Flexible Electronic/Optoelectronic Microsystems with Scalable Designs for Chronic Bio-Integration

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Abstract

Flexible, bio-compatible electronic systems that leverage key materials and manufacturing techniques associated with the consumer electronics industry have potential for broad applications in biomedicine and biological research. This study reports scalable approaches to technologies of this type, where thin, microscale device components integrate onto flexible polymer substrates in interconnected arrays to provide multimodal, high performance operational capabilities as intimately coupled bio-interfaces. Specificially, the material options and engineering schemes summarized here serve as foundations for diverse, heterogeneously integrated systems. Scaled examples incorporate >32,000 silicon microdie and inorganic microscale light emitting diodes derived from wafer sources distributed at variable pitch spacings and fill factors across large areas on polymer films, at full organ-scale dimensions such as human brain over ~150 cm^2. *In vitro* studies and accelerated testing in simulated biofluids, together with theoretical simulations of underlying processes, yield quantitative insights into the key materials aspects. The results suggest an ability to operate in a biologically-safe, stable fashion with projected lifetimes of several decades without leakage currents or reductions in electrophysiological performance. The versatility of these combined concepts suggests applicability to many classes of bio-integrated semiconductor device platforms.

Significance Statement

Emerging classes of flexible electronic systems designed to interface to soft tissues of the human body serve as the foundations for bioelectronic forms of medicine, with capabilities that can complement those of traditional pharmaceutical approaches. This work establishes the engineering science of categories of bio-integrated microsystems that include assemblies of tens of thousands of microdevices interconnected into functional networks on thin flexible polymer substrates with areas that approach those of the human brain. Detailed *in vitro* studies suggest the ability of these systems to provide sophisticated electronic and optoelectronic function with stable, biologically-safe operation for many decades. The results define concepts and technology approaches with widespread utility in the field of bioelectronics.

Introduction

Large-scale electronic/optoelectronic platforms that support intimate, functional bio-interfaces offer important capabilities in monitoring and/or stimulation of living tissues, of relevance to both biological research and clinical therapy (1-7). Emerging classes of flexible bio-integrated systems offer many powerful options in this context, as implants for long-term, biologically-safe operation (8-13), with examples that range from flexible sheets of electronics for electrophysiological mapping on endo- and epicardial surfaces (14,15) to thin optoelectronic probes for optical stimulation/recording of neural activity in the depths of the brain (16,17). An essential feature of such technologies is that they can bend, flex and twist while in contact with soft, moving biological tissues, to minimize damage and to support long-term stable operation. Although approaches based on organic semiconductors, nanowires/particles and two dimensional materials are of some interest, those that exploit micro/nanoscale forms of well-established inorganic semiconductors often provide superior levels of functionality and performance, in some cases at levels that compare favorably to those of conventional electronic/optoelectronic devices built on planar, rigid semiconductor wafers (18-26). The most sophisticated embodiments include arrays of transistors based on silicon nanomembranes (Si-NMs) distributed on shape-conformal sheets, with designs that provide signal amplification and multiplexed addressing at each unit cell across the system (27-29). Here, high quality, thin layers of SiO_2 can serve as flexible biofluid barriers and/or capacitive measurement interfaces (30-32). The dense, defect-free nature of SiO_2 formed by thermal growth on device-grade silicon wafers (referred to here as t-SiO_2) act as remarkably effective barriers across macroscopic areas, with lifetimes projected to extend to many decades, where a slow hydrolysis process causes eventual failure (33,34).

Although these concepts enable interesting classes of bio-integrated devices, they require custom processing steps, some of which are most well suited to academic cleanrooms

and manual operation. Schemes that retain these essential ideas but align with the highly automated manufacturing infrastructure that supports the consumer electronics industry could facilitate broad distribution of similar platforms for use by the research community and, ultimately, for translation to human healthcare. In this context, microscale transfer printing techniques for rapid, parallel transfer of micro/nanomaterials and devices from source wafers to target surfaces are highly relevant, as previously demonstrated with microscale inorganic light emitted diodes (μ-ILEDs), photodetectors and piezoelectric microcomponents for use in optogenetics, oximetry, and biopsy (35-37) and, separately, in small collections of complementary metal-oxide-semiconductor (CMOS) microdies (38,39), with industrially proven uses in photovoltaics, information display and others.

The results presented here combine and extend these approaches in ways that provide access to deterministic assemblies of large collections of silicon microdies and compound semiconductor μ-ILEDs, both sourced from semiconductor wafers compatible with processing at commercial vendors, but released and distributed in dense and/or sparse arrays with variable controls on thin flexible polymer substrates. The scales of the demonstrations significantly exceed those of the past publications, in terms of overall areas (from ~1 cm^2 to 150 cm^2) (27), numbers of functional elements (from ~2000 to ~64,000) (29), numbers of measurement/stimulation channels (from ~300 to ~32,000) and assembly throughput (from ~300 to ~1000 micro-components per printing operation) for applications such as those in neural/cardiac electrophysiology, optogenetics and optical monitoring (27-29,35,37). More generally, the schemes offer a manufacturable route to heterogeneous integration with high registration accuracy at spatially variable densities, layouts and geometries. Specific examples include interconnected electronic-optoelectronic microsystems that exploit thin, printable microdies and μ-ILEDs as pixelated funtional components, illustrating the concepts for building combined electronic/optoelectronic systems in thin/flexible formats. Co-integration

with t-SiO_2 biofluid barriers yields long-term stability, over timeframes that project to many decades of immersion in simulated biofluid environments. Performance evaluations, yield studies, accelerated immersion tests, temperature-dependent *in vitro* measurements and related theoretical simulations highlight the key features. These ideas have potential as the basis of long-lived, highly functional semiconductor device interfaces to living organisms, of particular relevance to neural and cardiac systems.

Results and Discussion

High speed, deterministic assembly of electronic/optoelectronic microdies. As illustrated in previous publications (40-42), powerful classes of large-area, flexible electronic microsystems can be realized by combining conventional electronic materials and microfabrication processes with transfer printing techniques. Here, the transfer process allows for rapid, deterministic manipulation and assembly of microdies released from fully processed semiconductor wafers with advanced undercut etching techniques. The results can yield large-scale arrays in arbitrary layouts over large areas on substrates of interest in ambient conditions. Fig. 1*A* presents a schematic illustration and optical micrographs of advanced implementations of this scheme, starting with (*i*) controlled release of silicon CMOS microdie via a combination of reactive ion etching (RIE) and wet chemical etching, to form freely suspended arrays tethered to an underlying wafer by thin, narrow bridges that serve as anchors, (*ii*) selective retrieval, *i.e.* 'inking' (43), of selected collections of these microdies onto the patterned surface of an elastomeric stamp and (*iii*) aligned transfer of these components by contact printing onto a substrate of interest. In this study, each microdie includes a pair of n-channel metal-oxide semiconductor (NMOS) transistors (channel length L = 10 μm, width W = 33 μm, silicon thickness of 100 nm) released after fabrication on a silicon-on-insulator (SOI) wafer (1 μm thick buried-oxide (BOX) layer). These microdies serve effectively as pixelated

electronic components that yield functional microsystems upon electrical interconnection. Detailed information appears in *SI Appendix*, Fig. S1.

