

CLAIMS

1. An apparatus for mapping one or more cells, the apparatus comprising:
a semiconductor substrate, comprising:
a plurality of electrodes exposed at a surface of the semiconductor substrate;
active circuitry coupled to the plurality of electrodes and configured to:
measure a first set of cross-electrode currents between a first electrode of the plurality of electrodes and some or all of the remaining electrodes;
measure a second set of cross-electrode currents between a second electrode of the plurality of electrodes and some or all of the remaining electrodes; and
one or more processors configured to receive the measured cross-electrode currents from the active circuitry and to generate a map of the one or more cells based on the first set and second set of cross-electrode currents.
2. The apparatus of claim 1, wherein the active circuitry is further configured to apply a stimulus signal at the first electrode of the plurality of electrodes, and to apply a reference voltage at the remaining electrodes where the cross-electrode currents are being measured from.
3. The apparatus of claim 2, wherein the stimulus signal has a frequency of less than 10 kHz and preferably between 0.1 and 5 kHz.
4. The apparatus of any one of claims 1-3, wherein the plurality of electrodes are arranged in an array having a pitch of less than 30 μm and preferably less than 5 μm .
5. The apparatus of any one of claims 1-4, wherein the semiconductor substrate comprises silicon.
6. The apparatus of any one of claims 1-5, wherein the semiconductor substrate comprises a silicon substrate, and wherein the active circuitry comprises complimentary metal-oxide semiconductor (CMOS) components in the silicon substrate.

7. The apparatus of any one of claims 1-6, wherein the plurality of electrodes comprise a plurality of pads disposed on an insulative surface of the semiconductor substrate.
8. The apparatus any one of claims 1-7, wherein the active circuitry comprises a plurality of recording circuits, each recording circuit configured to measure a current at an electrode of the plurality of electrodes.
9. The apparatus of claim 8, wherein the plurality of recording circuits comprises at least 8 recording circuits, at least 10 recording circuits, and preferably at least 4000 recording circuits.
10. The apparatus of claim 8, wherein each recording circuit comprises a transimpedance amplifier (TIA).
11. The apparatus of claim 8, wherein the TIA comprises an impedance component having a resistance of at least 10 M Ω , at least 100 M Ω , or between 10 M Ω and 1 G Ω , wherein an output voltage of the TIA is proportional to a voltage across the impedance component.
12. The apparatus of claim 11, wherein the impedance component comprises a switching capacitor.
13. The apparatus of any one of claims 1-12, wherein the one or more cells are disposed in a first well of a multi-well plate, and the plurality of electrodes is a first electrode array exposed to the first well, and wherein the apparatus further comprises a second electrode arrays exposed on the surface of the semiconductor substrate, and exposed to a second well of the multi-well plate.
14. The apparatus of claim 13, wherein the multi-well plate comprises at least 24, at least 96 , or at least 384 wells.
15. The apparatus of claim any one of claims 1-14, wherein the plurality of electrodes are sized such that more than one electrode are configured to be in contact with one cell of the one or more cells.

16. The apparatus of claim 7, wherein the plurality of pads comprises Au.
17. The apparatus of claim 7, wherein the plurality of pads comprises Pt.
18. A method for mapping one or more cells in contact with an electrode array disposed on a surface area of a semiconductor substrate, each electrode in the electrode array having an electrode location on the surface area, the method comprising:
 - for each electrode of at least one electrode of the electrode array:
 - applying a stimulus signal at the electrode;
 - measuring a set of cross-electrode currents between the electrode and some or all of the remaining electrodes in the electrode array;
 - generating a representative value associated with the electrode position of the electrode based on the set of cross-electrode currents; and
 - generating a map of representative values on the surface area based on the generated representative values and respective associated electrode locations of the at least one electrode.
19. The method of claim 18, wherein generating the representative value comprises:
 - selecting a maximum current value of the set of cross-electrode current as the representative value.
20. The method of any one of claims 18 or 19, wherein generating the representative value comprises:
 - selecting a maximum current value of the set of cross-electrode current as the representative value.
21. The method of any one of claims 18-20, wherein the at least one electrode includes all electrodes in the electrode array.
22. The method of any one of claims 18-21, wherein the map has a spatial resolution of 20 μm or less and preferably 5 μm or less.
23. The method of any one of claims 18-22, further comprising:

based on the generated map of representative values, identifying a cluster of cells adjacent the semiconductor substrate with single cell resolution.

