Published in final edited form as:

Nano Lett. 2019 June 12; 19(6): 4180–4187. doi:10.1021/acs.nanolett.9b01727.

Advanced One- and Two-Dimensional Mesh Designs for Injectable Electronics

Robert D. Viveros^{†,⊥}, Tao Zhou^{‡,⊥}, Guosong Hong[‡], Tian-Ming Fu[‡], Hao-Yu Greg Lin[§], and Charles M. Lieber^{*,†,‡,||}

[†]John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, United States

[‡]Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

[§]Center for Nanoscale Systems, Harvard University, Cambridge, Massachusetts 02138, United States

^{||}Center for Brain Science, Harvard University, Cambridge, Massachusetts 02138, United States

Abstract

The unique structure and mechanical properties of syringe-injectable mesh electronics have enabled seamless tissue integration and stable chronic recording of the activities of the same neurons on a year-scale. Here, we report studies of a series of structural and mechanical mesh electronics design variations that allow injection using needles at least 4-fold smaller than previously reported to minimize the footprint during injection of the electronics in soft matter and tissue. Characterization of new ultraflexible two-dimensional (2D) and one-dimensional (1D) probes has demonstrated reproducible injection of the newly developed mesh electronics designs via needles as small as 100 μm in inner diameter (ID) with reduced injection volumes. *In vitro* hydrogel and *in vivo* mouse brain studies have shown that ultraflexible 2D and 1D probes maintain their structural integrity and conformation post-injection after transfer through the reduced diameter needles. In addition, analysis of the variation of the post-injection mesh cross-sections suggests a smaller degree of tissue deformation and relaxation with decreasing needle diameters. The capability to implement rational design for mesh electronic probes that can be delivered via much smaller diameter needles should open up new opportunities for electronics integration with tissue and soft matter in fundamental and translational studies.

Graphical Abstract

*Corresponding Author: cml@cmliris.harvard.edu.

[⊥]Author Contributions

R.D.V. and T.Z. contributed equally to this work.

The authors declare no competing financial interest.

Supporting Information Available

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.nanolett.9b01727.

Materials and Methods, fabricated ultraflexible mesh electronics (Figure S1), loading of mesh probes into glass capillary needles (Figure S2), injection of ultraflexible mesh electronics into vitreous humor mimic hydrogel (Figure S3), microcomputed tomography of mesh electronics in brain tissue (Figure S4), and supplementary references (PDF)

Keywords

tissue-like electronics; ultrasmall needle; minimal footprint; ultraflexible probe; one-dimensional probe; soft material integration

Integrating electronic probes into synthetic and natural soft materials provides the opportunity for monitoring dynamic behavior through and deep within these structures.^{1–8} Microwire^{9, 10} and silicon probes^{11, 12} can be mechanically-inserted in a controlled manner into soft materials, and in the case of the brain, can offer superior spatiotemporal resolution compared to surface probes^{13–19} and imaging modalities,^{20, 21} independent of depth. Despite these advantages, such implantable probes generally have substantial mechanical and other mismatches with soft materials that hinder stable integration.^{22–25} In the case of the brain, the mechanical and structural mismatches with neural tissue lead to a chronic immune response, which results in a buildup of glial cells immediately adjacent to the probe surface, and micromotion that together make single neuron tracking over extended periods of time difficult, if not impossible.^{24–26}

Mesh electronics offer a novel paradigm of implantable soft electronics with brain-like structure and mechanics, which circumvent issues associated with conventional approaches.^{27–33} The unique macroporous topology with submicron thickness and cell soma-scale width mesh elements allow for stable and seamless tissue integration by virtue of their unique mechanical and structural properties.^{27, 29, 30} Previous studies of mesh electronics have demonstrated stable chronic recording from the same individual neurons for at least 8 months,²⁹ and more recent work has demonstrated opportunities for substantially increased multiplexity³² as well as efficient interfacing with external electronic systems.³¹ The macroporous mesh electronics platform has also achieved seamless interfacing with other soft materials, including (1) collagen, alginate, and PLGA fibrous scaffolds,¹ (2) organic gels and polymers,² as well as (3) the first interface with retinal ganglion cell layer of the mouse eye capable of awake chronic recording.³³

While these previous studies have validated the unique three-dimensional (3D) integration of mesh electronics with different soft materials, challenges related to delivery still exist. Due to the high intrinsic flexibility of the probe which precludes direct insertion, syringe-injection, similar to standard pharmaceutical administration, has been used as a method for mesh electronics probe implantation into target materials.²⁷ Previous studies have focused on relatively large 400 μm inner diameter (ID)/550³⁴ – 650^{28–32} μm outer diameter (OD)

needles to allow for smooth injection of the probes into brain tissue given their structural and mechanical properties. These relatively large needles can produce acute disturbance of the local tissue,³⁰ although studies to date have demonstrated tissue healing following implantation without the foreign body/immune response found for more rigid probes. To explore further the acute impact of these relatively large needles and simultaneously determine diameter limits of smaller delivery needles requires innovation in the structural and mechanical design to improve the flexibility of the mesh electronics. Herein, we present systematic studies that demonstrate new 2D and 1D mesh electronics designs with reduced and vanishing transverse bending stiffness (D_t) values, respectively, that allow high yield controlled low-volume injection via 100 μm ID glass needles into representative synthetic and biological soft materials.