Similar to previous research (38,39), the engineering schemes for creating printable silicon microdie utilize photolithography and inductively coupled plasma reactive ion etching (ICP-RIE) through the BOX layer at the periphery of each die (Fig. 1*A*) to establish trenches that expose the underlying Si wafer. Undercut release follows from anisotropic etching of the wafer by immersion in a bath of tetramethylammonium hydroxide (TMAH, 8.3%). Here, a bilayer of SiO_2/SiN_x (1 μm/600 nm) formed by plasma-enhanced chemical-vapor deposition (PECVD) at 350 °C encapsulates the front side of the microdies as protection from exposure to TMAH. The released microdies remain tethered to their original locations in freely suspended forms joined to the underlying wafer by anchor structures of SiN_x (15 × 100 μm^2, 600-nm thick), while the BOX layer serves as an etch stop and back side protection. Detailed information on microdie architecture appears in *SI Appendix*, Fig. S2, where the dimensions are 220 μm × 150 μm × 3 μm. Retrieval of selected sets of these suspended microdies occurs with stamps of poly(dimethylsiloxane) (PDMS) with relief features and spacing matched to the sizes and layouts of the microdie. Specifically, an automated control system provides precise alignment and control over contact for the selective "inking" process. The anchors fracture mainly as a result of pressure associated with contact to stamp, such that retraction of the stamp leaves collections of microdies weakly bonded by van der Waals forces to the surface of the PDMS. Printing of the microdie 'inks' onto a target substrate yields heterogeneously integrated systems. In examples reported here, a coating of a low-modulus polymer (Intervia photodielectric 8023, ~2 μm) serves as an adhesive to ensure nearly 100% yields in transfer, reproducibly. Multiple cycles of this printing process, conducted in a step and repeat fashion, can yield distributed arrays of microdies over areas that are much larger than those of the original SOI wafer. For plastic substrates, the resulting systems offer

excellent degrees of bendability, particularly for thin microdies configured to lie near the neutral mechanical plane by use of overcoats with suitable thicknesses, without any adverse effect on the performance characteristics. The electrical properties of representative transistors (on/off ratio ~10^7, mobility ~600 cm^2 $V \cdot s^{-1}$ and threshold voltage (V_T) ~ 1 V) are in *SI Appendix*, Figure S3.

Figs. 1*B* to *D* present a series of optical micrographs of a PDMS stamp after retrieval of a collection of microdies, captured at various levels of magnification (from left to right). This example involves ~1000 microdies distributed over an area of 1.5 × 1.5 cm^2 on the surface of a stamp (100-μm relief and 4-mm-thick substrate; Fig. 1*B*). As in Fig. 1*C*, an automated tool allows for alignment and registration with positioning accuracy of ~1 μm. Fig. 1*D* shows side (scanning electron microscope (SEM) image), bottom and top views (optical micrographs) of a representative microdie (~3-μm thick) inked on the stamp relief. Careful control of the release and transfer mechanics enables manipulation of large-scale arrays with high throughput, as in Fig. 1*E*. Here, two SEM images (left and right) highlight different areas across a processed SOI wafer (mid, optical image) before and after selective retrieval, showing freely suspended microdie arrays tethered by SiN_x anchors and their removal, respectively.

Figs. 1*F* and *G* feature the architecture of a microdie released from the source wafer and after transfer printing. The schematic illustration of the cross-sectional undercut profile (Fig. 1*F*) includes the structures and thicknesses of the different layers. The SEM and profilometry images (Fig. 1*G*) in sequence show the released/printed structure (~3 μm) and undercut profile, where the sidewall angle of 54.7° results from the anisotropic etching process. Here, the SiO_2/SiN_x (1 μm/600 nm) bilayer on top has internal stresses that balance those of the released microdie, thereby eliminating any significant bowing.

Transfer printing at variable densities of microdie arrays. Figure 2 demonstrates other key features that follow from a transfer-printing approach to heterogeneous integration. Engineering the distribution of patterned relief structures on the stamps creates efficient routes to assemblies of microdie at variable densities and layouts, with increasing versatility as the number of relief features decreases and the number of step and repeat cycles of printing increases. The schematic illustrations in Fig. 2*A* highlight examples, where dense arrays of relief structures compose the letter "N" with sparse distributions in the background regions. The insets are optical images of corresponding relief structures; *W* and *L* stand for the lateral and longitudinal pitch between each pixel, with 350 μm × 440 μm (*W*×*L*) and 100 μm × 110 μm (*W*×*L*) for sparse and dense distributions, respectively. Aligned printing of these two disparate collections of microdies onto a same substrate yields a system with different densities at different regions.

As mentioned previously, repetitive cycles of transfer printing can produce arrays of microdies with a range of desired layouts and areal coverages. Fig. 2*B* shows an example of ~32,000 microdies printed onto a thin, flexible sheet of polyethylene terephthalate (PET) cut into the approximate outline shape of an adult brain model, at actual size (~150 cm^2). The layout includes pitch spacings of 100 μm × 110 μm or 350 μm × 440 μm in a geometry suggestive of demands for spatial resolution in electrical mapping or stimulation of different sensory functions in the brain, as a conceptual demonstration of the possibilities. Specifically, the regions of dense distribution (100 μm × 110 μm) correspond to the locations of primary sensory cortex for visual, auditory, somatic, gustation and olfactory sensory functions. The sparse distributions appear in motor areas responsible for control of voluntary movements. Such high-definition networks of active electronics have potential relevance in monitoring of electrophysiological activity associated with micro-seizures and microscale discharges of neurons in the brain in ways that could complement traditional microelectrocorticography

(44,45) by significantly increasing the total number and density of addressable channels with local amplification and active multiplexed schemes for addressing. The insets in Fig. 2*B* show the microdie distributions at different levels of magnification, where the optical images highlight the hybrid distribution at the boundaries between sparse/dense arrays (upper) and include magnified views for local sparse (mid, blue frame) and dense (lower, black frame) regions. Fig. 2*C* shows such a system while bending to a radius of curvature at ~3 cm, indicating mechanical flexibility sufficient for conforming to large-scale features of the brain and other soft tissue systems. A statistical analysis of printing yield, defined as the percentage of functional microdie, indicates values >96% for transfer of 256 microdies, or more, in a single operation. Printing failures correspond mainly to fractured/twisted devices (*SI Appendix*, Fig. S4) or associated dislocations. These sorts of defects can be reduced by use of composite stamp designs (46-48) and/or operation in an environment with reduced levels of dust/debris.

