Perovskite nickelates as bio-electronic interfaces

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Functional interfaces between electronics and biological matter are essential to diverse fields including health sciences and bio-engineering. Here, we report the discovery of spontaneous (no external energy input) hydrogen transfer from biological glucose reactions into SmNiO3, an archetypal perovskite quantum material. The enzymatic oxidation of glucose is monitored down to $\sim 5 \times 10^{-16}$ M concentration via hydrogen transfer to the nickelate lattice. The hydrogen atoms donate electrons to the Ni $d$ orbital and induce electron localization through strong electron correlations. By enzyme specific modification, spontaneous transfer of hydrogen from the neurotransmitter dopamine can be monitored in physiological media. We then directly interface an acute mouse brain slice onto the nickelate devices and demonstrate measurement of neurotransmitter release upon electrical stimulation of the striatum region. These results open up avenues for use of emergent physics present in quantum materials in trace detection and conveyance of bio-matter, bio-chemical sciences, and brain-machine interfaces.
Functional interfaces between biological and synthetic matter can greatly benefit from hydrogen transfer, which is of broad relevance to bio-sensing and bio-chemical sciences. Sensing media that respond to low concentrations of bio-markers are of great interest in this context, however, must be functional near room (or body) temperature while constantly exposed to complex biological media. As a promising candidate, the perovskite nickelate SmNiO₃ (SNO, space group Pnnm) is water-stable, and belongs to a class of strongly correlated quantum materials, whose properties are highly sensitive to the occupancy of electrons in their partially filled orbitals. When doped with charge carriers, SNO shows massive electronic structure changes: For one electron/unit cell doping from hydrogen, the electrical resistance changes by ~10 orders of magnitude. In previous work, perovskite nickelates have shown potential for electric field detection in salt water media. In nature, glucose can be oxidized into gluconolactone by losing hydrogen in the presence of glucose oxidase (GOx) enzyme, and this reaction is seen across various organisms. Utilizing an external electric field, perovskite oxide nano-particles have been used for glucose detection. An important strategy to understand such biological and bio-chemical reactions involves measurement of the hydrogen transfer processes. Here, we present enzyme-mediated spontaneous hydrogen transfer between glucose reaction and SNO devices, as well as interfacing perovskite devices with acute mouse brain slices.

**Results**

**Reaction mechanism.** Figure 1a shows the schematic pathway for spontaneous atomic hydrogen transfer between glucose–GOx reaction and a perovskite, where the nickelate participates in the reaction by accepting the hydrogen in the glucose–enzyme–oxide transfer chain. The reaction mechanism is described in Fig. 1b. During the glucose–enzyme–SNO reaction, the hydrogen atoms from the glucose are first transferred to the GOx enzyme as it occurs in nature, and then into the SNO lattice. This process occurs spontaneously without the need for any external energy input. The hydrogen then bonds with oxygen anions and occupies interstitial sites among the oxygen octahedra in SmNiO₃, contributing an electron to the d orbitals of nickel. The hydrogen acts as a donor dopant in the lattice. As a result, the singly occupied Ni e₉ orbitals in glucose-reacted SNO (GSNO) become doubly occupied and the additional electron in the e₉ orbital imposes large on-site Mott–Hubbard electron–electron repulsion, leading to localization of the charge carriers and resistivity increase, as shown in Fig. 1c. Such a hydrogen-induced condensation suppression serves as a sensitive platform for chemical transduction at the interface between the nickelate films and biological glucose reaction.

