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Review Article

SemiSynBio: A new era for neuromorphic computing

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ABSTRACT

Neuromorphic computing has the potential to achieve the requirements of the next-generation artificial intelligence (AI) systems, due to its advantages of adaptive learning and parallel computing. Meanwhile, biocomputing has seen ongoing development with the rise of synthetic biology, becoming the driving force for new generation semiconductor synthetic biology (SemiSynBio) technologies. DNA-based biomolecules could potentially perform the functions of Boolean operators as logic gates and be used to construct artificial neural networks (ANNs), providing the possibility of executing neuromorphic computing at the molecular level. Herein, we briefly outline the principles of neuromorphic computing, describe the advances in DNA computing with a focus on synthetic neuromorphic computing, and summarize the major challenges and prospects for synthetic neuromorphic computing. We believe that constructing such synthetic neuromorphic circuits will be an important step toward realizing neuromorphic computing, which would be of widespread use in biocomputing, DNA storage, information security, and national defense.

1. Introduction

The human brain is a dynamically reconfigurable neural network comprising approximately 100 billion neurons connected by approximately 100 trillion synapses [1]. Each of these neurons communicates simultaneously with thousands of others via synapses. A synapse is defined as the junction between two neurons and serves as an important pathway for transmitting nerve impulses from presynaptic neurons to postsynaptic neurons [2]. When an electrical signal is sent to a presynaptic neuron, an electrical spike called action potential is generated. The action potential then triggers impulses in a postsynaptic neuron by releasing chemicals (called neurotransmitters) through the synaptic cleft. Neurons are the computing units by which the brain exchanges and transmits information via discrete action potentials or "pulses", while synapses act as storage units for memorizing and learning [1,2]. A pulse-based temporal processing mechanism makes information transmission in the brain extremely efficient. This ability is attributed to the brain's fundamental properties as described by neuroscience, including its extensive connectivity, hierarchical structure, functional organization, and time-dependent neuronal and synaptic functionality [1–3]. Neuromorphic computing derives inspiration for the design of neuromorphic circuits from the topology of the brain, with hardware systems mimicking the calculation modes of neurons and synapses based on pulse-driven communication, simulating the operational mode of the brain and enabling such systems to decrease power consumption [3–8].

With ongoing advances in synthetic biology, biocomputing has become a fast-growing and innovative interdisciplinary field. The nanomaterials used in biocomputing are biological materials (such as DNA, RNA, and proteins) rather than traditional silicon [9–12]. DNA molecules have complementary base pairing properties that allow for specific molecular recognition [13], self-assembly [14], and large-scale parallel reactions [15–18]. The emergence of biocomputing based on

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DNA-strand-displacement reactions has shown that biomolecular systems can exhibit autonomous behaviors that mimic brain-like computing [13,19–26]. Using a simple DNA logic gate structure with amplified multilayer digital circuits, any linear threshold circuit or ANN model can be systematically converted into a DNA-mediated strand-displacement cascade with functions similar to those of small neural networks [26–28]. This method even facilitates the use of fully connected artificial neurons to realize associative memory, where such artificial neurons record single-strand DNA (ssDNA) patterns after training and identify the most similar pattern. Therefore, DNA-strand displacement enables automatic biochemical systems to recognize molecular patterns, make decisions, and then respond to the environment, thus realizing neuromorphic computing capabilities.