Envisioned applications of this printed, large-scale electronic network include shape-conformal bioelectronic interfaces for neural recording or stimulation, configured for mapping on dynamic, curved surfaces of tissues. Fig. 2*D* schematically illustrates contact on a brain model, where the dense arrays align with locations of primary sensory cortex (red hightlight). Co-integration of electrode arrays (Au, 300×300 μm^2, 300 nm thick, Fig. 2*E*) and interconnection traces (inset, Fig. 2*E*) yields functional systems with multiplexing capabilities for efficient capture of spatio-temporal patterns of electrical activity with a dramatically reduced number of addressing wires compared to that required for otherwise similar arrays in passive designs, without microdies. Fig. 2*F* summarizes statistical results for the peak effective mobility (μ_{eff}), V_T and the on/off ratios of 300 representative transistors in printed microdies, derived from standard field effect transistor models (see *SI Appendix*) (45). The results suggest excellent uniformity and consistency in the performance across the system.

Integration of electronic/optoelectronic microsystems with biofluid barriers of t-SiO_2. A fundamental challenge in the development of flexible electronic systems for applications in biology is that their operational lifetimes are often limited by biofluid ingress. Encapsulation strategies (49) that rely on titanium (50) or ceramic (51) enclosures are effective for electronic implants that do not require mechanical bendability or intimate interfaces with biology but they are unsuitable for the types of systems envisioned in bio-integrated device research or in bioelectronic medicines, for instance. A recently developed approach that avoids limitations associated with coatings deposited or cast over preformed electronics exploits an thin layer (sub-micron thick) of SiO_2 (t-SiO_2) thermally grown on the surfaces of device-grade silicon wafers (32). Here, the t-SiO_2 serves as an encapsulation layer that forms first, followed by transfer printing of microdies and layer-by-layer fabrication of interlayer dielectrics/interconnects to yield functional, flexible electronics upon casting of a polymer support and removal of the silicon wafer. Transfer of an additional layer of t-SiO_2 can encapsulate the backside surface of such a system. The encapsulation process (Fig. 3*A*) begins with transfer printing of microdies onto a layer of t-SiO_2 (1 μm) on a silicon wafer, followed by lamination of the printed device onto a separately formed layer of t-SiO_2 (900 nm) with a commercial adhesive (Kwik-sil, World Precision Instruments) on a polymer film/glass plate as temporary support. Dry etching techniques remove the silicon wafer and terminate at the back surface of the t-SiO_2. Peeling the multilayer stack from the glass plate yields a piece of flexible electronics encapsulated on both sides by t-SiO_2 as long-lived, flexible biofluid barriers. Details appear in *SI Appendix*. Fig. 3*B* presents a photogragh of a system that consists of 2×2 interconnected array of printed microdies, wrapped around a cylindrical tube to illustrate the high level of mechanical flexibility.

Immersion in phosphate-buffered solution (PBS) at 96 ^{o}C and at a pH of 7.4, with a continuous electrical bias (alternating current (a.c.), sine wave, 3 V, 100 Hz) applied between

transistor electrodes (source, drain and gate) and a platinum (Pt) reference probe in PBS (Fig. 3*C*), provides a means for accelerated testing of lifetime at elevated temperatures. The transfer characteristics of the transistors and the associated leakage current appear in Figs. 3*D* and *E*, respectively. Stable operation occurs throughout ~9 days of immersion, comparable to timescales of over 60 years at physiological temperature (37 ^{o}C) based on Arrhenius scaling (30). Similarly, soak testing of t-SiO_2-encapsulated magnesium (Mg) thin films (200 nm, electron-beam evaporation) in settings and layouts similar to those of the microdie arrays reveals that the failure mechanism is hydrolysis of the t-SiO_2, as shown in *SI Appendix*, Fig. S5.

The encapsulation strategy outlined in Fig. 3*A* is compatible not only with silicon electronics but also with other types of printable semiconductor devices, such as μ-ILEDs, of relevance for combined electronic-optoelectronic systems that offer advanced capabilities in neuroscience research, for instance. Fig. 3*F* provides an example of this type, with co-integration of indium gallium nitride-based (InGaN) μ-ILEDs and microdies into a common platform with dual-sided t-SiO_2 encapsulation (900 nm), using previously reported procedures for transistos (38) and μ-ILEDs separately (35). The resultant star-burst layout facilitates contact over certain types of non-planar topography, *e.g.*, here shown on a table-tennis ball with a diameter of 4.5 cm. The optical images show a group of magnified views of an integrated microdie, an entire system and a printed μ-ILED in on- and off- states, respectively. As shown in Fig. 3*G*, the performance of the μ-ILED and transistor (inset) remain unchanged after 10^3 cycles of bending into cylindrical shapes with radii of curvature of ~2 cm and after 9-days of immersion in 96 ^{o}C PBS.

Printed microelectronic assemblies for multiplexed electrophysiological mapping. Integration of printed microdie with t-SiO_2 encapsulation serves as the basis of active platforms with multiplexed addressing capabilities in high-fidelity, spatio-temporal recording

of bio-potential distributions across soft tissues, including those of the brain. Fig. 4*A* shows an interconnected array for this purpose. Details of the fabrication process appear in *SI Appendix*, Fig. S6. The overall system includes 64 sensing sites (8 columns, 8 rows, area of ~1 cm^2) with active matrix readout, each of which contains a printed microdie (Fig. 4*B*) with two underlying Si transistors for multiplexed addressing and local buffering (insets of Fig. 4*B* and *SI Appendix*, Fig. S7) (45). The encapsulating layer of t-SiO_2 (900 nm) also serves as a dielectric interface to soft tissue for capacitive sensing via coupling to the underlying electrodes and buffer transistor for amplification (32). The other transistor (as multiplexer) allows readout of signal from each pixelated unit in a rapid time sequence controlled by a back-end data acquisition (DAQ) system (*SI Appendix*, Figs. S7 and S8) with a minimal number of addressing connection wires (27). Additional details on the operation of the system appear in *SI Appendix*.

Figs. 4*C* and *D* show results that demonstrate coupling/sensing operation and summarize bending tests. Immersion in PBS (37 ^{o}C, pH of 7.4) while electrically biasing the PBS via a Pt reference electrode results in coupled responses of the multiplexed arrays, thereby allowing tests of their functionality (*SI Appendix*, Fig. S9). Fig. *4C* displays the output characteristics of a representative unit cell in response to an a.c. input (~ 2 mV, 10 Hz), where the voltage gain is ~0.98 (defined as ratio between output voltage (V_{out}) and input voltage (V_{in})). At a bending radius of 1 cm (inset in Fig. 4*D*), the yield (ratio between the number of working sensing sites divided by the total site number) remains ~100% throughout 2000 cycles (Fig. 4*D*). Fig. 4*E* presents a histogram plot of voltage gain across all sensing sites in a 64-channel system in response to an a.c. input (~ 2 mV, 10 Hz), with an average gain value of 0.98. The inset shows the corresponding spatial map for the statistics of all gain values. The results indicate excellent uniformity across the full array, and also 100% yield. Details of *in vitro* experiments are in *SI Appendix*, Figs. S10 and S11. Figs. 4*F* and *G* summarize the

performance of 10 different arrays. The statistics of test transistor mobility, V_T (*SI Appendix*, Fig. S12), average gain and array yield show minor sample-to-sample variations.