To enable the use of reduced diameter needles for probe implantation, we first assessed the mechanical properties of the mesh electronics for different structural configurations. Key points related to the standard mesh electronics design are highlighted in Figure 1a,b. First, standard mesh electronics probes have periodic structures that can be defined using a unit cell (Figure 1a,b). In the unit cell of the mesh, we define longitudinal elements parallel to the injection direction and transverse elements oriented at angle $\alpha = 45^\circ$ relative to the longitudinal direction (Figure 1b).^{28–32} Second, the longitudinal elements are composite structures, consisting of gold (Au) interconnects which are sandwiched by two layers of biocompatible photoresist SU-8.³⁵ The longitudinal elements terminate at one end with sensor or stimulation devices, such as metal electrodes^{4, 27–31} or nanowire transistors,^{1, 2, 4, 27} and at the opposite end with input/output (I/O) pads that remain external to the target material and are used to interface to external electronics. Third, the transverse elements consist of two SU-8 layers with a total thickness of approximately 800 nm and width of 20 μm . The transverse elements determine D_t of the overall mesh structure, and correspondingly, how readily or not mesh probes roll-up when loaded into needles.²⁷ Lastly, both longitudinal and transverse elements contribute to the longitudinal bending stiffness (D_l) of the mesh probes, where sufficiently large D_l helps to maintain the overall linear structure during injection.^{27, 28} Therefore, our focus in this study was to reduce D_t while maintaining approximately constant D_l for the different the probe designs.

To explore how key design parameters affected D_t and D_l , we investigated (i) the relative angle α between longitudinal and transverse elements, (ii) the total transverse element thickness, t_t , and (iii) the transverse element width, w_t . Ultraflexible 2D mesh electronics designs with increases in α up to 70° , where $\alpha = 0^\circ$ defines a rectangular unit cell, as well as decreases in w_t and t_t by factor of 2 to 10 μm and 400 nm, respectively, were studied (Figure 1c). We also considered a 1D structural region by investigating the impact of removing the transverse elements, corresponding to $w_t = 0 \mu\text{m}$ and $t_t = 0 \text{ nm}$, from the implanted portion of the probe (Figure 1d). Other design parameters remained unchanged relative to the standard design paradigm, with $w_l = 20 \mu\text{m}$, $w_m = 10 \mu\text{m}$, and the longitudinal interconnect metal thickness, $t_m = 105 \text{ nm}$.

We used finite element analysis (FEA) of the mesh electronics unit cell (Materials and Methods in Supporting Information)^{27, 30, 32} to quantify the impact of these design variations on probe stiffness. Simulations were performed on probe unit cells with α

between 0 and 70°, $w_t = 20$ or 10 μm , and $t_t \approx 800$ or 400 nm. These results are summarized in Figure 2a,b and highlight several key points. D_t of the 2D mesh electronics decreased substantially when increasing α , decreasing w_t , and most notably decreasing t_t with other design parameters fixed (Figure 2a). Increasing α from 0° to the standard 45° with fixed w_t and t_t reduced D_t by ~30%; importantly, further increasing α from 45 to 70° resulted in D_t reduction by ~75%. Furthermore, with fixed t_t and α , reducing w_t in half (from the blue curve to the gray curve for $t_t \approx 800$ nm, or from the green curve to the yellow curve for $t_t \approx 400$ nm) generally reduced D_t by ~50%. In addition, halving t_t with fixed α and w_t (from the blue curve to the green curve for $w_t = 20$ μm , or from the gray curve to the yellow curve for $w_t = 10$ μm) produced the most significant reduction in D_t of ~85%. Significantly, the simulations demonstrate that these design variations can achieve up to ~60-fold reduction in D_t (0.08 pN•m, yellow curve at $\alpha = 70^\circ$), compared to the previous standard design^{28–31} (4.6 pN•m, blue curve at $\alpha = 45^\circ$).

