrane potential. How *m*, *h*, and *n* affect channel conductance can be found in Fig. 2. (c) Membrane potential and the conductance of ion channels. (All membrane potential values are scaled by 0.01 for clarity.)



of ions flow **separately** in opposite directions through respective channels. A simulation of the dynamic evolution of channel current and membrane potential as a result of their interdependence is shown in Figure 3; the evolution of channel **conductance** with varying membrane potential is also taken into account. With influence landscape shown in Figure 2, the **separation** of respective concentrations as driving forces and the **coupling** through shared membrane potential give rise to a wide range of temporal dynamics, allowing effective encoding of plentiful input patterns—the **diversity** is one of the crucial requirements while designing our proposed system.

2.2 Directional signal transmission with waveform preserved

In biological neural networks, information is encoded and transmitted through neurons' membrane potential. The ability to preserve the **causality** relation and signal integrity for each node-to-node segment is crucial for the applicability of the knowledge learned.

However, voltage by itself has no directional preference and can potentially spread to all connected neurons including those upstream, disturbing the correct **causality** relation. The **refractory period** right after each spike (resulted from the **inactivation** gating mechanism of Na_v and the delayed closing of K_v) thus holds great importance as it can prevent a spike from re-exciting its source neuron. In the first (**absolute**) part of the refractory period, the neuron that produced the spike cannot fire again no matter how great the stimulation. In the second (**relative**) part, a stronger than usual stimulus is required to trigger the spike. The two periods are distinguished based on whether Na_v has returned from **inactivated** to **close** state. After the refractory period, the neuron will again fire upon reaching the original neural threshold, allowing **directional** propagation of electrical signals in the form of **solitary** waves.

On the other hand, signal integrity concerns the **timing** and the **quality** of the signal—*does it reach the destination **when** it is supposed to? Is the waveform intact upon its arrival?* In biological neural network, the shape and velocity of propagating action potential can be kept nearly constant between connected neurons, so the information encoded by the source neuron can be well-preserved till reaching the next "processing unit." The signal integrity with well-preserved waveform is achieved in a way similar to how we transfer electrical signals through cables of extended length. The biological counterparts are the cooperation between axon **myelinated** with appropriate thickness and properly distanced **nodes Ranvier**.

As will be shown by simulation in later section 3.3, the signal transmitted through our proposed modules is not only well preserved with precise timing and oscillating frequency, but can also be amplified through the cascade. The signal integrity achieved is critical for the proposed system's applicability.

3 PROPOSED CELL-COMPATIBLE SYSTEM

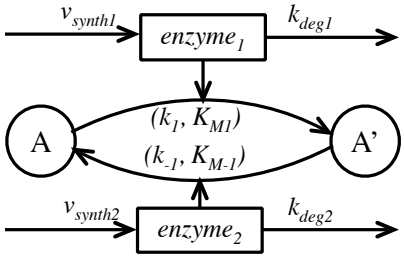
In this section, we describe and verify the implementation of our modularized, FPGA-like biomolecular system, which allows for both **self-** and **externally-**reconfiguration. Self-reconfigurability is the mechanism behind self-adaptability. In the case of synapses, this "plasticity" is achieved by autonomously modifying the effect of an incoming pre-synaptic spike on the post-synaptic neuron. Our implementation with cell signaling motif as basic unit relies on exploiting **functional** resemblance between the two realms. However, due to the natural lack of one-to-one correspondence, our identified motif as basic unit actually covers both roles of neuron and synapse. **Motif** and **module** will be used interchangeably unless ambiguity occurs.

As identified in previous sections 2.1 and 2.2, the rich output dynamics for encoding a wide range of input patterns and signal

Table 1: Analogies between Hodgkin-Huxley neuron and cell signaling pathway

Item	Hodgkin-Huxley Neuron	Cell Signaling Pathway
Input	Externally applied *charging* current	Synthesis rate of $enzyme_1$ (v_{synth1})
	Externally applied *discharging* current	Synthesis rate of $enzyme_2$ (v_{synth2})
Output	Membrane potential (V_m)	Concentration of A'
Feedback Mechanism	V_m-dependent ion channel conductance	Concentration-controlled reaction rate
Encoding Format	Oscillation amplitude	Oscillation frequency

Figure 4: The recurring motif across various signaling pathways. A and A' are two inter-convertible forms of a signaling molecule with constant total amount; the enzymatic reactions involved are assumed to follow Michaelis-Menten kinetics, with *catalytic rate constant* and *Michaelis constant* denoted in form (k_i, K_{Mi}).



transmission integrity are two key factors behind neural network's self-adaptability. To verify our implementation, respective simulation results are given in sections 3.2 and 3.3 to demonstrate the two key factors.