Chronic stability and biocompatibility assessments. Accelerated testing involves immersion in PBS at high temperatures. Here, Fig. 5*A* shows an exploded-view illustration of an actively multiplexed array (sensing area ~1 cm^2), with thicknesses of the different layers from top to bottom (with a total thickness of ~38 μm), where t-SiO_2 serves as encapsulation (1.05×1.05 cm^2, 900 nm thickness). The bonding layers are polymers (*e.g.* polyimide, PDMS and Kiwk-sil film) and the electrode materials are Cr (10 nm) and Au (500 nm). Results of tests that involve immersion in 96 ^oC PBS (pH of 7.4) appear in Figs. 5*B* and *C* in the form of average gain, noise amplitude and yield. The system shows high, stable gain values and yields, with low nosie operation until failure of t-SiO_2 by complete hydrolysis after 9 days. The inset in Fig. 5*B* presents a spatial map of gain values across the array after failure, consistent with liftetimes defined by rates of hydrolysis of t-SiO_2 ($SiO_2+2H_2O \rightarrow Si(OH)_4$, ~100 nm/day in 96 ^oC PBS) (30) and by separate experiments (*SI Appendix*, Fig. S5).

Inductively-coupled-plasma optical emission spectrometry (ICP-OES) measurements yield important information on the elemental species that are released and/or dissolved in biofluids surrounding the implants during immersion, and their concentrations. Fig. 5*D* illustrates the concentration of Si as a function of time during the immersion of an active array (Fig. 5*A*) in PBS at 96 ^oC and pH of 7.4 (40 ml). Measurements show a linear dependence throughout the functional lifetime of the system (~ 9 days) with a rate of ~0.27 ppm/day, suggesting that hydrolysis of the t-SiO_2 barrier proceeds with a stable rate at the exposed surface (~100 nm/day in 96 ^oC PBS). After full dissolution of the t-SiO_2, the system fails immediately and the Si concentration saturates at ~2.5 ppm. The simulated results (green) agree well with experiments (red) (see *SI Appendix*). Fig. 5*E* shows the metal concentrations (*e.g.* Au and Cr) in the surrounding fluid after system failure (from Day 10). These

concentrations increase with dissolution and/or delamination processes after consumption of the t-SiO_2. As a result, Fig. 5*F* highlights remnants of various materials in biofluids with a single multiplexed device, with amounts of 96 μg for Si, 32 μg for Au and 2.9 μg for Cr after 20-day immersion in 96 ^{o}C PBS. Specifically, the release of Cr (2.9 μg) from the multiplexed device into PBS corresponds to amounts well below the toxicity levels according to the standard of World Health Organization (WHO/SDE/WSH/03.04/04, 50 μg).

Figs. 5*G* and *H* summarize thickness-dependent and temperature-dependent studies related to chronic stability. The data indicate a linear dependence of the lifetime on thickness of the t-SiO_2 in 96 °C PBS (Fig. 5*G*), as might be expected, with a good agreement between simulated (line) (52) and experimental results (symbols), consistent with previous reports (30). Fig. 5*H* illustrates lifetimes (with 900-nm-thick t-SiO_2 barrier) at different temperatures, where the simulated results suggest a survivability over decades (~60 years) at a physiological temperature (37 °C), also consistent with projections based on previous measurements of the rate of hydrolysis of t-SiO_2 (~0.04 nm/day in 37 °C PBS) (33,53). Details of simulation appear in *SI Appendix,* Fig. S13.

Conclusion

In summary, the results presented here establish a scalable approach for building combined electronic-optoelectronic microsystems with potential to serve as functional interfaces to soft tissues. Demonstrations include deterministic assemblies of as many as tens of thousands (>32,000) of thin, microscale functional elements derived from source wafers, as interconnected networks across areas that approach those of the human brain, where dense layers of silica serve as encapsulation for chronically stable operation in biofluids. Alignment of this scheme with state-of-art technologies in the consumer electronics industry is a critically important feature, not only for high performance operation but also for scaled

deployment with spatial diversity and variable densities, layouts and geometries. Detailed studies highlight the robustness and functionality at the materials and device levels. On-going work seeks to exploit systems of the type described here as implants for animal studies in brain and cardiac research, with ultimate potential for use as therapeutic devices in humans.

Materials and Methods

Details of fabrication steps, device structures, printing processes, transistor characteristics, encapsulation strategies, procedures for soak tests and failure mechanism analyses appear the *SI Appendix*. Operation of the multiplexing and DAQ systems, *in vitro* performance of the active matrix systems, and reactive diffusion modeling and simulations of t-SiO_2 dissolution are also in the *SI Appendix*.

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Author contributions

E.S., J.Z., J.-K.C., and J.A.R. designed the research; E.S., J.Z., Y.X., L.L., Yuming Huang, S.M.W., K.J.Y., X.S., J.-K.C. and J.A.R. performed the research; E.S., C.H.C, R.L.,

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Figure Legends

Fig. 1. Scalable approaches for deterministic assembly of semiconductor microdevices into flexible systems for bio-integration. (*A*) Processing schemes for printing of flexible silicon microdie: 1. Formation of trenches on a wafer substrate; 2. Retrieval with a PDMS stamp; 3. Printing on a polymeric substrate. Insets are optical images of arrays of microdie on a source wafer before/after transfer, and silicon microdie printed onto a receiving substrate. The scale bar is 100 μm. (*B*) Photographs of a PMDS stamp 'inked' with ~1000 microdies. (*C*) Magnified image of an array of microdie on a PDMS stamp. (*D*) Scanning electron microscope (SEM) and optical images of an 'inked' PDMS stamp in side, bottom and top views (scale bar: 100 μm). (*E*) Left: SEM image of a large array of microdie released from the source wafer after undercut etching. Middle: Photograph of an entire source wafer. Red and blue frames correspond to areas with and without released arrays of microdie, respectively. Right: SEM image of an etched structure after complete removal of an array of microdie. (*F*) Schematic illustration of the material stack layout and thicknesses of the different layers at the location of a microdie after complete release. (*G*) A group of SEM and optical profilometry images shown in sequence for a representative unit cell after undercut, after removal and after priniting onto a target substrate. The undercut angle in the silicon is 54.7^{o}, consistent with the anisotropic behavior of the etchant.

Fig. 2. Microtransfer printing of microdie at different densities. (*A*) Schematic illustration for printing in the geometry of an "N": 1. Preparation of a PDMS stamp for deterministic assembly by transfer printing. Insets are optical images of PDMS stamps with sparse/dense distributions of relief features, where *W* and *L* are the width and length of the space between pixels; 2. Printing on a flexible substrate in the geometry of an "N" pattern. (*B*),(*C*) Photographs of a large collection of microdies (total ~32,000) printed on a large polymer film

cut into the approximate outline of a human brain, while flat (*B*) and bent (*C*). (*B*) Insets are optical images (upper) of the printed array at different densities, with magnified images (mid and lower insets) of sparse (blue frame) and dense regions (black frame), respectively. (*C*) Inset is printing yield as function of printing number. (*D*) Schematic illustration of contact of the system on the surface of a brain model. Dense arrays align to areas of primary sensory cortex. (*E*) SEM image of a microdie array integrated with sensing electrodes (Au, 300 nm). Inset shows the subsequent metal interconnect. (*F*) Statistics of the peak effective mobility (μ_{eff}), V_T, and the on/off ratio of 300 printed transistors.

