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A New Method for Multianalyte Point of Care Diagnostics

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ABSTRACT

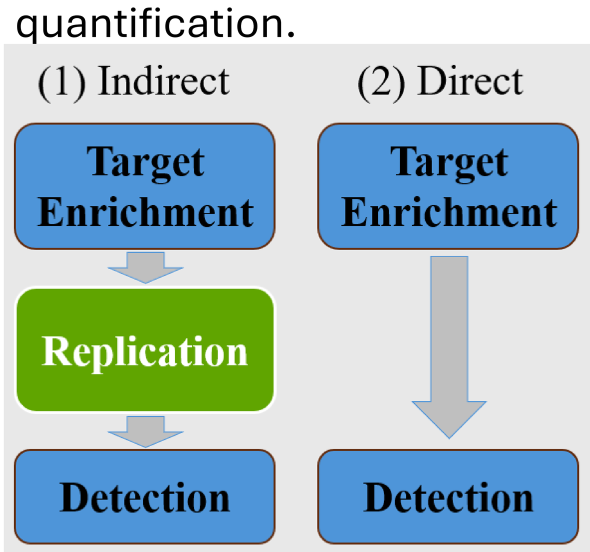
We introduce a new method of molecular detection, combining DNA, RNA, antibody and antigen testing in a single bead-based assay. It employs PNA probes for high specificity in nucleic acid testing, antigenic peptide epitopes for capture of antibodies, and a digital CMOS sensor chip for detection, quantification, and digital readout. Results are presented for detection and quantification of HIV1 & HIV2 antibodies from HIV-positive patient plasma, for detection of HIV-1 spiked RNA @ 500 copies/mL from 200uL human plasma, and @1000 cp/mL from 100uL of whole-human blood, filtered via a finger-pressure membrane filter device.

The assay is in the process of being miniaturised (with The Cambridge Design Partnership, UK) into a low-cost single-use disposable cartridge and a solid-state portable, stand-alone instrument. This integration and automation is further reducing the limit of-detection (LOD), and the time-to-result, targeting < 1hr.

Combining serology and nucleic acid detection in a single sample-to-result workflow will enable rapid triage and diagnosis at Point-of-Care (POC), distinguishing past from current infections and supporting early intervention. The simplicity of the reagents, instrument and cartridge enables compliance with the WHO REASSURED criteria[1], providing a non-capex commercially viable diagnostic[2] across all regions of the world.

ASSAY OVERVIEW

The assay has two variants: (1) Direct & (2) Indirect. In both, beads from the upstream assay are delivered to the CMOS sensor, for capacitive detection and quantification.



Direct (Quantitative): The nucleic acid (NA) or antibody analyte is captured directly from the raw sample, by PNA probes or antigenic peptides respectively. This method is suitable for genotyping, gene-expression, and antibody quantification.

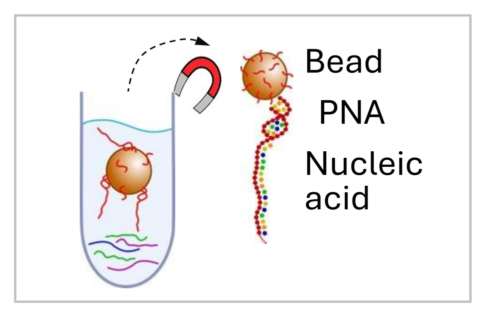
Indirect (Qualitative): See Fig.6:

The assay begins with sample lysis followed by non-specific total nucleic acid extraction using magnetic silica beads. Reverse transcription and HIV-specific recombinase polymerase amplification (RPA) steps generate DNA amplicons, which are tagged and hybridised to a second magnetic bead via peptide nucleic acid (PNA) probes. These DNA-tagged beads are electromagnetically moved through wash steps and tethered to a CMOS sensor using a second HIV-specific PNA probe. The beads act as proxies for the target analyte and are detected by fringe-field capacitive sensing on the CMOS sensor chip, providing a qualitative digital result corresponding to RNA captured from the sample.