The goal of neuromorphic computing is to create brain-like systems with learning and adaptive abilities to achieve next-generation intelligent devices and autonomous systems [4,5]. However, numerous technical challenges must be overcome to achieve this goal. These include establishing accurate neural-network models of the brain, finding materials and technologies to construct devices that support these models, developing a programmable framework that enables the system to learn automatically, and creating applications with brain-like functions. Owing to its various biological characteristics, biocomputing has provided new inspiration for the development of neuromorphic computing, which has promoted synthetic neuromorphic computing based on synthetic biological systems with digital and analog computing. With the breakthroughs in synthetic neuromorphic computing, a new generation of semiconductor synthetic biology (SemiSynBio) technologies has been proposed. SemiSynBio aims to harness the significant energy efficiency of biological systems along with the advantages of semiconductor-based information processing technology. It integrates methodologies such as DNA computing and neuromorphic computing, leveraging the intrinsic energy efficiency of biological mechanisms and the sophisticated computational prowess of neuromorphic systems to forge advanced computing technologies that are both potent and energy-efficient [29,30]. SemiSynBio has the potential to fundamentally redefine semiconductor design and manufacturing, creating an industry completely different from what is currently perceived. In this review, we briefly describe neuromorphic and DNA computing, highlight the advances in DNA computing along with synthetic neuromorphic computing, and discuss future challenges in the field and its relevance today (Fig. 1).

2. Neuromorphic computing

In the late 1980s, Carver Mead at the California Institute of Technology proposed “neuromorphic computing”, also known as “neuromorphic engineering”, a discipline in which the nervous system is modeled as an equivalent circuit for constructing analog electronic devices and systems that simulate the computing architectures of the neural systems in the human brain and thereby perform similar functions [3]. The design of neural networks by this bionic approach is the core concept of brain-inspired neuromorphic computing, which simulates the biological structures of human neurons and synapses using mathematical models combined with multilevel conduction. This allows simulation of a large number of neuronal connections and the construction of artificial neural networks (ANNs) that could be used to solve challenging problems [4,5]. The quantitative, accurate, and simplistic descriptions of neurons and synapses in neuromorphic computing directly determine the performance, power consumption, and complexity of ANNs. Although the most widely used neural networks in the field of AI depend on simulating the brain’s hierarchical structure and neural synaptic framework, AI computing systems are very different from the neural system of the human brain in terms of topology and the way in which they process information [5]. For example, deep learning is based on artificial hierarchical structures consisting of multiple layers, such as convolutional layers, pooling layers, and fully connected layers, which represent different potential input features.

Maass [31] classified ANNs for neuromorphic computing into three generations based on their potential neuronal functions: perceptrons (Fig. 2A), deep learning networks (DLNs; Fig. 2B); and spiking neural networks (SNNs; Fig. 2C). The first-generation, ANNs as described by the McCulloch-Pitts perceptron model, could perform threshold operations and produce a digital output (1 or 0) [32]. The second generation, DLNs, was established based on the first generation by adding a nonlinear activation function such as sigmoid or rectified linear unit (ReLU) [32], causing the neurons to be continuously nonlinear and changing the evaluation results from 0 or 1 to arbitrary real numbers within a certain range. This nonlinear enhancement achieved in second-generation networks plays a key role in the scaling of neural networks for complex applications. In addition to nonlinearity, DLNs expanded the number of hidden layers between the input layer and the output layer. Owing to the nature of their network structure, such models support the gradient