Fig. 3. Integration of electronic/optoelectronic microsystems with thin biofluid barriers of t-SiO_2. (*A*) Schemes for encapsulating systems with t-SiO_2. (*B*) Optical image of a 2×2 transistor array with t-SiO_2 on both sides. Inset shows a single mircodie covered by t-SiO_2. (*C*) Schematic diagram of a system immersed in PBS solution while under electrical bias. (*D*), (*E*) Accelerated soak test results for a single printed microdie with transfer characteristics (*D*) and leakage currents (*E*) collected during immersion in PBS solution at 96 ^{o}C and pH 7.4. Insets show the point of catastrophic failure after a stable lifetime and schematic illustrations of the soak test, repectively. The applied voltage (V_{app}) for the leakage analysis is d.c. 3 V. (*F*), (*G*) Printed co-integration of optoelectronic and electronic components into a system encapsulated by t-SiO_2 layers. (*F*) Photograph of printed μ-ILEDs and microdie in a starburst-shaped system wrapped over a table-tennis ball. Insets are optical images of a transistor and an μ-ILED in off and on states. (*G*) Bending tests and accelerated soak tests of a system with printed μ-ILEDs and transistors. Inset shows transistor performance.

Fig. 4. Systems of printed assemblies of microdie with multiplexing capabilities for electrophysiological mapping. (*A*) An exploded-view schematic illustration of the key

functional layers and (*B*) a photograph of a flexible sensing system with 128 silicon transistors in a slightly bent state. ZIF (zero insertion force) connectors provide interfaces to external electronics for data acquisition. Insets in (*B*) are an optical microscope image (upper, scale bar of 80 μm) and a circuit diagram (lower) of a cell unit. (*C*) Left: an image of a device completely immersed in 37 ^{o}C PBS solution, pH 7.4. Right: Output response of a unit cell with respect to an input sinewave (2 mV, 10 Hz). (*D*) Yield as a function of cycles of bending at a radius of curvature of 1 cm. Inset is an optical image of a system under bending. (*E*) Histogram (with Gaussian lineshape fitting) of gain values from 64 channels of a typical system. The results indicate 100% yield and near-unity average gain. Inset is a spatial map of gain values. (*F*) and (*G*) Cumulative statistics of average gain and yield of 10 different array of this type.

Fig. 5. Chronic stability and biocompatibility assessments. (*A*) Exploded view schematic illustration of the layer configuration for a 8×8 array of printed microdie for multiplexed adressing. (*B*), (*C*) *In vitro* results of an active system during soak tests at 96 ^{o}C, including gain, noise amplitude and yield. Inset is a map of gain after 10-day soaking in 96 ^{o}C PBS. (*D*), (*E*) ICP OES results. (*D*) Si concentration in the PBS used for the accelerated tests. The simulated (green) and measured (red) results show a linear relationship with a rate of ~0.27 ppm/day, followed by saturation after dissolution of the t-SiO_2 layer. (*E*) Metal concentration in PBS. Electrode materials such as Au (left) and Cr (right) start to release in PBS solution (from Day 10) after dissolution of the t-SiO_2. (*F*) Biocompatibility assessment of the active microdie array. (*G*) Thickness-depenent and (*H*) temperature-dependent lifetimes of a t-SiO_2 barrier with simulated (line) and measured (symbols) results. Inset in (*G*) is the schematic illustration.