The longitudinal bending stiffness, D_l , was also assessed for the same 2D probe designs (Figure 2b). For a given transverse element dimension set, increase in α from 0 to 45° and from 45 to 70° yielded D_l increases of ~90% and 115 – 140%, respectively. For modification of the transverse element dimensions, D_l was reduced by ~5% from the $w_t = 20$ μm , $t_t \approx 800$ nm design (blue curve) to the $w_t = 10$ μm , and $t_t \approx 400$ nm design (yellow curve) with $\alpha = 45^\circ$; the reduction was ~15% with $\alpha = 70^\circ$ between those designs. The minor reduction of D_l with reduced transverse element dimensions suggests that these design components contribute minimally to D_l for the examined α . On the other hand, increasing α increases the stiffness contribution from the transverse elements in the longitudinal direction, which would expectedly increase D_l . In addition, D_l of the implanted portion of the 1D probes (Figure 2b, blue diamond) was roughly identical to that of the various 2D $\alpha = 0^\circ$ designs; that is, for a rectangular ($\alpha = 0^\circ$) cell the transverse elements provide effectively no contribution to D_l , behaving similarly to the 1D designs. It should be noted that while the unit cell does exhibit increases in D_l for several designs (Figure 2b), the stiffness of each individual longitudinal element per unit width remains constant for these design variations because the geometrical cross-section of these elements is unchanged.³⁰

To explore experimentally the consequences of these design variations, we fabricated new 2D and 1D mesh electronics probes using standard photolithography procedures as previously reported (Materials and Methods in Supporting Information).^{27–33} Briefly, the bottom SU-8 layer mesh structure was patterned on a silicon wafer coated with a sacrificial nickel (Ni) layer. Next, the Au interconnects and platinum (Pt) sensor electrodes were patterned and deposited in sequential steps. Lastly, the top SU-8 layer of the mesh structure, which encapsulates and insulates the interconnects while keeping the sensor electrodes and I/O pads exposed, was patterned.

Probes were characterized by optical microscopy prior to release from substrate. A tiled image that provides a view of the entire structure of the lowest D_t 2D design ($\alpha = 70^\circ$, $w_t = 10$ μm , $t_t \approx 400$ nm) shows the contiguous mesh structure with good alignment of distinct layers and regions (Figure 2c, i), including the I/O pads for electrical interfacing at the left side (zoom, Figure S1a) and sensor electrodes at the right side (zoom, Figure S1b). A tiled image of a 1D probe (Figure 2c, ii) shows similar features to the 2D design, including I/O

pads for electrical interfacing at the left side (Figure S1c), as well as the absence of transverse elements at the right side containing the electrode sensor elements (Figure 2c, ii; Figure S1d). Higher resolution images (Figure 2d) comparing the 2D/1D transition region in the 1D mesh and same position in the full 2D mesh (Figure 2c blue and black dashed boxes, respectively) highlight the removal of transverse mesh elements that is expected to minimize transverse constraints on the 1D sensing element region once implanted into a soft material.

We first investigated loading and injection of the new 2D and 1D mesh design as a function of capillary needle ID to determine practical mechanical flexibility and suitability for syringe-based injection into soft materials (Figure 3). Fabricated mesh electronics probes were released from substrates by etching the sacrificial Ni layer, washed in deionized (DI) water and then suspended in 1X phosphate buffered saline (PBS; Materials and Methods in Supporting Information). Optical images (Figure 3a) show that the lowest D_t design ($\alpha = 70^\circ$, $w_t = 10 \mu\text{m}$, $t_t \approx 400 \text{ nm}$) could be successfully loaded within 400/650, 200/330, 150/250, and 100/170 $\mu\text{m ID}/\mu\text{m OD}$ glass needles. Close examination of these images (Figure 3b; Figure S2a–c) show that the lowest D_t 2D mesh probes are loaded with linear elongated conformations, without apparent compression, in the reduced diameter needles. The 1D probe, which has the lowest D_t design for its 2D region, exhibited a similar linear conformation in the reduced diameter needles (Figure 3c; Figure S2d–f), illustrating that the 2D and 1D probes demonstrate similar in-needle loading behavior. These results demonstrate facile loading in substantially smaller diameter injection needles compared to previous studies where 400/650^{28–32} and 400/550³⁴ needles were used.