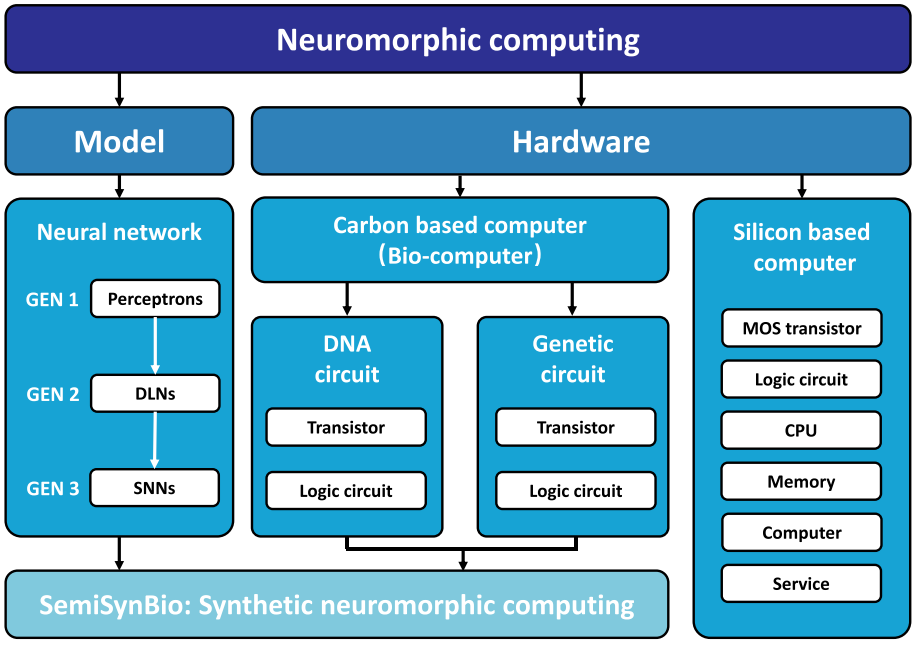

Fig. 1. A framework of neuromorphic computing based on biomolecules.

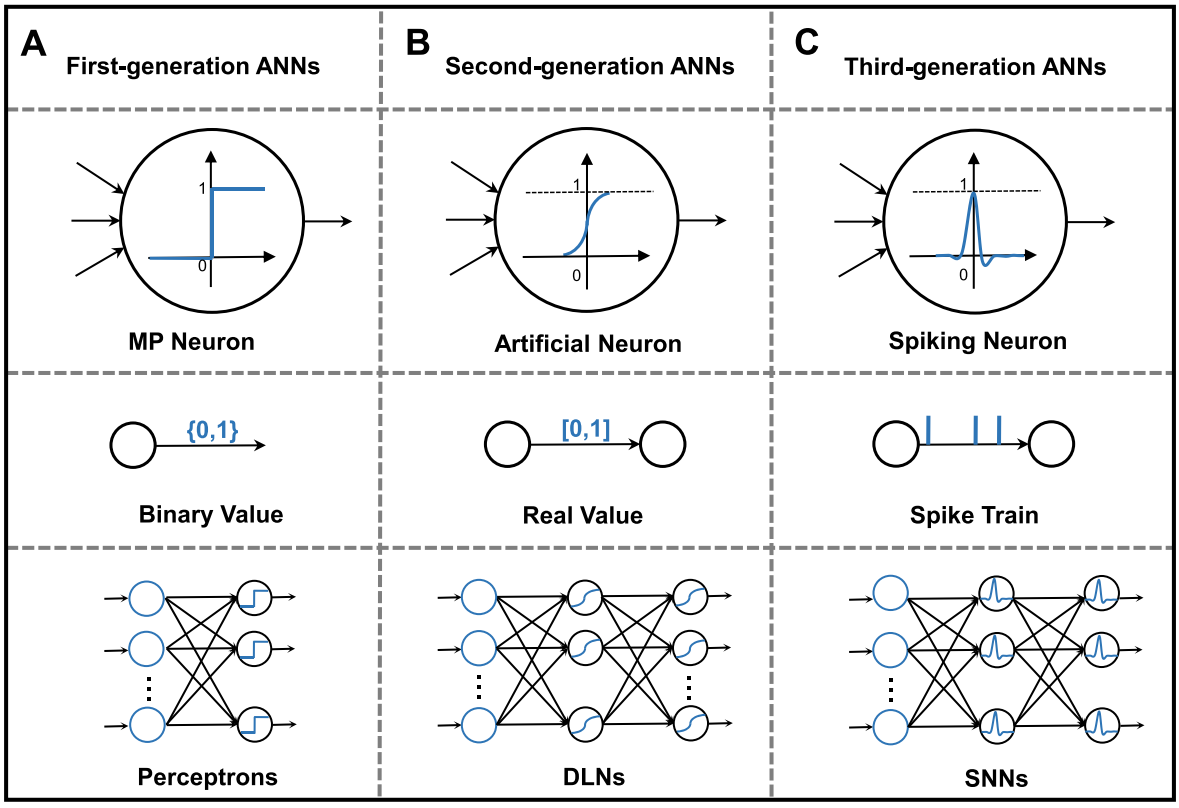

Fig. 2. Artificial neural networks for neuromorphic computing into three generations based on their potential neuronal functions: perceptrons (A), deep learning networks (DLNs; B); and spiking neural networks (SNNs; C). The layers with neurons in blue represent the input layers.