**Electrical characterization.** To demonstrate the hydrogen transfer from the glucose–GOx reaction to SNO, SNO devices with GOx-modified Au electrodes were first fabricated, as schematically shown in Fig. 2a (for details, see Supplementary Methods and Supplementary Fig. 1). Next, atomic force microscopy (AFM) and cyclic voltammetry (CV) measurements were performed to verify the successful decoration of GOx on Au surface. As shown in Fig. 2b, bright GOx dots were observed on the Au surface. A line scan along AB indicates the height of GOx is around 5 nm, which is consistent with the actual size of GOx. The pristine Au surface is smooth with a roughness of ~0.7 nm (Supplementary Fig. 2). In the CV scan, a pair of reversible electron transfer peaks were observed at the position characteristic of the GOx enzyme (Fig. 2c). No CV peak was found at this voltage range when the measurement is performed on a bare Au electrode surface (Supplementary Fig. 3). With these measurements, we can confirm the existence of GOx on the Au surface. The reaction between the enzyme–SNO device and glucose solution was initiated by applying a droplet (20 µL) of 0.5 M glucose solution (in deionized water (DI) water) on top of the device, as schematically shown in Fig. 2a. After the glucose droplet was applied, a sharp increase of resistance of the enzyme–SNO device was observed, see the red curve in Fig. 2d. However, if there is no GOx decoration on the SNO device, no reaction occurs between the glucose solution and the nickelate device, as shown in the black curve of Fig. 2d. The reacted solution was subsequently characterized by Fourier-transform infrared (FTIR) spectroscopy measurement, and the formation of gluconolactone was observed (Supplementary Fig. 4), which is consistent with the reaction mechanism described in Fig. 1b. The reaction occurs spontaneously without any external electric fields (Supplementary Fig. 5). The resistance of the device can be reversed back to original state by annealing, due to the room temperature metastable trapping of the hydrogen in the

![Fig. 1](image_url) Spontaneous hydrogen transfer between perovskite and glucose–enzyme reaction. **a** Schematic figure of the atomic hydrogen transfer from the glucose to perovskite. The glucose oxidase (GOx) enzymes are anchored on the gold electrode via cystamine bonding (details are described in Supplementary Fig. 1). Figure not drawn to scale for clarity. **b** Reaction mechanism of glucose–SnO₂ transformation to gluconolactone–SnO₂. The GOx enzyme serves as a catalyst and transfers hydrogen from glucose to SmNiO₃, referred to as G-SmNiO₃. The hydrogens bonded with carbons are omitted for figure clarity. **c** The electron filling configuration of the Ni 3d orbitals in SmNiO₃ and G-SmNiO₃. For the pristine SmNiO₃, the e₉ orbitals are singly occupied. In the case of G-SmNiO₃, the donors doped from the hydrogen occupy an e₉ orbital, resulting in large on-site Coulomb repulsion energy U, and localizing the charge carriers resulting in reduction of electronic conductivity.
Resistance of the enzyme \( R \) zoomed in with glucose oxidase (GOx) decorated Au electrodes. Before the reaction, glucose solution was added on top of the device surface, as shown in the zoomed in figure on the right. The enzyme–SNO device after 0.5 M glucose solution is applied as shown in (a). A clear increase in resistance is observed after the glucose solution is applied (red curve). No change in resistance was observed for the control SNO sample without any GOx modification (black curve in the inset). \( R_0 \) is the resistance of the pristine enzyme–SNO device. (b) Resistance increase of the enzyme–SNO device after the device is soaked in glucose solution for 1 h with different concentration. (c) Cyclic voltammetry (CV) measurements with GOx-modified Au surface as a working electrode. Electrochemical reduction and oxidation peaks of GOx were observed as expected. The SNO devices were highly responsive to dilute glucose concentrations and showed good selectivity. For the responsivity test, the enzyme–SNO device was soaked in glucose solution with different concentrations for one hour and then the resistance ratio \( \Delta R/R_0 \) was plotted in Fig. 2e. In all the cases, the device resistance increased after the reaction, and \( \Delta R/R_0 \) becomes larger with increasing glucose concentration. The \( \Delta R/R_0 \) at the dilute limit of the glucose concentration is shown in the inset of Fig. 2e and the detection limit is determined as \( 5 \times 10^{-16} \) M (signal to noise ratio >3). The error bar shown in inset plot was determined from the standard deviation of 10 measurements.