Next, we asked how the total solution volume required to fully eject mesh probes from capillary needles varies as a function of the different mesh design parameters and needle ID. First, data acquired from studies of 2D probes with the four basic structural designs (w_t , t_t) for angles α of 45, 60, and 70°, in addition to 1D probes with 2D regions corresponding to the four basic structures at $\alpha = 70^\circ$, injected through 200/330 $\mu\text{m ID}/\mu\text{m OD}$ needles (Figure 3d) show several key points. Overall, the data show that all designs could be reproducibly ejected from 200 $\mu\text{m ID}$ needles, although the total volumes varied over an order of magnitude. Increasing α or decreasing w_t or t_t generally reduced the injection volume. The standard transverse element dimensions ($w_t = 20 \mu\text{m}$, $t_t \approx 800 \text{ nm}$, blue curve) demonstrated injection volume reduction from ~240 μL to 75 μL when increasing α from 45 to 70°. Injection volume further reduced to ~15 μL with $w_t = 10 \mu\text{m}$, $t_t \approx 400 \text{ nm}$ designs (yellow curve) for all α , where α -dependence became less impactful for reduced w_t and t_t . Lastly, the 1D probe designs exhibited injection volumes similar to or slightly lower than the corresponding 70° α -values for each of the four basic structural (w_t , t_t) designs.

Importantly, several of the more flexible/lower D_t also enabled reproducible injection through substantially smaller diameter needles (Figure 3e,f). For 150 $\mu\text{m ID}$ needles (Figure 3e) the $w_t = 20 \mu\text{m}$, $t_t \approx 800 \text{ nm}$ designs (blue curve, Figure 3d) could not be reproducibly loaded for α from 45 to 70°. However, reducing w_t to 10 μm (green curve) allowed for reliable probe loading and yielded injection volumes of ~40 and 30 μL for $\alpha = 60$ and 70°, respectively. Additionally, reducing t_t in half allowed for reproducible probe injection using 30 μL with $w_t = 20 \mu\text{m}$ ($\alpha = 70^\circ$, gray curve) and 20 μL with $w_t = 10 \mu\text{m}$ ($\alpha = 45, 60$, and

70°, yellow curve). The corresponding 1D probe designs exhibited injection volumes similar to the corresponding 70° α -values for each of the basic structural (w_t , t_t) designs.

Notably, the more flexible/lower D_t designs also enabled reproducible injection through 100 μm ID needles (Figure 3f), that have 4 times smaller IDs than our previous work. While the $w_t = 20\text{ }\mu\text{m}$, $t_t \approx 800\text{ nm}$ designs (blue curve, Figure 3d) could not be loaded for any value of α , reducing w_t in half (green curve) permitted loading and ejection with ~ 70 and $55\text{ }\mu\text{L}$ for $\alpha = 60$ and 70° , respectively. Reducing t_t to $\sim 400\text{ nm}$ enabled ejection of the $w_t = 20\text{ }\mu\text{m}$ designs (gray curve) using ~ 55 and $20\text{ }\mu\text{L}$ for $\alpha = 60$ and 70° , respectively, and also reducing w_t to $10\text{ }\mu\text{m}$ (yellow curve) allowed for injection using $\sim 20\text{ }\mu\text{L}$ for α from $45 - 70^\circ$. The 1D probe designs exhibited injection volumes similar or slightly lower than the corresponding 70° α -values for each of these basic structural (w_t , t_t) designs. Together, these results demonstrate that rationally designed mesh electronics with reduced D_t can enable controlled and reproducible loading into and ejection through capillary needles with up to 4 times smaller ID than our previous work. Lastly, the injection volume in the optimal designs, $10 - 25\text{ }\mu\text{L}$, is less than prior studies using the larger $400\text{ }\mu\text{m}$ ID needles.^{28, 29, 31}

We investigated injection into non-living and living soft materials to characterize the post-injection conformations of ultraflexible 2D and 1D mesh electronics as a function capillary needle size. The lowest D_t 2D and 1D probes ($\alpha = 70^\circ$, $w_t = 10\text{ }\mu\text{m}$, $t_t \approx 400\text{ nm}$) were implanted using a field-of-view (FoV) injection methodology²⁸ to a depth of 4 mm deep (Figure 4a–c) into 0.5% (wt/vol) agarose hydrogel that is a good mimic of dense brain tissue with similar Young's and shear moduli^{36, 37} (Materials and Methods in Supporting Information). Optical images of a 2D (Figure 4b, i) and 1D (Figure 4b, ii) probe implanted using 150/250 μm ID/ μm OD capillary needles yielded notable differences in overall conformation. Specifically, the 2D mesh probe appeared confined within the initial insertion region defined by the needle OD, while the 1D mesh probe demonstrated regions where the 1D longitudinal elements were compressed to dense structures within the boundaries defined by the needle OD.