descent algorithm for backpropagation learning [33], which is currently the standard algorithm for training DLNs. The third generation, SNNs, use integrate-and-fire spiking neurons and exchange information through spiking [34]. The primary difference between the second- and third-generation networks lies in their information-processing approaches. Second-generation DLNs use real values (such as signal amplitudes) for computations, while third-generation SNNs use signal time characteristics (spikes) to process information. Spikes are binary events, i.e. 0 or 1. As shown in Fig. 2C, the neurons in SNNs are only active when receiving or sending spikes, so these networks are event-driven, which helps to improve their energy efficiency for a given time period as SNN units without any events remain idle. In contrast, all cells in DLNs are active, regardless of the states of the real-valued inputs or outputs.

Luping Shi at Tsinghua University proposed a brain-inspired global–local learning framework incorporating neuromorphic computing [35]. This framework can be used to develop online hybrid learning hardware with reduced energy consumption and can also be combined with several existing effective learning algorithms, increasing the efficiency of learning algorithms and potentially realizing the synergistic development of neuromorphic algorithms and neuromorphic computing chips. However, these generations of ANNs are based on silicon chips, which have disadvantages such as poor energy utilization and low storage densities, so materials that can replace silicon are urgently needed. The emergence of biomaterials has provided a potential solution to this problem.

3. Biocomputing

Biocomputing, a more specific extension of synthetic biology, uses biomolecular parts as the hardware to perform human-defined computations [19,20]. DNA computing is a type of biocomputing that exploits a variety of biochemical and biophysical reactions of DNA and enzymes to perform computing, mainly those based on the double-helix structure and the complementary-base-pairing principles of DNA molecules [21–23]. Integrated circuits are combinations of digital logic based on silicon components, so logic gates are the basic building blocks of digital circuits. DNA-based Boolean logic gates that can be assembled into complex computational circuits have been investigated in the field of DNA computing [13,36]. In particular, DNA-strand-displacement-based logic gates generate an output signal in response to specific oligonucleotide inputs.

In 2002, Stojanovic et al. proposed a logic gate based on DNA, which made a pioneering exploration for designing multi-layer circuits using DNA-based logic gates [41]. However, when outputs signals through enzymatic reactions, the molecular composition of the output signals are different from the input signals, which makes it difficult to carry out further cascade, thus limiting its development. Seelig et al. [37] proposed an enzyme-free nucleic acid logic circuit based on DNA-strand-displacement reactions termed 'toehold-mediated strand displacement' (TMSD). This process involves binding a signal strand to the exposed sticky end of a single gate compound strand undergoing a random walk process (branch migration), replacing the signal strand initially bound to the gate, providing a signal output or an input for a downstream circuit. The cleavage of a dye-quenching agent complex provides measurable fluorescence, which can be used to quantitatively analyze the output. The reaction kinetics of reversible TMSD can be adjusted by techniques such as single-strand sticky end isolation [37] and single-strand sticky end exchange [38]. And the reaction rate can be adjusted by multiple orders of magnitude by changing the lengths or sequence compositions of the single-strand sticky ends [39]. TMSD with these simple and universal components can be used to design complex and scalable DNA computing architectures.

Based on the study described above, Qian et al. created a new type of logic gate, termed the 'seesaw' gate, using DNA strand concentrations as the input and output [36]. Complex multilayer circuits based on the seesaw gate, such as the square-root calculator, have been tested *in vitro*,

and the flexibility and robustness of complex multilayer seesaw circuits have been verified [28]. Due to their advantages of high storage density and small size, the biomaterials used in DNA computing are also ideal materials for neuromorphic computing, taking the position of traditional silicon-based electronic components [40].