Fig. 2 Electrical response of nickelate devices interfaced with glucose without external energy. (a) Schematic figure of the enzyme–SmNiO₃ (SNO) device, with glucose oxidase (GOx) decorated Au electrodes. Before the reaction, glucose solution was added on top of the device surface, as shown in the zoomed in figure on the right. The surface morphology of GOx-modified Au surface measured by atomic force microscopy (AFM). The GOx molecules are the bright dots on the surface and a line scan along AB shows the height of the GOx is around 4–5 nm. (b) Cyclic voltammetry (CV) measurements with the GOx-modified Au surface as a working electrode. Electrochemical reduction and oxidation peaks of GOx were observed as expected. The SNO devices were stable in water and the doping from glucose was non-volatile at room temperature (Supplementary Figs. 8 and 9). The SNO devices also function at body temperature (37 °C), see Supplementary Fig. 10. The high detection limit in our enzyme–SNO devices is a unique attribute of strong electron correlations, a quantum mechanical effect wherein miniscule perturbation to the electron occupancy of orbitals can result in giant modulation of the transport gap. The detection of glucose is reproducible as shown in Supplementary Fig. 11. The GOx–SNO devices also function at body temperature (37 °C), see Supplementary Fig. 12. To test the selectivity of the enzyme–SNO device, 20 µL of 0.5 M mannose, galactose and glucose solutions were separately applied to the enzyme–SNO device, no reaction was observed for the mannose and galactose solution as seen from electrical characterization (Supplementary Fig. 13).
**Synchrotron X-ray-based characterization.** X-ray diffraction measurements were performed to study the structural evolution in glucose reacted nickelates (GSNO) with scans around LaAlO$_3$ substrate 002 peak (pseudocubic notation). The sample abbreviation and treatment conditions are summarized in Supplementary Table 1. The pristine SNO 002 peak was observed with a lower $Q_z$ value compared to the LaAlO$_3$ substrate due to its larger out of plane lattice parameter, see Supplementary Fig. 14. Figure 3a shows position-specific x-ray diffraction data of the reacted GSNO sample with patterned electrodes. Red solid curve is on top of a GOx-modified Au electrode, while blue dashed curve is on a Pd electrode without any GOx modification. After the reaction, an extra peak with smaller $Q_z$ (arising from the hydrogen doping-induced lattice expansion) was found in the red curve besides the...
Two key steps are involved: the kinetics of the spontaneous hydrogen transfer mechanism. There is a combination of classical molecular dynamics (MD) and quantum chemical simulations. While the energetic cost to dehydrogenate FADH2 is high (~2.2 eV/hydrogen), the presence of SNO allows for spontaneous hydrogen transfer from FADH2 to SNO (see Supplementary Fig. 18 and Supplementary Methods for details).

To simulate the dynamics of FADH2 interaction with SNO, we perform classical MD simulations to adequately sample sterically acceptable configurations of FADH2 at the active SNO sites, i.e. surface O (see the simulation box in Supplementary Fig. 19). The classical MD simulations suggest that the conformational dynamics of FADH2 is a slow process and the diffusion of FADH2 molecules to the SNO (001) (pseudocubic notation) surface occurs at timescales of tens of nanosecond (see Fig. 3c for snapshots from a representative trajectory and Supplementary Movie 1). The FADH2 molecules undergo a series of conformational changes before adsorbing onto the SNO (001) surface. We sample several such energetically favorable near surface configurations of FADH2 from the classical MD and use it as starting configurations for smaller ab initio MD (AIMD) models to study the effects of strong correlation and its role in FADH2 dehydrogenation (see Supplementary Fig. 20). Figure 3d shows snapshots from two representative AIMD trajectories that depict the temporal evolution of the FADH2 molecules near the SNO surface. The magnified images track the FADH2 and the NiO$_6$ octahedra near the SNO surface (top panel of Fig. 3d). For both the cases shown, we observe spontaneous hydrogen transfer to surface oxygen of SNO within 2 ps of simulation, also see Supplementary Movie 2. This picture is consistent with the enzyme-assisted hydrogen transfer mechanism depicted schematically in Fig. 1. We find that the conformations of the FADH2 play a key role in dictating the hydrogen transfer: If the FADH2 conformations are sterically favorable, the process is spontaneous (see Supplementary Fig. 21 and Supplementary Movie 3).

Classical and quantum mechanical simulations. We use a combination of classical molecular dynamics (MD) and quantum chemical simulations to understand the thermodynamics and kinetics of the spontaneous hydrogen transfer mechanism. There are two key steps involved: the first reductive half-reaction of β-phenylalanine (β-Phe) and the second reductive half-reaction of β-alanine (β-Ala). The second step involves hydrogen transfer from FADH2 to the strongly correlated oxide SNO. We evaluate the energetics of dehydrogenation of FADH2 using quantum chemical simulations. While the energetic cost to dehydrogenate FADH2 is high (~2.2–3.2 eV/hydrogen), the presence of SNO allows for spontaneous hydrogen transfer from FADH2 to SNO (see Supplementary Fig. 18 and Supplementary Methods for details).