We characterized the cross-sectional diameters of the lowest D_t 2D and 1D probes post-injection as a function of needle ID/OD to quantify the above differences. A summary of these data (Figure 4c) shows several key results. 2D probes injected using the standard needle size (400/650 μm ID/ μm OD) yielded a distribution of probe diameters with median of $270\text{ }\mu\text{m}$. This value is $\sim 40\%$ of the injection needle OD and suggests substantial relaxation of the hydrogel brain tissue mimic upon removal of the injection needle. The diameters of the 2D probes implanted using 150/250 and 100/170 needles exhibited post-injection diameters much closer to the needle OD with median values/percentage of injection needle ODs of $202/80$ and $185\text{ }\mu\text{m}/109\%$, respectively. Differences in 2D cross-sectional diameter were statistically-significant between the 400/650 and 150/250 injections ($P < 0.01$) in addition to the 400/650 and 100/170 injections ($P < 0.001$); however, the 2D 150/250 and 100/170 injections were not statistically-significantly different ($P > 0.05$). On the other hand, the cross-sectional diameters of the 1D probes implanted using 150/250 and 100/170 needles exhibited median diameters/percentage OD of $137/55$ and $96\text{ }\mu\text{m}/57\%$, respectively, thus showing a greater and statistically-significant reduction in diameter and

occupied volume compared to the corresponding 2D probes ($P < 0.0001$ in both 2D vs. 1D cases).

To further explore these observations we prepared 0.14% agarose hydrogel as a mimic of the vitreous humor of the eye,³⁸ given recent studies where mesh electronics probes have been injected onto the concave surface of the retina cup.³³ Optical images of the lowest D_t 2D and 1D probes post-implantation (Figure S3) showed that in this hydrogel the lowest D_t 2D and 1D probes have diameters and conformations consistent with the needle OD or even expand beyond the OD, which contrasts the results in the more dense brain-tissue mimicking hydrogel.

Lastly, we characterized the structures of the lowest D_t 2D and 1D probes implanted into the brains of mice for different ID/OD injection needles (Figure 4d). The mesh probes were implanted to a depth of 4 mm using the FoV method,²⁸ and then mice were euthanized and the brains fixed 1 hour following mesh injection to provide a view of the acute probe/tissue structure (Materials and Methods in Supporting Information). Micro-computed tomography (micro-CT) images (Figure 4e; Figure S4) highlight several key features. Overall, these images all appear similar with only slightly greater transverse spread observed for 2D versus 1D probes injected through the 150/250 and 100/170 needles. Measurements of the cross-sectional diameters from these images are summarized in Figure 4f and reveal several key results. First, the injection of the 2D probes demonstrated consistent cross-sectional diameters for the 400/650, 150/250 and 100/170, needles with median mesh diameters/percentage of needle ODs of 213/33, 220/88, and 215 μm /127%, respectively. Differences in the 2D cross-sectional diameters were not statistically-significant across the 400/650, 150/250, and 100/170 needles ($P > 0.05$ in all cases). Second, the significant transverse compression post-injection of the lowest D_t 2D probes, relative to needle OD, found from injection using the 400/650 needles was not observed for the reduced diameter needles. Third, the 1D probes injected through 150/250 and 100/170 needles had median mesh diameters/percentage of needle ODs of 167/67 and 134 μm /79%, respectively, thus showing compression relative to needle OD compared to 2D probes. Statistical analyses of these data show that the 1D compression relative to the corresponding 2D probes is statistically significant for both the 150/250 ($P < 0.001$) and 100/170 ($P < 0.0001$) needles studied. These results show that the substantial tissue relaxation following removal of the larger 400/650 needles from the brain post-implantation is largely eliminated with the 2.6 and 3.8 times smaller diameter needles. Additionally, the presence of transverse elements in the ultraflexible 2D mesh probes is important to avoid compression of the longitudinal sensing elements as observed in 1D probes. We suggest that mesh electronics conformational volumes that are commensurate with injection needle OD allow for optimal probe integration with and electrode sampling of the tissue as opposed to a smaller volume than that perturbed during injection, which was observed with the largest needles for 2D probes and smaller needles for 1D probes. Lastly, we note that the injection of the lowest D_t 2D and 1D probes through the 150/250 or 100/170 needles required only $15.7 \pm 1.8 \mu\text{L}$ or $21.1 \pm 1.6 \mu\text{L}$, respectively, which is significantly less than 100 μL volumes reported previously^{28–31}.