3.1 Universal cell-signaling motif and analogies exploited

The responses of biological cells to extra-cellular stimuli—such as hormones, growth factors, nutrients and stress—are coordinated by networks of protein-based signaling pathways. Signaling pathways can not only **transmit**, but also **process** complex stimuli patterns and **encode** extracted information into signaling patterns compatible with targeted down-stream systems. Considering the large variety of control tasks required of the relatively scarce resources, it comes as no surprise that the specificity of diverse physiological signal-response relations is achieved by delicate temporal control over the (de)activation between a *restrictive set of signaling proteins*, rather than by designating specific, independent pathways for each type of stimulation.

In fact, complex temporal dynamics can arise from modifying *reaction kinetics and/or feedback relations* of a heavily-conserved pathway motif as shown in Figure 4, **without changing its topological structure** that recurs across signaling networks. More specifically, each **feedback** relation describes how concentration of one biochemical species can inhibit (negative feedback) or promote (positive feedback) certain reaction in the motif. Listed in Table 1 are the analogies found in respective properties of the two systems; our proposed way to **realize** those analogies to bring neuronal plasticity to cell signaling pathways are given in Figure 5.

In our proposed cell-signaling realization, A' is the output and can be conceptually regarded as *membrane potential* V_m. In the case of neuron, V_m influences two opposite ionic currents differently through channel conductance, while the two opposite flows of Na^+ and K^+ increases and decreases V_m, respectively. Since Na^+ flow increases V_m, influences of V_m on sodium channel are mapped to the upper half of the motif—as enzymatic reactions on the upper half convert A to A'. Similarly, influences of V_m on potassium channel are mapped to the lower half of the motif.

Cell-signaling counterparts of V_m's influences on channel conductance are realized through feedback design. Take sodium channel as example, its dependence on V_m consists of two terms: m of fast channel activation and h of delayed channel deactivation. The *fast channel activation* is realized through a *positive* feedback to directly promote reaction $A \rightarrow A'$; the *delayed channel deactivation*, on the other hand, is realized as a *negative* feedback to inhibit $enzyme_1$ synthesis, indirectly impeding A' formation. The same reasoning goes for potassium channel.

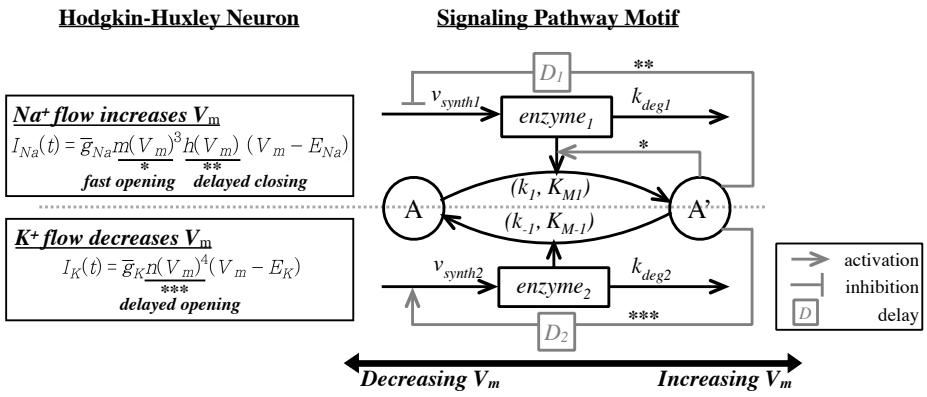
3.2 Reconfigurable dynamics of a single module

In this section, simulation results are presented to demonstrate the reconfigurability of our proposed implementation. The implementation is based on aforementioned analogies between (1) neuron of Hodgkin-Huxley model with *synaptic plasticity*, and (2) cell-signaling pathway motif with *tunable feedback strength*. The aim is to demonstrate the feasibility of employing feedback design to realize neuronal plasticity in cell-signaling network.

The first simulation with result in Figure 6 consists of two parts. For the first half where **time** = 0 ~ 60 **(arbitrary unit)**, the synthesis rate of $enzyme_1(v_{synth1})$—which will be used as the motif's input port for module interconnects—is varied from 150 to 400 (arbitrary unit). It can be observed that the output oscillation **frequency** of A' reflects the changes correspondingly. The frequency first increases with the input value, then decreases while the input value keeps increasing. Finally, the output response to the input becomes a one-to-one value correspondence **without oscillation.** At least *qualitatively*, this *bifurcation* behavior is consistent with that predicted of Hodgkin-Huxley model as depicted in Figure 7, and can be regarded as a justification that our proposed analogy between the two systems is eligible.

The purpose of the second half of the simulation where **time** = 60 ~ 100 **(arbitrary unit)** is to verify v_{synth2}'s propensity as an additional tuning knob, which can provide additional flexibility for

Figure 5: Compared to Fig. 4, feedback relations are added to the motif backbone to realize our proposed analogies between neuron and signaling pathway dynamics. Each channel gating variable (i.e. m, h, n) on the left is mapped to a corresponding feedback branch on the right, indicated by matching number of *.