To simulate the dynamics of FADH2 interaction with SNO, we perform classical MD simulations to adequately sample sterically acceptable configurations of FADH2 at the active SNO sites, i.e. surface O (see the simulation box in Supplementary Fig. 19). The classical MD simulations suggest that the conformational dynamics of FADH2 is a slow process and the diffusion of FADH2 molecules to the SNO (001) surface occurs at timescales of tens of nanosecond (see Fig. 3c for snapshots from a representative trajectory and Supplementary Movie 1). The FADH2 molecules undergo a series of conformational changes before adsorbing onto the SNO (001) surface. We sample several such energetically favorable near surface configurations of FADH2 from the classical MD and use it as starting configurations for smaller ab initio MD (AIMD) models to study the effects of strong correlation and its role in FADH2 dehydrogenation (see Supplementary Fig. 20). Figure 3d shows snapshots from two representative AIMD trajectories that depict the temporal evolution of the FADH2 molecules near the SNO surface. The magnified images track the FADH2 and the NiO$_6$ octahedra near the SNO surface (top panel of Fig. 3d). For both the cases shown, we observe spontaneous hydrogen transfer to surface oxygen of SNO within 2 ps of simulation, also see Supplementary Movie 2. This picture is consistent with the enzyme-assisted hydrogen transfer mechanism depicted schematically in Fig. 1. We find that the conformations of the FADH2 play a key role in dictating the hydrogen transfer: If the FADH2 conformations are sterically favorable, the process is spontaneous (see Supplementary Fig. 21 and Supplementary Movie 3).

Interfaceing with mouse brain slice. We further extended the experimental studies to another important bio-marker dopamine (DA), which is a neurotransmitter that plays a significant role in motivation and learning. Low levels of DA are causal to the progression of Parkinson’s disease (PD), and are hypothesized to be implicated in schizophrenia and attention deficit hyperactivity disorder (ADHD). Consequently, detection of low concentrations of DA is required for future studies of these diseases and for the development of pharmacological therapies. DA can be monitored by our nickelate devices using the horseradish peroxidase (HRP) enzyme, as schematically shown in Supplementary Fig. 22a. The HRP–SNO device is responsive to DA both in DI water down to $5 \times 10^{-17}$ M (Supplementary Fig. 22b and Supplementary Fig. 23 for comparison with literature). The HRP–SNO devices were also functional in biological media and responded to DA in artificial cerebrospinal fluid (ACSF) (see Fig. 4a). As control experiments, the HRP–SNO device was found to be stable in both pure ACSF and DI water, and the HRP enzyme is essential for the hydrogen transfer process to the nickelate lattice (Supplementary Fig. 24). Enzymatic selectivity coupled with the spontaneous ion–electron transfer therefore ensures robustness of the nickelate quantum material in various biological and brain environments.

We then directly interfaced an acute mouse brain slice onto the nickelate devices to monitor DA release triggered by electrical stimulation of the striatum, the brain area enriched with dopaminergic projections, as schematically shown in Fig. 4b and c. In this experiment, an acute mouse striatal slice was placed on a HRP–SNO device in a chamber continuously perfused with oxygenated ACSF solution (see the Supplementary Methods section for complete details), and electrical stimulation was applied to trigger the release of DA from the striatum. Figure 4d shows the corresponding response of the HRP–SNO device to DA released from stimulated striatal slice. The resistance increase of the HRP–SNO device (~23%) approximately corresponds to DA concentration of $10^{-10}$–$10^{-9}$ M, based on the DA-concentration-dependent experiments shown in Fig. 4a. Such an estimation is consistent with stimulation experiments under similar conditions, considering that only a small fraction of the DA molecules diffuse out from the brain synapses and reach the HRP–SNO device surface. As a control experiment, the HRP–SNO device was interfaced with a striatal slice without electrical stimulation.
The error bar was determined from the standard deviation of 10 measurements in each case. The process of interfacing acute mouse brain slice with the HRP enzyme was performed at the Allen Institute for Brain Science. Allen Brain Atlas API. Available from: http://mouse.brain-map.org/. Through the hydrogen transfer assisted by the HRP enzyme, the brain anatomy image is adapted with permission from an open data resource © 2015 Allen Institute for Brain Science.