In conclusion, we have demonstrated that we can rationally design mesh electronics to enable facile loading into and ejection from capillary needles with ID 4-fold smaller than

previously attainable and with reduced injection volumes. These results suggest substantial opportunity for applications in brain mapping where smaller diameter injection needles could reduce acute damage to native neural circuitry. Finally, we note that the reduced diameter implantation needles for mesh electronics implantation could extend the capabilities of this exciting probe technology to chronic scientific and clinical applications such as enabling targeting of sensitive nervous tissue, including rodent spinal cord, which would otherwise be precluded by more invasive probes and delivery mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

C.M.L. acknowledges support of this work by the NIH Director's Pioneer Award 1DP1EB025835-01, Air Force Office of Scientific Research grant FA9550-14-1-0136, Harvard University Physical Sciences and Engineering Accelerator award, and a Cutting-Edge Basic Research Award under National Institutes of Health/National Institute on Drug Abuse Grant No. 3R21DA043985-02S1. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE1144152 and DGE1745303 (R.D.V.). G.H. Acknowledges support of this work by the American Heart Association Postdoctoral Fellowship 16POST27250219 and National Institutes of Health Pathway to Independence Award from NIA 1K99AG056636-01. This work was performed in part at the Harvard University Center for Nanoscale Systems (CNS), a member of the National Nanotechnology Coordinated Infrastructure Network (NNCI), which is supported by the National Science Foundation.

REFERENCES

1. Tian B; Liu J; Dvir T; Jin L; Tsui JH; Qing Q; Suo Z; Langer R; Kohane DS; Lieber CM *Nat. Mater* 2012, 11, 986–994. [PubMed: 22922448]
2. Liu J; Xie C; Dai X; Jin L; Zhou W; Lieber CM *Proc. Natl. Acad. Sci. U. S. A* 2013, 110, 6694–6699. [PubMed: 23569270]
3. Luan L; Wei X; Zhao Z; Siegel JJ; Potnis O; Tuppen CA; Lin S; Kazmi S; Fowler RA; Holloway S; Dunn AK; Chitwood RA; Xie C *Sci. Adv* 2017, 3, e1601966. [PubMed: 28246640]
4. Dai X; Hong G; Gao T; Lieber CM *Accounts Chem. Res* 2018, 51, 309–318.
5. Jiang Y; Tian B *Nat. Rev. Mater* 2018, 473–490.
6. Rastogi SK; Kalmykov A; Johnson N; Cohen-Karni T J. *Mater. Chem. B* 2018, 6, 7159–7178.
7. Zhang J; Liu X; Xu W; Luo W; Li M; Chu F; Xu L; Cao A; Guan J; Tang S; Duan X *Nano Lett* 2018, 18, 2903–2911. [PubMed: 29608857]
8. Hong YJ; Jeong H; Cho KW; Lu N; Kim DH *Adv. Funct. Mater* 2019, 1808247.
9. Jackson A; Fetz EE *J. Neurophysiol* 2007, 98, 3109–3118. [PubMed: 17855584]
10. Schwarz DA; Lebedev MA; Hanson TL; Dimitrov DF; Lehew G; Meloy J; Rajangam S; Subramanian V; Ifft PJ; Li Z *Nat. Methods* 2014, 11, 670–676. [PubMed: 24776634]
11. Scholvin J; Kinney JP; Bernstein JG; Moore-Kochlacs C; Kopell N; Fonstad CG; Boyden ES *IEEE Trans. Biomed. Eng* 2016, 63, 120–130. [PubMed: 26699649]
12. Berényi A; Somogyvári Z; Nagy AJ; Roux L; Long JD; Fujisawa S; Stark E; Leonardo A; Harris TD; Buzsáki GJ *Neurophysiol* 2013, 111, 1132–1149.
13. Son D; Lee J; Qiao S; Ghaffari R; Kim J; Lee JE; Song C; Kim SJ; Lee DJ; Jun SW *Nat. Nanotechnol* 2014, 9, 397–404. [PubMed: 24681776]
14. Tee BCK; Chortos A; Berndt A; Nguyen AK; Tom A; McGuire A; Lin ZC; Tien K; Bae W-G; Wang H; Mei P; Chou H-H; Cui B; Deisseroth K; Ng TN; Bao Z *Science* 2015, 350, 313–316. [PubMed: 26472906]
15. Imani S; Bhandodkar AJ; Mohan AV; Kumar R; Yu S; Wang J; Mercier PP *Nat. Commun* 2016, 7, 11650. [PubMed: 27212140]