24. The method of any one of claims 18-23, wherein the generated map is a first map generated at a first time and comprises a plurality of pixels, and the method further comprises: generating a second map of representative values on the surface area at a second time subsequent to the first time, wherein the second map comprises a plurality of pixels;

determining a first count of pixels in the first map having a representative value within a predetermined range;

determining a second count of pixels in the second map having a representative value within the predetermined range; and

determining a cell adhesion characteristic based on a comparison of the first count with the second count.

25. The method of any one of claims 18-24, wherein the map comprises a plurality of pixels, each pixel associated with a representative value.

26. The method of claim 25, wherein

the at least one electrode comprises a first electrode having a first electrode location and a second electrode having a second electrode location, the first electrode and the second electrode adjacent each other on the surface area, and wherein

the map comprises a first pixel and a second pixel corresponding to the first electrode location and the second electrode location, respectively, and

generating the map comprises:

determining an up-scaled representative value associated with a third pixel between the first and second pixels.

27. The method of claim 26, wherein determining the up-scaled representative value comprises:

calculating an up-scaled electrode current by:

dividing a cross-electrode current I_{12} between the first and second electrode when a stimulus signal is applied at the second electrode with a product of a first current I_1 and a second current I_2 , wherein I_1 is a sum of cross-electrode currents measured at all of the remaining electrodes when a stimulus signal is applied at the first electrode,

and I_2 is a sum of cross-electrode currents measured at all of the remaining electrodes when a stimulus signal is applied at the second electrode.

28. The method of claim 27, wherein a number of pixels in the map is more than a number of electrodes in the electrode array.

29. The method of any one of claims 18-28, wherein electrode locations in the electrode array are arranged in a plurality of rows and a plurality of columns.

30. The method of claim 29, wherein the electrode array has M rows and N columns, and the map has at least $3M \times 3N$ pixels.

31. A system for mapping one or more cells, the system comprising:
a plurality of electrodes exposed at a surface area of a semiconductor substrate;
circuitry disposed in the semiconductor substrate that is controllable to apply a stimulus signal and/or measure a current at one or more electrodes of the plurality of electrodes;
at least one non-transitory computer-readable medium having stored thereon executable instructions; and
at least one processor programmed by the executable instructions to perform a method comprising acts of:
for each electrode in the plurality of electrodes:
controlling the circuitry to apply a stimulus signal at the electrode;
controlling the circuitry to measure a set of cross-electrode currents between the electrode and some or all of the remaining electrodes in the plurality of electrodes;
generating a representative value associated with the electrode location of the electrode based on the set of cross-electrode currents; and
generating a map of representative values on the surface area based on the generated representative values and respective associated electrode locations of the plurality of electrodes.

32. The method of claim 31, wherein generating the representative value comprises:
selecting a maximum current value of the set of cross-electrode current as the representative value.

33. The method of any one of claims 31 or 32, wherein generating the representative value comprises:

- selecting a maximum current value of the set of cross-electrode current; and
- calculating an impedance based on the selected maximum current value as the representative value.

34. The method of any one of claims 31-33, wherein the generated map is a first map generated at a first time and comprises a plurality of pixels, and the method further comprises:

- generating a second map of representative values on the surface area at a second time subsequent to the first time, wherein the second map comprises a plurality of pixels;

- determining a first count of pixels in the first map having a representative value within a predetermined range;

- determining a second count of pixels in the second map having a representative value within the predetermined range; and

- determining a cell adhesion characteristic based on a comparison of the first count with the second count.

35. The method of any one of claims 31-34, wherein the map comprises a plurality of pixels, each pixel associated with a representative value, and wherein

- the plurality of electrodes comprises a first electrode having a first electrode location and a second electrode having a second electrode location, the first electrode and the second electrode adjacent each other on the surface area, and wherein

- the map comprises a first pixel and a second pixel corresponding to the first electrode location and the second electrode location, respectively, and

- generating the map comprises:

- determining an up-scaled representative value associated with a third pixel between the first and second pixels.