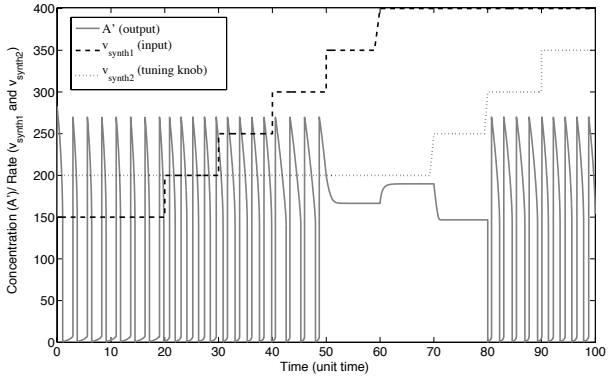


Figure 6: Simulation shows output concentration's frequency response to changes in v_{synth1} and v_{synth2}. Note that changes in either is enough to influence the module's behavior.

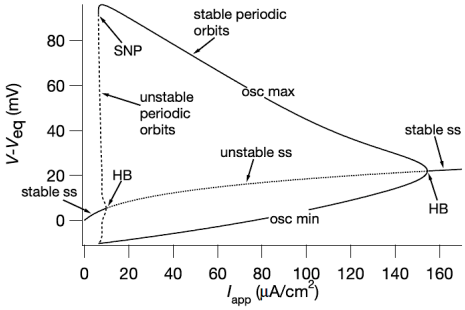


Figure 7: Bifurcations of Hodgkin-Huxley neuron with applied current I_{app} as the bifurcation parameter. *osc max* and *osc min* denote, respectively, the maximum and minimum oscillating amplitude, and *ss* denotes a steady state without oscillation. Note that the predicted oscillating amplitude shares the same trend with the oscillation frequency in our simulation (Fig. 6) as applied input current increases, which is consistent with our proposed analogy. Image Source: [9].

external control. During this period, the motif's self-configured input value v_{synth1} remains unchanged. It can be observed that the output can really be controlled by the tuning knob alone.

3.3 Signal transmission through modules

A possible way to connect motifs into layered networks is given in Figure 8. The connected motif constructs the structural backbone which, when combined with appropriate feedback design both **in** and **between** modules, can serve different purposes such as signal amplification, generation of discontinuous bistable dynamics and oscillations from hysteresis, etc., thus can be used to encode complex relationships between input stimuli and output cellular responses. More importantly, the **versatility** of the motif is valid with universal compatibility—while conserved in structure, what is upstream and downstream can vary widely across species and cells. Systems based on the motif can thus adapt effectively to different types of receptors, substrates and cellular endpoints. The second simulation involves two modules connected as shown in

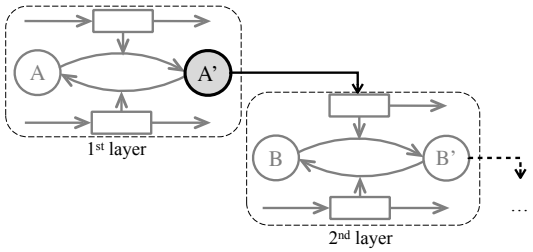


Figure 8: Module cascade through enzyme synthesis rate.

Figure 8. The module upstream (first layer) transmit the signal to the downstream module (second layer) through v_{synth1}. As can be observed from the outputs of the two modules ([A'] and

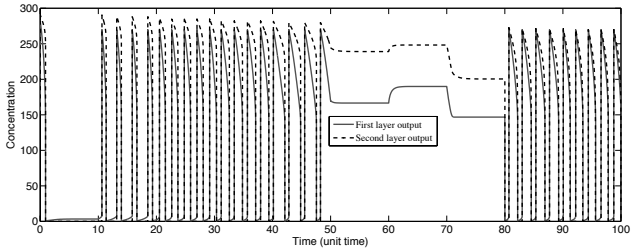


Figure 9: Simulation result showing the output relation of two connected modules.

[B'], respectively), both the spiking frequency and timing are faithfully preserved throughout the cascade. Furthermore, the signal is amplified without additional design.

4 CONCLUSION

This paper proposed a modularized way to realize **cell-compatible** neuromorphic computation based on existing cell signaling pathways. Analogies between neural networks and cell signaling pathways are identified and exploited. Two simulations help verify the *signal encoding reconfigurability* of a module as well as *signal transmission integrity* across connected modules, which are central to neural network's adaptability.

Encouraged by reported successes in synthetically reshaping the dynamics of cell signaling pathways [2, 10], the proposed FPGA-like, module-based architecture holds potential to help promote instinctive migration of self-adapting and reconfiguration capabilities from neural system to multiple types of cells in general.

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