Additionally, Chen et al. developed a set of two-input AND, OR, NAND, NOR, XNOR, and NOT gates [41]. The gates were built from de novo designed proteins that all have a similar structure but where one module can be designed to interact specifically with another module. The construction of two-input or three-input gates was facilitated by employing monomers and covalently linked monomers as inputs, with specificity being encoded by strategically designed networks of hydrogen bonds to enable competitive binding. These gates can regulate protein associations affecting functions such as enzyme activity and transcriptional processes, with applications demonstrated *in vitro*, in yeast, and in primary human T cells.

4. Synthetic neuromorphic computing

From perception, pattern recognition, and memory formation to decision-making and movement control, the ability of the human brain constantly inspires AI research [42,43]. Information processing in the human brain is realized by constructing neural networks *in vivo* through biological materials such as DNA. Related studies based on DNA computing and strand-displacement circuits have demonstrated how molecular systems exhibit autonomous neuromorphic computational approaches *in vitro* [27,28,44]. Based on DNA-strand-displacement cascades, Qian et al. designed a neural network with four neurons connected to each other by 112 different DNA strands, and this molecular system autonomously behaves like the human brain [43](Fig. 3A). In the Hopfield associative memory experiment, neurons that were trained by a computer simulation were able to remember four ssDNA patterns and recall the most similar pattern when confronted with an incomplete pattern. These results indicate that DNA-strand-displacement-cascade reactions could enable autonomous biological systems to recognize molecular event patterns, make decisions, and respond to their environments. However, this method is limited and cannot recognize more than four patterns. Furthermore, each pattern is composed of only four different DNA molecules.

To address the scale limitations, Qian et al. proposed a new neural network based on DNA molecules construction strategy, which is called “winner takes all” (WTA) (Fig. 3B). WTA networks represent a typical circuit that is found in multiple parts of the neocortex [45,46]. Theoretical studies have shown that such networks provide fundamental computational units that can stabilize the denoising of neuronal dynamics [47]. These properties have been validated with neuromorphic SNN implementations that produced robust behaviors within closed sensorimotor loops. Since WTA networks were able to create sustained activations to maintain neuronal state active, they can provide working memory models, even after the network inputs have been removed [45–47]. Cherry et al. reported a WTA neural network constructed according to DNA-strand-displacement reactions; their approach had a strong computational ability with simplified molecules and was not limited by the number of patterns and the complexity of the system [28]. They implemented pattern recognition by categorizing handwritten digits from “1” to “9”. The network successfully classified the test patterns and recognized a large number of simple patterns and a small number of complex patterns.

In recent years, synthetic neuromorphic computing has seen significant advancements, prompting researchers to explore how biomimetic methods and materials, such as DNA and enzymes, can be employed to create more efficient and adaptable computational models. In 2022, Xiong et al. developed a systematic molecular implementation of a convolutional neural network algorithm with synthetic DNA regulatory circuits [26]. The DNA-based weight-sharing convolutional neural network can simultaneously implement parallel multiply–accumulate operations for 144-bit inputs and recognize patterns in up to eight categories autonomously. Furthermore, enzymatic reaction networks could also support neuromorphic architectures. Okumura et al. introduced DNA-encoded enzymatic neurons with tunable weights and biases, which are assembled into multilayer architectures for classifying nonlinearly separable regions [48]. This work explored the potential of neuromorphic architectures combining the programmability of DNA with the efficiency of enzymatic processing. Luna et al. implemented the "perceptgene" in Escherichia coli cells to achieve neuromorphic computing with complex temporal computing tasks in living cells [49].