Fig. 1

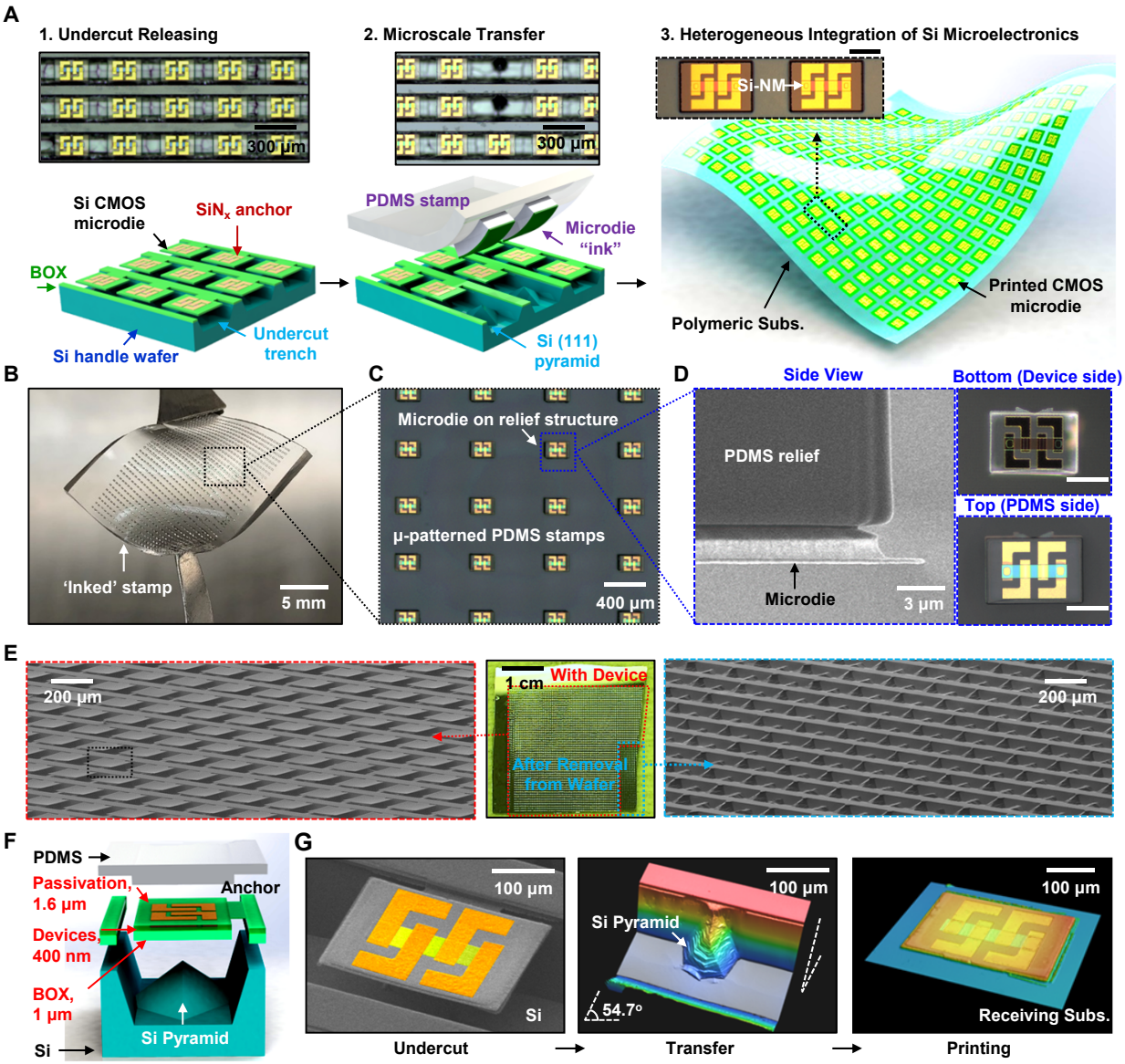

A
1. Undercut Releasing
2. Microscale Transfer
3. Heterogeneous Integration of Si Microelectronics
300 μm
300 μm
Si-NM
Si CMOS microdie
SiNx anchor
BOX
Si handle wafer
Undercut trench
PDMS stamp
Microdie "ink"
Si (111) pyramid
Polymeric Subs.
Printed CMOS microdie
B
'Inked' stamp
5 mm
C
Microdie on relief structure
μ-patterned PDMS stamps
400 μm
D
Side View
Bottom (Device side)
PDMS relief
Top (PDMS side)
Microdie
3 μm
E
200 μm
1 cm
With Device
After Removal from Wafer
200 μm
F
PDMS
Passivation, 1.6 μm
Anchor
Devices, 400 nm
BOX, 1 μm
Si
Si Pyramid
G
100 μm
Si
100 μm
Si Pyramid
54.7°
100 μm
Receiving Subs.
Undercut
Transfer
Printing

Fig. 2

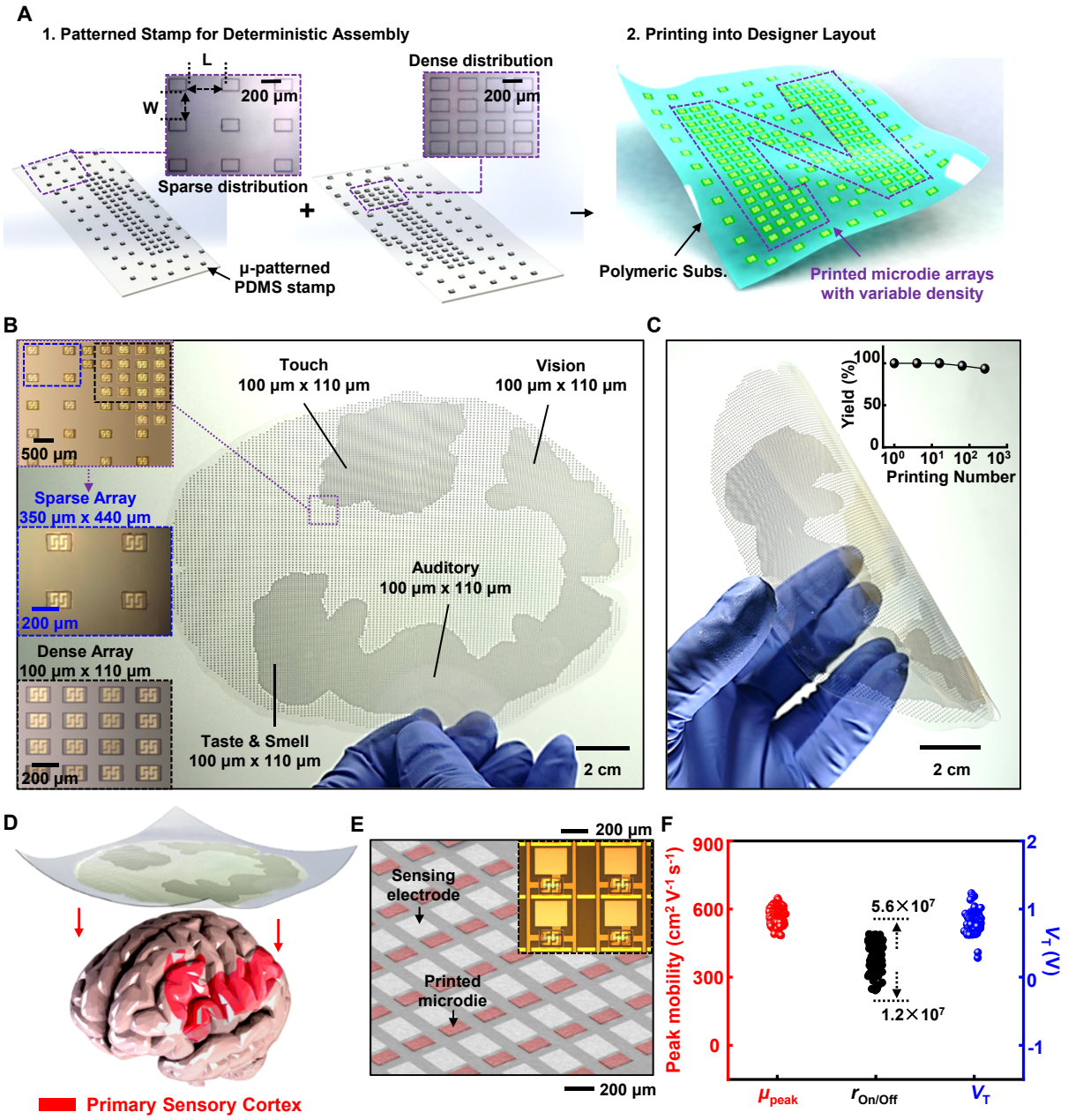

A
1. Patterned Stamp for Deterministic Assembly
2. Printing into Designer Layout
L
W
200 μm
Sparse distribution
Dense distribution
200 μm
μ-patterned
PDMS stamp
Polymeric Subs.
Printed microdie arrays
with variable density
B
Touch
100 μm x 110 μm
Vision
100 μm x 110 μm
500 μm
Sparse Array
350 μm x 440 μm
200 μm
Auditory
100 μm x 110 μm
Dense Array
100 μm x 110 μm
200 μm
Taste & Smell
100 μm x 110 μm
2 cm
C
Yield (%)
100
50
0
10^0 10^1 10^2 10^3
Printing Number
2 cm
D
Primary Sensory Cortex
E
200 μm
Sensing
electrode
Printed
microdie
200 μm
F
Peak mobility (cm² V⁻¹ s⁻¹)
900
600
300
0
5.6×10^7
1.2×10^7
2
1
0
-1
V_T (V)
μ_peak
r_On/Off
V_T