16. Timko BP; Cohen-Karni T; Yu G; Qing Q; Tian B; Lieber CM *Nano Lett* 2009, 9, 914–918. [PubMed: 19170614]
17. Sekitani T; Yokota T; Kuribara K; Kaltenbrunner M; Fukushima T; Inoue Y; Sekino M; Isoyama T; Abe Y; Onodera H; Someya T *Nat. Commun* 2016, 7, 11425. [PubMed: 27125910]
18. Kim D-H; Viventi J; Amsden JJ; Xiao J; Vigeland L; Kim Y-S; Blanco JA; Panilaitis B; Frechette ES; Contreras D; Kaplan DL; Omenetto YH; Hwang K-C; Zakin MR; Litt B; Rogers JA *Nat. Mater* 2010, 9, 511–517. [PubMed: 20400953]
19. Khodagholy D; Doublet T; Quilichini P; Gurfinkel M; Leleux P; Ghestem A; Ismailova E; Hervé T; Sanaur S; Bernard C *Nat. Commun* 2013, 4, 1575. [PubMed: 23481383]
20. Poldrack RA; Farah MJ *Nature* 2015, 526, 371–379. [PubMed: 26469048]
21. Gong Y; Huang C; Li JZ; Grewe BF; Zhang Y; Eismann S; Schnitzer MJ *Science* 2015, 350, 1361–1366. [PubMed: 26586188]
22. Polikov VS; Tresco PA; Reichert WM *J. Neurosci. Meth* 2005, 148, 1–18.
23. Lacour SP; Courtine G; Guck J *Nat. Rev. Mater* 2016, 1, 16063.
24. Hong G; Yang X; Zhou T; Lieber CM *Curr. Opin. Neurobiol* 2018, 50, 33–41. [PubMed: 29202327]
25. Hong G; Viveros RD; Zwang TJ; Yang X; Lieber CM *Biochemistry* 2018.
26. Feiner R; Dvir T *Nat. Rev. Mater* 2018, 3, 17076.
27. Liu J; Fu T-M; Cheng Z; Hong G; Zhou T; Jin L; Duvvuri M; Jiang Z; Kruskal P; Xie C; Suo Z; Fang Y; Lieber CM *Nat. Nanotechnol* 2015, 10, 629–636. [PubMed: 26053995]
28. Hong G; Fu T-M; Zhou T; Schuhmann TG; Huang J; Lieber CM *Nano Lett* 2015, 15, 6979–6984. [PubMed: 26317328]
29. Fu T-M; Hong G; Zhou T; Schuhmann TG; Viveros RD; Lieber CM *Nat. Methods* 2016, 13, 875–882. [PubMed: 27571550]
30. Zhou T; Hong G; Fu T-M; Yang X; Schuhmann TG; Viveros RD; Lieber CM *Proc. Natl. Acad. Sci. U. S. A* 2017, 114, 5894–5899. [PubMed: 28533392]
31. Schuhmann TG Jr.; Yao J; Hong G; Fu T-M; Lieber CM *Nano Lett* 2017, 17, 5836–5842. [PubMed: 28787578]
32. Fu T-M; Hong G; Viveros RD; Zhou T; Lieber CM *Proc. Natl. Acad. Sci. U. S. A* 2017, 114, E10046–E10055. [PubMed: 29109247]
33. Hong G; Fu T-M; Qiao M; Viveros RD; Yang X; Zhou T; Lee JM; Park H-G; Sanes JR; Lieber CM *Science* 2018, 360, 1447–1451. [PubMed: 29954976]
34. Yang X; Zhou T; Zwang TJ; Hong G; Zhao Y; Viveros RD; Fu T-M; Gao T; Lieber CM *Nat. Mater* 2019, 1.
35. Nemani KV; Moodie KL; Brennick JB; Su A; Gimi B *Mater. Sci. Eng. C Mater. Biol. Appl* 2013, 33, 4453–4459. [PubMed: 23910365]
36. Chen Z-J; Gillies GT; Broaddus WC; Prabhu SS; Fillmore H; Mitchell RM; Corwin FD; Fatouros PP *J. Neurosurg* 2004, 101, 314–322. [PubMed: 15309925]
37. Ahearne M; Yang Y; El Haj AJ; Then KY; Liu K-K *J. R. Soc. Interface* 2005, 2, 455–463. [PubMed: 16849205]
38. Nickerson CS; Karageozian HL; Park J; Kornfield JA *Invest. Ophth. Vis. Sci* 2004, 45, 37.

Figure 1. Structural design of ultraflexible syringe-injectable mesh electronics.

(a) Schematic of conventional mesh electronics probe. (b) Schematic of the mesh electronics unit cell, highlighting key probe design parameters, including angle between longitudinal and transverse elements, α , longitudinal element width, w_l , transverse element width, w_t , longitudinal interconnect metal width, w_m , and transverse element thickness, t_t , for the previous standard mesh with $\alpha = 45^\circ$, $w_l = 20 \mu\text{m}$, $w_t = 20 \mu\text{m}$, $w_m = 10 \mu\text{m}$, and $t_t \approx 800 \text{ nm}$. (c) Schematic of ultraflexible 2D mesh electronics to facilitate loading and injection using reduced diameter needles and injection volumes, where $\alpha = 70^\circ$, $w_l = 10 \mu\text{m}$, $w_t = 10 \mu\text{m}$, $w_m = 10 \mu\text{m}$, and $t_t \approx 400 \text{ nm}$; parameters for the longitudinal elements are the same as in the standard design highlighted in (b). (d) Schematic of ultraflexible 1D mesh electronics with transverse element removal in the implantation site, such that w_t and $t_t = 0$, and parameters for the longitudinal elements and transverse elements external to the implantation region are the same as the 2D probe highlighted in (c). Orange represents the Au interconnects, dark blue represents two SU-8 layers for interconnect insulation, and cyan represents a single SU-8 layer.