Fig. 4: Direct interfacing of HRP-SNO device with acute mouse brain slice. a) Electrical response of the horseradish peroxidase-SmNiO$_3$ (HRP-SNO) devices to varying dopamine concentration in artificial cerebrospinal fluid. The device resistance change is presented as ratio before and after the reaction ($R/R_0$). The error bar was determined from the standard deviation of 10 measurements in each case. b) A schematic (drawing not to scale for clarity) showing the process of interfacing acute mouse brain slice with the HRP-SNO device. The black dash lines in the brain anatomy map show where the striatum slice and primary visual cortex slice were cut. Under electrical stimulation, dopamine molecules are released from the striatum slice and dope the SNO device through the hydrogen transfer assisted by the HRP enzyme. The brain anatomy image is adapted with permission from an open data resource © 2015 Allen Institute for Brain Science. Allen Brain Atlas API. Available from: http://mouse.brain-map.org/. c) A photo of the experimental set up during the interfacing between striatum slice and HRP-SNO device. The experiment was performed in an aqueous artificial cerebrospinal fluid environment and the stimulation electrode was used to trigger dopamine release from the striatum slice. The striatal brain slice is ~10 × 5 mm and the HRP-SNO device region (red rectangle) is fully covered under the slice. d) I–V characteristics of the HRP-SNO device interfaced with striatal brain slice. When stimulated, the striatal brain slice releases dopamine which can be monitored by the HRP-SNO devices as seen from change in channel resistance. e) The HRP-SNO device was interfaced with striatum slice in the same way as described in Fig. 4c, but with no electrical stimulation (and thus no dopamine release). No resistance change was seen, and the device was stable in the spinal fluid environment. f) The primary visual cortex part of the mouse brain which releases little or no dopamine under electrical stimulation[24] was interfaced with the HRP-SNO device. After the electrical stimulation, much smaller response (only ~2% change in resistance) was observed compared to that of striatum slice stimulation.

Another control experiment, identical electrical stimulation was applied to a primary visual cortex (V1) slice where there is expected to be little or no DA innervation, and therefore minimal or no DA was expected to be released[24]. A much smaller response (only ~2% resistance change) was found from the HRP–SNO device interfaced with stimulated V1 slice compared to the case of stimulated striatal slice, suggesting the large response observed with striatum slice stimulation is from DA release (see Fig. 4f). The much smaller response observed with V1 stimulation is likely from small amounts of DA-like species such as serotonin[25]. Also, the HRP enzyme was found to be critical in transferring the hydrogen from DA to SNO. No change in resistance was found when the SNO device with only gold electrodes (without HRP enzyme) was interfaced with the striatal slices while the same electrical stimulation was applied (see Supplementary Fig. 25).

**Discussion**

We have presented the discovery of room temperature enzyme-mediated spontaneous hydrogen transfer from model biological reactions and brain matter into a perovskite quantum material. The hydrogen transfer from biological reactions at the nickelate interface trigger a unique response: strong Coulomb repulsion that localizes charge carriers and suppresses electrical conduction. Coupled with the ability to function at body temperature in brain and biological environments enables response to ultra-low concentrations of bio-markers. The results open up directions for exploring correlated quantum systems in health sciences, brain interfaces and biological routes to dope emerging semiconductors.
Reporting summary. Further information on experimental design is available in the Nature Research Reporting Summary linked to this article.

Data availability
All data presented in the main text and the supplementary information are available.

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Author contributions
H.-T.Z., F.Z., and S.R. conceived the study. H.-T.Z. and F.Z. fabricated the SNO films and performed electrical measurements. H.-T.Z. performed FTR measurements. F.L. and J.H.C. performed the enzyme decoration and AFM measurements. Q.W., H.-T.Z. and A.A.C. performed the interfacing experiment of SNO device with acute mouse brain slices. H.C., B.N., G.K. and S.K.R.S.S. carried out DFT, classical MD and ab-initio MD calculations. Z.Z. and H.Z. performed XRD and XAS measurements. K. Ramadoss performed temperature-dependent transport analysis. I.C., G.S. and K. Roy performed finite element analysis. H.-T.Z., S.K.R.S.S. and S.R. wrote the manuscript. All authors participated in discussing the results and providing comments for the paper.

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