Fig. 3

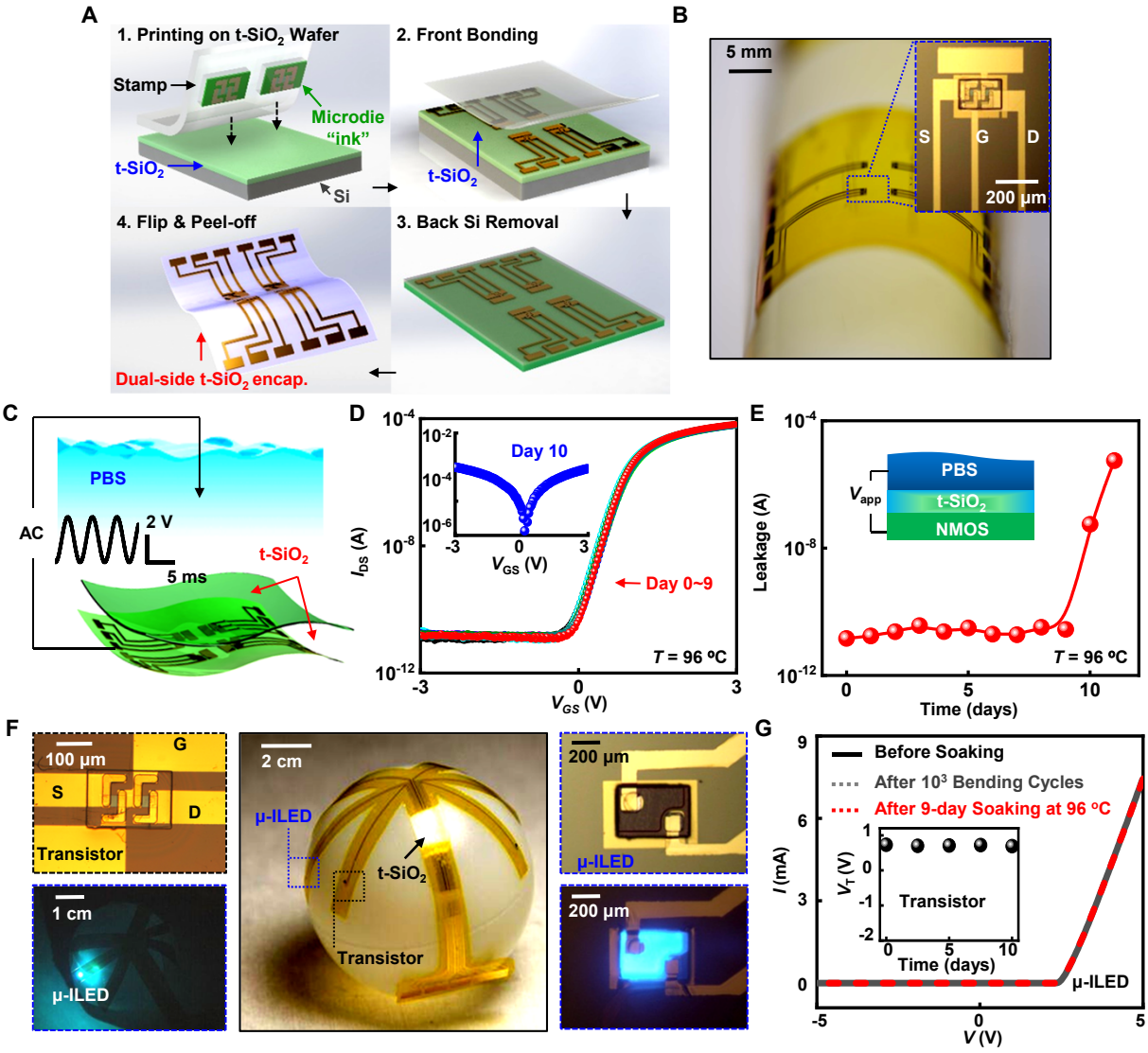

A
1. Printing on t-SiO2 Wafer
Stamp
Microdie "ink"
t-SiO2
Si
2. Front Bonding
t-SiO2
3. Back Si Removal
4. Flip & Peel-off
Dual-side t-SiO2 encap.
B
5 mm
S
G
D
200 μm
C
PBS
AC
2 V
5 ms
t-SiO2
D
Day 10
Day 0~9
T = 96 °C
IDS (A)
VGS (V)
E
PBS
Vapp
t-SiO2
NMOS
Leakage (A)
T = 96 °C
Time (days)
F
100 μm
G
S
D
Transistor
1 cm
μ-ILED
2 cm
μ-ILED
t-SiO2
Transistor
200 μm
μ-ILED
200 μm
G
Before Soaking
After 10³ Bending Cycles
After 9-day Soaking at 96 °C
VT (V)
Transistor
Time (days)
I (mA)
μ-ILED
V (V)