Figure 2. Analysis and fabrication of advanced mesh electronics designs.

(a) α -dependence of D_t determined using FEA of the mesh electronics unit cell. The four analyzed transverse element dimension parameterizations were blue curve, $w_t = 20 \mu\text{m}$, $t_t \approx 800 \text{ nm}$; green curve, $w_t = 20 \mu\text{m}$, $t_t \approx 400 \text{ nm}$; gray curve, $w_t = 10 \mu\text{m}$, $t_t \approx 800 \text{ nm}$; and yellow curve, $w_t = 10 \mu\text{m}$, $t_t \approx 400 \text{ nm}$. Inset: log-scale plot of α -dependence of D_t between 45 and 70° (b) α -dependence of D_t determined using FEA of the mesh electronics unit cell. The same four transverse element parameterizations were analyzed from (a), using the same color scheme, in addition to the $w_t = 0 \mu\text{m}$, $t_t = 0 \text{ nm}$ (1D probe; cyan diamond) design. (c) Tiled bright-field optical microscopy images of fabricated ultraflexible 2D (i) and 1D (ii) mesh electronics with $w_t = 10 \mu\text{m}$ and $t_t \approx 400 \text{ nm}$. Scale bars are 2 mm. (d) Bright-field optical microscopy images of corresponding outlined regions from (c) of 2D (i) and 1D (ii) mesh electronics. Scale bars are 100 μm .

Figure 3. *In vitro* loading and injection of mesh electronics using reduced diameter needles.

(a) Photograph of the lowest D_t 2D mesh electronics probe loaded within glass capillary needles with 400/650, 200/330, 150/250, and 100/170 μm ID/ μm OD from left to right. (b) Bright-field microscopy image of the lowest D_t 2D mesh electronics loaded into a 150/250 glass needle. (c) Bright-field microscopy image of a 1D mesh probe, which has similar 2D structure as in (b), loaded into a 150/250 glass needle. PBS injection volume for complete mesh ejection using (d) 200/330, (e) 150/250, and (f) 100/170 glass capillary needles for mesh designs that were successfully loaded in the different needles. The design parameters are as follows: blue curve, $w_t = 20 \mu\text{m}$, $t_t \approx 800 \text{ nm}$; green curve, $w_t = 10 \mu\text{m}$, $t_t \approx 800 \text{ nm}$; gray curve, $w_t = 20 \mu\text{m}$, $t_t \approx 400 \text{ nm}$; and yellow curve, $w_t = 10 \mu\text{m}$, $t_t \approx 400 \text{ nm}$. The 1D mesh electronics have a 4 mm long 1D region, and the remaining portion of the structure is a 2D mesh, where the parameters are kept the same as the $\alpha = 70^\circ$ probe of the corresponding 2D design.

Figure 4. Mesh electronics injection into tissue and tissue-like media.

(a) Schematic representation of mesh electronics injection into hydrogel. (b)

Photomicrographs are of 2D (i) and 1D (ii) probes injected into 0.5% agarose hydrogel using 150/250 μm ID/ μm OD glass needles. Insets are of separate injections, and needle dimensions are represented by dashed white boxes. Inset scale bars are 200 μm . (c) Cross-

sectional diameters of the 2D and 1D mesh electronics injected into 0.5% agarose hydrogel versus capillary needle ID/OD with numbers in micrometers. The diameters were obtained from direct measurement of bright-field microscopy images. (d) Schematic representation of

mesh electronics injection into a mouse brain. (e) Micro-CT images of 2D (i, iii) and 1D (ii, iv) mesh electronics injected into a mouse brain such that one of each probe type was

injected using both a 150/250 (i-ii) and a 100/170 (iii-iv) glass needle. Scale bars are 500 μm . The mouse brains with implanted mesh probes were fixed at 1 hour post-implantation (Materials and Methods in Supporting Information). (f) Cross-sectional diameters of

ultraflexible 2D and 1D mesh electronics injected into a mouse brain using several distinct glass needle sizes. All injections were performed using the lowest D_t 2D and 1D mesh probes. The red and blue indicate P-values for 2D vs. 2D and 2D vs. 1D measurements,

respectively, where NS (not significant) indicates $P > 0.05$, ** indicates $P < 0.01$, *** indicates $P < 0.001$, and **** indicates $P < 0.0001$ (by two-tailed t-test).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript