Single-molecule reliable detections with a large-area electronic interface

Luisa Torsi
Organization, Address, City, Country (Calibri 10) Dipartimento di Chimica, Università degli Studi di Bari Aldo Moro, Bari (I), The Faculty of Science and Engineering, Åbo Akademi University, Turku (FI)
luisa.torsi@uniba.it

Label-free protein detections at a single-molecule resolution are implemented with nanometric interfaces hosting a few recognition elements. The cross-section of the interaction is low so a target protein concentration of at least nanomolar is essential. When a large millimeter-wide electronic interface is engaged, a single molecule (entity) limit of detection can be reliably reached in detecting antigens (Immunoglobulins, C-reactive proteins, spike 1, HIV p-24, …), antibodies (anti-immunoglobulins, anti-spike 1, …) peptides, viruses (SARS-Cov-2), bacteria (Xylella fastidiosa), and even DNA strands (KRAS, miR-182). This technology is called SiMoT - Single-Molecule with a large Transistor.[1] Selectivity is assured by covering the gate electrode with a large number (10^{11} - 10^{12} / cm^2) of a suitable recognition element to affinity binding of the target element.

With the SiMoT a single entity can be detected directly in a droplet (0.1 mL) of a real fluid such as saliva from COVID-19 patients, blood serum, pancreatic cysts juice, and olive saps from infected trees. Relevantly Brownian diffusion enables the entity to statistically hit the millimeter-wide interface in a few minutes.[2] Considering the footprint of a molecule on a millimeter-wide interface, it is like spotting a droplet of water falling on the surface of a 1 Km wide lake.

The applications span from a handheld intelligent single-molecule binary bioelectronic system for fast and reliable immunometric point-of-care testing of COVID-19 patients with an incidence of both false positives and false negatives of less than 1%. This means a fast (21 minutes time-to-results) and disposable immunometric test in saliva with a limit of detection of 20 zeptomolar (1+1 virus in 0.1 mL) and reliability (diagnostic sensitivity, specificity, and accuracy) of 99.2%. Meaning with the figures of merit of a PCR-based molecular test.[3] Moreover, a fast and reliable electronic assay of a Xylella fastidiosa single bacterium in infected plants sap is achieved, outperforming the PCR limit of quantification by at least one order of magnitude.

The phenomenon that enables this outstanding performance level was discovered in 2018.[4] While still under investigation, it is supposed to involve an amplification effect that starts from the single affinity binding event involving just one recognition antibody or complementary genic sequence. The extra energy associated only with the affinity binding locally generates a conformational change with its associated electrostatic impact, which is enough to trigger a collaborative response that propagates the change in surface potential involving at least 10^6 – 10^8 antibodies hence a very large portion of the gate area.

Future actions include deepening our understanding of the sensing mechanism and engaging in a campaign of thousands of clinical trials that will bring SiMoT beyond TRL5.

References

[1] E. Macchia *et al.* Chemical Review 2022, 122, 4636 DOI: 10.1021/acs.chemrev.1c00290
[2] E. Macchia *et al.* Advanced Science 2022, 2104381 DOI: DOI: 10.1002/advs.2021043811
[3] E. Macchia *et al.,* Science Advances 2022, 8 (27) DOI: 10.1126/sciadv.abo0881
[4] E. Macchia *et al.,* Nature Communication 2018, DOI: 10.1038/s41467-018-05235-z