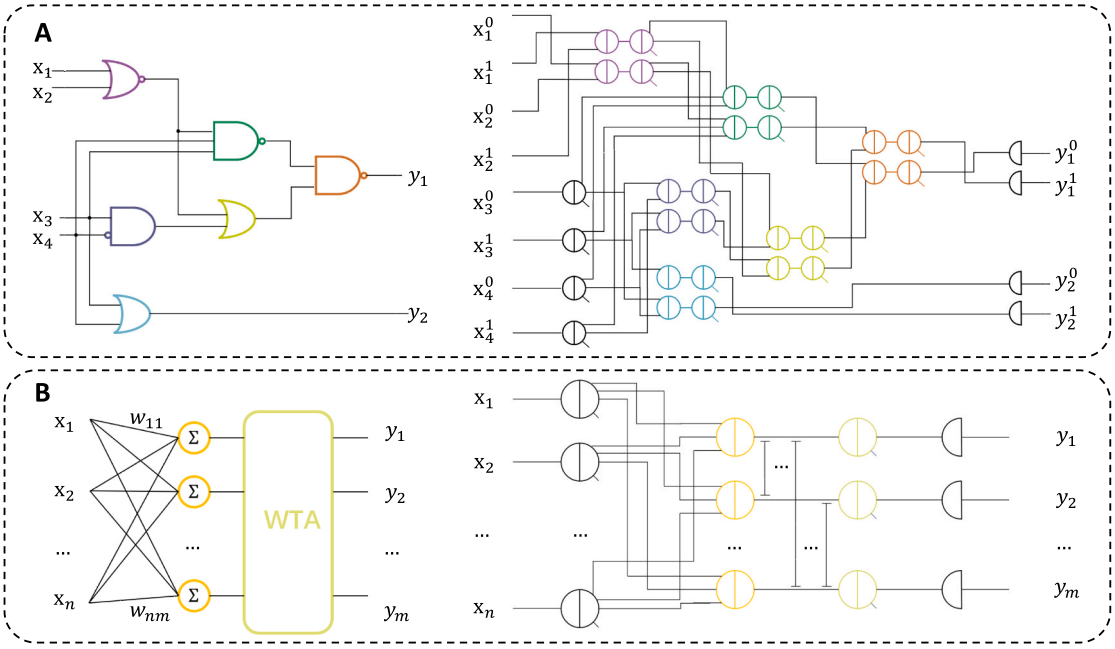

Fig. 3. (A) Schematic diagram and construction on DNA molecules of the artificial neural network. (B) Schematic diagram and construction on DNA molecules of the “winner-takes-all” neural network.

The researchers fine-tuned "perceptgene" parameters, enabling the devices to operate in the logarithmic domain and encode the minimum, maximum, and average values of analog inputs, which led to the construction of sophisticated multi-layer "perceptgene" circuits. Artificial Neural Networks, compatible with both digital and analog computing platforms, enable the development of an effective, precise, and scalable hybrid method for strong genetic modification of living cells.

5. Discussion

During the process of exploring neuromorphic computing, biocomputing as a branch of molecular computing has attracted extensive interest [20,50]. Researchers are attempting to establish a molecular computing strategy that could replace silicon-based computation in certain scenarios, which requires computer-like logic programming to be performed on biological components and modules that are combined to construct an artificial neural network [4,5,35,43,48]. The ultimate goal is to achieve brain-like intelligent computing. Although DNA computation is a promising approach in the field of neural morphology calculation, several limitations currently remain. Firstly, DNA is characterized by instability, facile degradation, and rapid decomposition, especially under certain conditions. Its intracellular environment is also comparatively hostile, often containing proteins that are capable of damaging nucleic acids. Moreover, molecular calculations based on DNA-strand-displacement reactions are preprogrammed, disposable systems that can be used only once. DNA and enzyme reactions are mostly irreversible reactions, leading to logic gates incapable of repeatedly opening and closing, and this issue fundamentally limits our ability to extend a DNA computing circuit from a single layer to a multilayer structure. To solve the problem of irreversible reactions, Teng et al. abandoned the traditional DNA-based approach and instead chose to use genetic circuits to construct ANNs [51]. Their results showed that neuromorphic computing was constructed for the first time by using genetic circuits, realizing linear classifications, nonlinear classifications, and pattern classifications in Fig. 4. This implies that bacteria could stably and continuously carry genetic circuits to complete neuromorphic computing, whereas, this is not readily achievable with existing DNA-based logic circuits. Moreover, complex synthetic neuromorphic circuits existing stably in living cells could generate output signals in response to input signals through the secretions between cells, which would better enable monitoring the changes in the chemical substances contained in organisms or environments [44,49,52,53]. Accordingly, this approach has great development prospects in the biosensor field.