Fig. 4

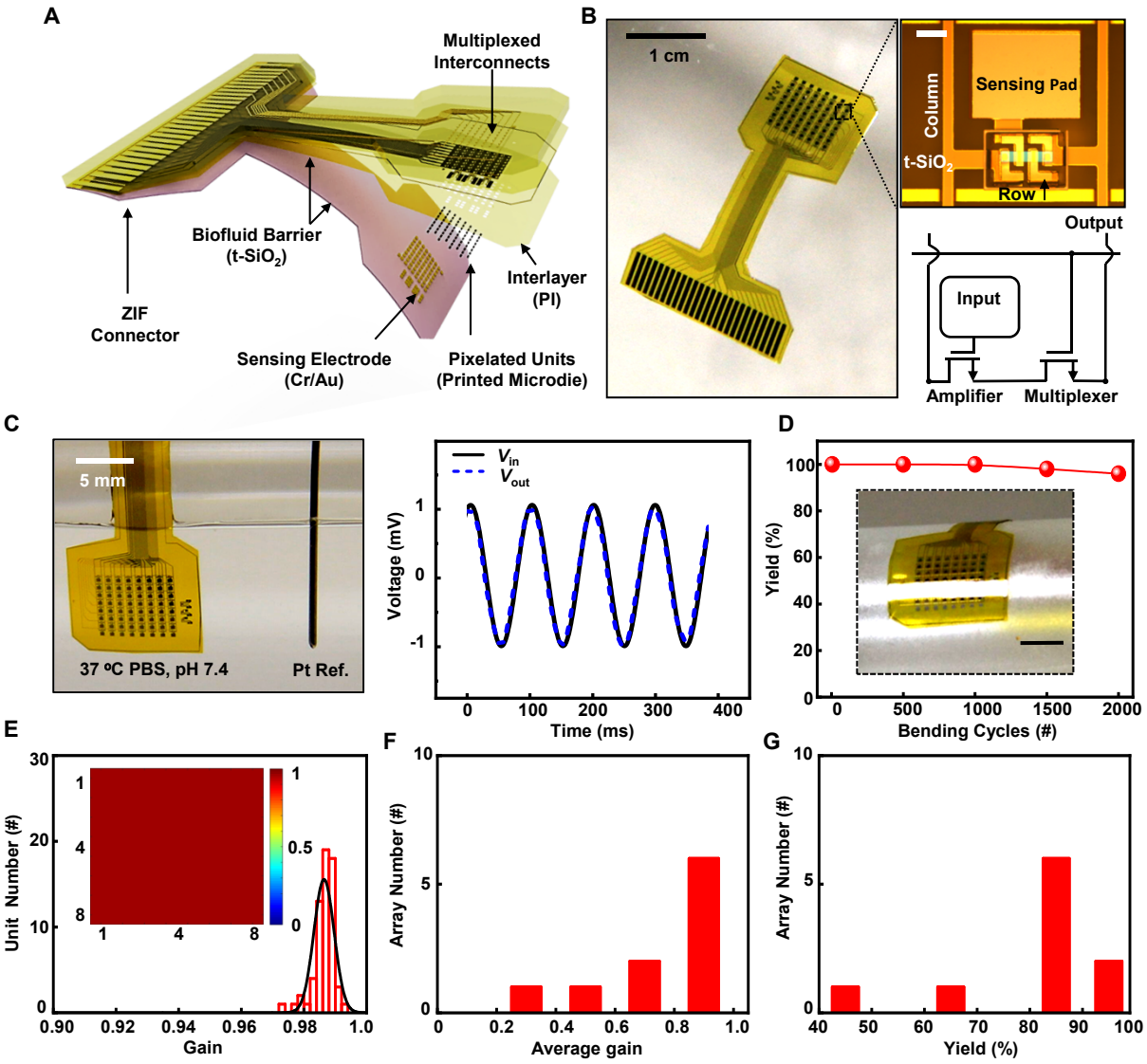
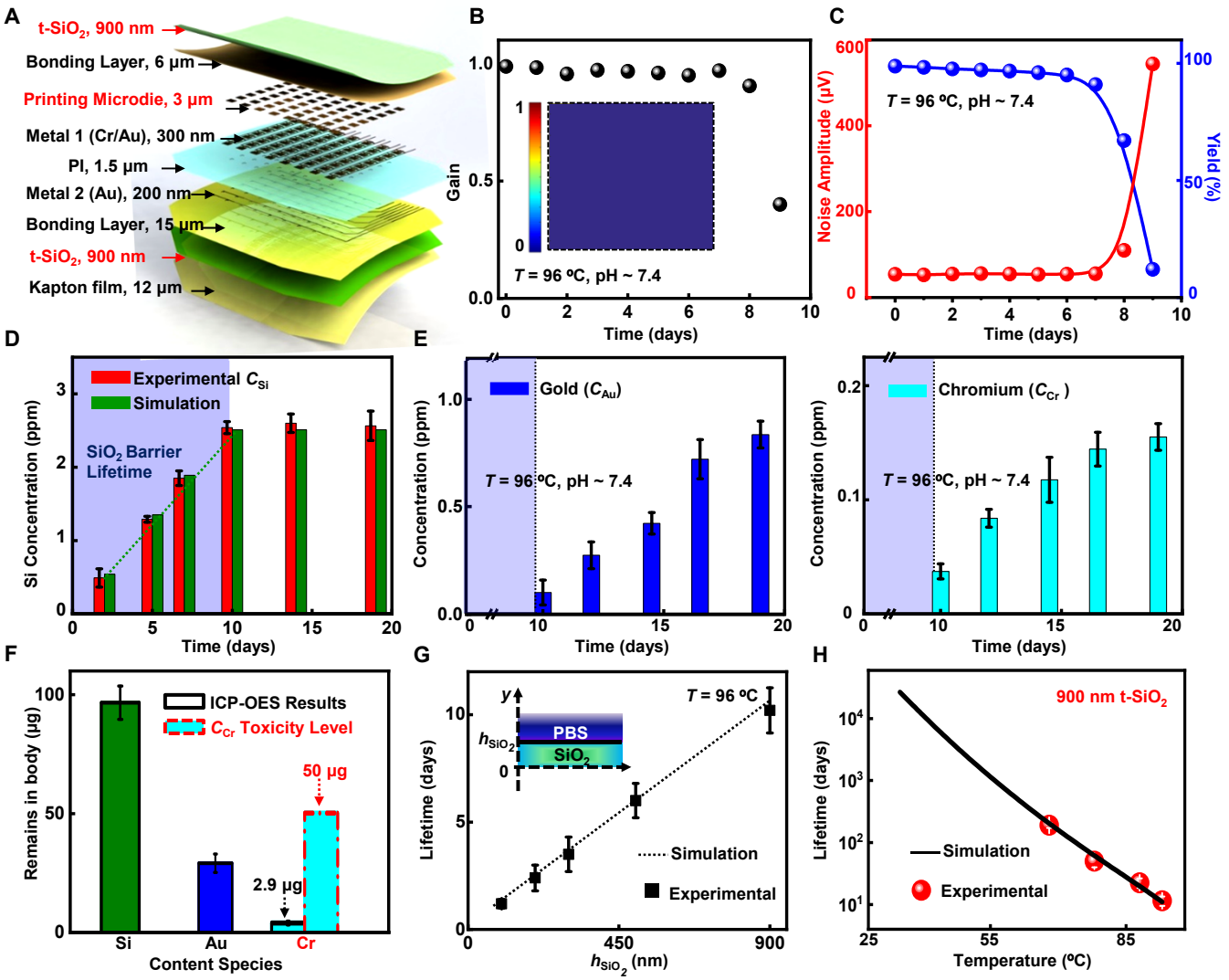

A
Multiplexed Interconnects
Biofluid Barrier (t-SiO2)
Interlayer (PI)
ZIF Connector
Sensing Electrode (Cr/Au)
Pixelated Units (Printed Microdie)
B
1 cm
Column
Sensing Pad
t-SiO2
Row
Output
Input
Amplifier
Multiplexer
C
5 mm
37 ºC PBS, pH 7.4
Pt Ref.
Vin
Vout
Voltage (mV)
Time (ms)
D
Yield (%)
Bending Cycles (#)
E
Unit Number (#)
Gain
F
Array Number (#)
Average gain
G
Array Number (#)
Yield (%)

Fig. 5


A
t-SiO2, 900 nm
Bonding Layer, 6 μm
Printing Microdie, 3 μm
Metal 1 (Cr/Au), 300 nm
PI, 1.5 μm
Metal 2 (Au), 200 nm
Bonding Layer, 15 μm
t-SiO2, 900 nm
Kapton film, 12 μm
B
Gain
T = 96 ºC, pH ~ 7.4
Time (days)
C
Noise Amplitude (μV)
Yield (%)
T = 96 ºC, pH ~ 7.4
Time (days)
D
Experimental CSi
Simulation
SiO2 Barrier Lifetime
Si Concentration (ppm)
Time (days)
E
Gold (CAu)
T = 96 ºC, pH ~ 7.4
Concentration (ppm)
Time (days)
Chromium (CCr)
T = 96 ºC, pH ~ 7.4
Concentration (ppm)
Time (days)
F
ICP-OES Results
CCr Toxicity Level
50 μg
2.9 μg
Remains in body (μg)
Si
Au
Cr
Content Species
G
T = 96 ºC
PBS
SiO2
hSiO2
Simulation
Experimental
Lifetime (days)
hSiO2 (nm)
H
900 nm t-SiO2
Simulation
Experimental
Lifetime (days)
Temperature (ºC)