terms in which species 6mA is present, enabling discrimination between 6mA in the metazoan genome and that in contaminating microorganisms (see the figure).

Existing SMRT-seq methods compare the interpulse duration ([IPD) the time between successive base additions, which is altered by DNA modifications] of native template with the reference genome, ignoring contaminating DNA with abundant 6mA. Kong et al. overcome this limitation by devising a reference-free approach. By using the long-read sequencing to exclusively sequence short (200 to 400 base pairs) DNA sequences, each molecule is heavily resequenced, which leads to higher-confidence circular consensus sequence (CCS) base-calling accuracy. A metagenomic analysis allows for CCS reads to be mapped to both the genome of interest and to potential contamination sources by using a comprehensive set of genomes, including those from microbiota. The 6mA/A ratios were estimated using a machine learning model trained with a broad range of 6mA content. As a proof of principle, the authors performed 6mASCOPE on two unicellular eukaryotes with high amounts of 6mA, Chlamydomonas reinhardtii (II) and Tetrahymena thermophila (22). They confirmed high 6mA in these protists and further refined the methylation motif (VAIT: V = A, C, or G; B = C, G, or T) and preference of 6mA to occur in specific locations in the linker regions between nucleosomes.

Kong et al. next applied 6mASCOPE to D. melanogaster, A. thaliana, and Homo sapiens—three multicellular eukaryotes with reported high 6mA abundances (~700 ppm for D. melanogaster embryos (2), 2500 ppm for A. thaliana seedlings (3), and 500 to 1000 ppm for H. sapiens lymphocytes (13) or primary glioblastomas (14). They found that bacteria in the gut of D. melanogaster or in the soil of A. thaliana samples, which made up a very small amount of the mapped reads, accounted for the majority of 6mA quantified by UHPLC-MS/MS. This led to 6mA abundance in D. melanogaster and A. thaliana genomes being quantified at ~2 to 3 ppm (near the limit of detection). These findings are bolstered by previous work that demonstrated that nematode worms (Caenorhabditis elegans) have substantially lower 6mA abundance (0.1 to 3 ppm) than previously estimated because of bacterial contamination in the gut and that zebrafish (Danio rerio) embryos have artificially increased 6mA quantifications because of bacteria adhering to the chorion membrane, which surrounds the embryo, as assessed by UHPLC-MS/MS (7).

6mASCOPE performed on peripheral blood mononuclear cells and two glioblastoma brain tissue samples yielded 6mA abundances of 17 and 2 ppm, respectively. A recent study suggested that 6mA is increased in mammalian mitochondrial DNA (15), but 6mASCOPE also failed to detect increased amounts of 6mA in the mitochondrial DNA of human HEK293 cells. Kong et al. confirmed earlier results (7, 10) that exogenous premethylated DNA can be incorporated into eukaryotic DNA and increases 6mA content. Together, these findings challenge high 6mA abundances in multicellular eukaryotes. Instead, 6mA is likely much rarer than previously thought and is possibly variable between different tissue samples or cell lines. It is also possible that 6mA increases only under specific stress conditions (15).

6mASCOPE’s limit of detection (~1 to 10 ppm) makes it hard to conclude whether estimated 6mA abundances of 2 to 3 ppm are real and above background. These limitations can be addressed through the development of sequencing methods that take advantage of the distinct chemistry of 6mA, similar to bisulfite sequencing for 5-methylcytosine. Additionally, future studies should combine this more-rigorous 6mASCOPE and optimized UHPLC-MS/MS methods (7) with a focus on stress conditions and mitochondrial DNA (15). Moreover, 6mASCOPE cannot discriminate potential misincorporation of either abundant messenger RNA containing 6mA or foreign methylated DNA that could be integrated into eukaryotic DNA through the nucleotide salvage pathway. Combining rigorous detection methods with the manipulations of putative 6mA-regulating enzymes and directed epigenomic editing of 6mA will help address whether rare 6mA in metazoans has a functional role in specific locations in the genome or is randomly localized as a potential by-product of misincorporation by the salvage pathway.

REFERENCES AND NOTES
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MATERIALS SCIENCE
An adaptive device for AI neural networks

The perovskite nickelate can transform among four different electronic components

By Rohit Abraham John

The human brain’s ability to maneuver the avalanche of unstructured data, learn from experience, and process information with extreme energy efficiency inspires the next generation of computing technologies (1, 2). Neuronal plasticity is defined as the capability of the brain to change its structure and function in response to experience. This functional and structural plasticity is what researchers are trying to achieve in the so-called “neuromorphic” circuits and computer architectures (3–6). Specific learning rules observed in biology have been faithfully replicated recently in electrical components (7, 8). However, the ability for a logical device to learn and modify from experience, and to grow and shrink when required, have yet to be explicitly demonstrated. On page 533 of this issue, Zhang et al. (9) present highly plastic perovskite nickelate devices that can be electrically configured and reconfigured to become resistors, memory capacitors, artificial neurons, and artificial synapses.

The material design principle for creating reconfigurable devices is based on protonation-induced doping of nickelates such as NdNiO₃ or NNO. At room temperature, an ideal NNO is a correlated metal, which means that electrons would interact among themselves inside the material instead of behaving independently. Hydrogen, an electron donor, can be inserted into the NNO lattice by annealing the material in hydrogen gas while connected to a catalytic electrode. This process modifies the electrons’
Hydrogen-doped perovskite nickelate as a versatile reconfigurable platform

By applying electric pulses, the hydrogen ions in the nickelate lattice can occupy metastable states and enable distinct functionalities. This allows the same device to be reconfigured on demand as a resistor, a memory capacitor, an artificial neuron, or an artificial synapse.

“This can enable compact and energy-efficient neuromorphic system designs of reservoir computing frameworks and dynamic neural networks.”

The reconfigurable device by Zhang et al. represents a substantial advance by having multiple neuronal and synaptic functionalities embedded within a single device. This can enable compact and energy-efficient neuromorphic system designs of reservoir computing frameworks and dynamic neural networks. However, to bring this vision to practical hardware implementation, researchers still have to find answers to many questions, such as how to deal with the nonuniformity of the devices, how to make the device connect to or disconnect from the neural network, how to rearrange the connections when the device is reconfigured from one function to another, and how to determine the role of each device and apply the correct voltage scheme on it.

The electrical circuits in use today are designed with multiple passive components such as resistors, capacitors, and inductors and active devices such as transistors. With the discovery of memristors, circuit designers now have an extra degree of freedom (10-12) when designing power-efficient, high-performance systems. However, from a material implementation perspective, the construction of these components still requires complex assembly of various conductive, semiconductor, and insulating materials. The ability to implement almost all of these elements with a single material platform can substantially change electronics. Hence, such reconfigurable electronic devices could have positive implications beyond neuromorphic computing and machine intelligence.
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