Biocomputing is expected to become widespread in many fields, such as DNA data storage and encryption, medical diagnosis, drug delivery, and intelligent biosensor [54–63]. Inspired by the computational power of “DNA strand displacement,” Wang et al. enhanced DNA storage with parallel “in-memory” molecular computation using strand displacement reactions to algorithmically modify data, showing that large cascades involving 244 strand exchanges can use naturally occurring DNA sequence from M13 bacteriophage, possibly expanding computational capacity and reducing costs [64]. Ma et al. developed an automated DNA computing–based platform [65]. It can accurately discriminate bacterial from viral causes of acute respiratory infection within 4 h by implementing a classification model, which has been trained in silico to recognize seven distinct mRNA expression patterns at the molecular level. Lv et al. reported a DNA integrated circuit system by integration of multilayer DNA-based programmable gate arrays (DPGAs) [66]. These DPGAs are capable of executing sophisticated computations, programmed with an instruction set of over 2000 oligonucleotides. They demonstrated that integration of a DPGA with an analog-to-digital converter enables the classification of disease-associated microRNAs.

In conclusion, with the technological advances that have been achieved based on Moore’s law and beyond, neuromorphic computing has emerged to meet increasing demand for computing speed and volume demands [8]. The combination of synthetic biology and semiconductor technology will break the technical bottleneck in the fields of materials and biological systems, and SemiSynBio has the potential to play a significant role in the evolution of more adaptive, robust, and scalable AI chips. Standing at the brink of innovation, SemiSynBio is ready to revolutionize the computing industry by integrating biological principles into the creation of systems that are more efficient, scalable, and adaptable than ever. This merger is expected to bring significant improvements in how we process and store data, aiming to match the brain’s unmatched energy efficiency and its ability to handle multiple tasks at once. Additionally, this strategy has the potential to greatly advance the development of smart devices and sensors, catering to a wide range of uses from monitoring the environment to healthcare. As these technologies advance, they promise to transform the landscape of computing, closing the gap between biological and electronic systems. While the all-around development of neuromorphic computing based on biomolecules still has a long way to go, we believe that synthetic neuromorphic circuits are an important aspect of future research into biocomputers and neuromorphic computing.

CRediT author statement

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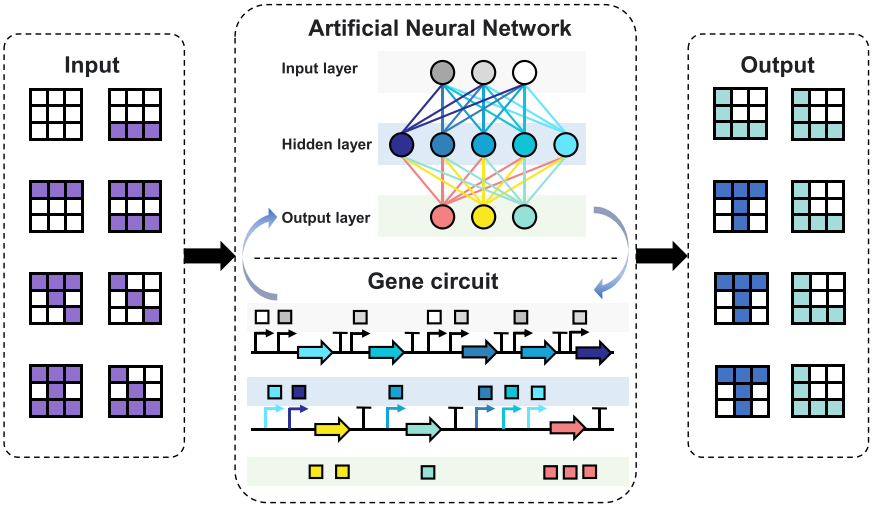

Fig. 4. Synthetic neuromorphic computing by genetic circuits.

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Declaration of competing interest

None of the authors have any competing interests to declare.

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