MATERIALS & METHODS

PNA Probes:

Peptide Nucleic Acids (PNA) are synthetic mimics of DNA which can be used as probes in diagnostic assays. Synthesised with FMOC chemistry, synthetic PNAs are not recognised or degraded by proteases and nucleases in biological matrices due to their unnatural backbone. This enables specific target capture directly from biological samples, eliminating centrifugation. Improved chiral ('Keychain') left-handed (LH) PNAs[3] have also been co-developed with the US National Institutes of Health, and are synthesised in-house. These offer significant extra assay flexibility, as biorthogonal tags for extra specificity.



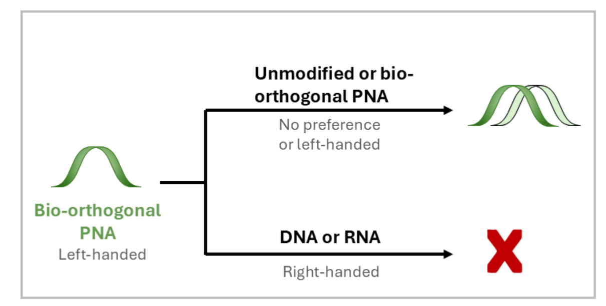
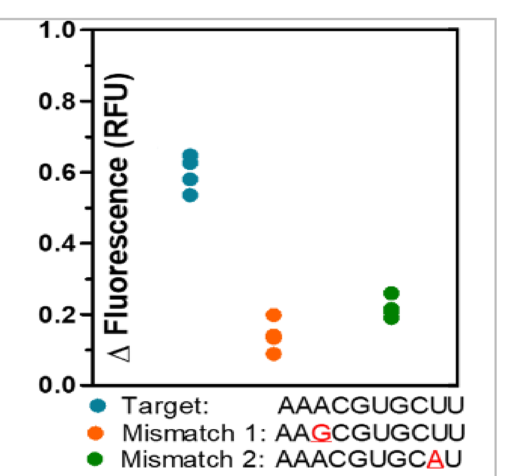


Fig.1:
(a) Human saliva sample in vial.
(b) Capture & extraction of viral NA

Fig.2:
Chiral LH PNAs attach to other LH PNA tags, but not to right-handed DNA or RNA

PNAs are known for their excellent specificity, for example to differentiate between single-base-mismatches (SBM).

Fig.3:
SBM specificity of SARS-CoV-2 capture by PNA probes from human saliva (BioIVT). (Evaluated by plate-reader for benchmarking.)
Probes designed by Altratech's ROCAP PNA probe design tool.



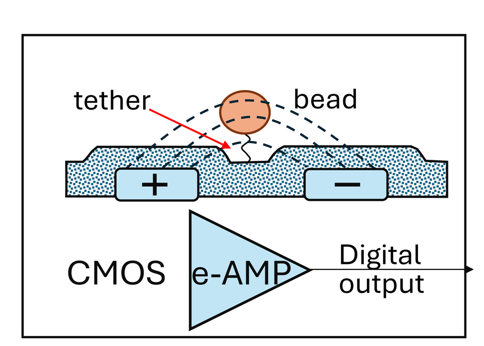
Superparamagnetic Beads:

PNA-coated superparamagnetic beads with captured target are magnetically moved through the assay extraction, wash, tether, and detection steps.

Digital CMOS Sensor Chip[4]:

Paramagnetic beads are specifically tethered by the target to Altratech's proprietary sensor and quantitatively detected by employing fringe-field sensing (Linearity: R^2=0.96). This digital standard-CMOS sensor chip replaces Optical Detection with Electronic Detection.

Fig.4:
The CMOS sensor 'fringe-field' capacitive sensing principle, and electronic signal amplification.



Antigenic Epitope Sequences:

These are synthesised with standard FMOC chemistry and conjugated to form keychain-epitope conjugates. These are used for specific antibody capture from the raw sample. Fig.5 shows an example of the keychain-epitope tethering an HIV antibody to the sensor chip.

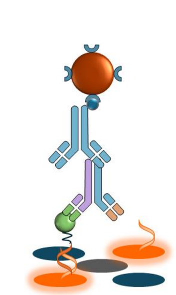


Fig.5

ASSAY OPERATION

Sample-to-result Assay Schematic:

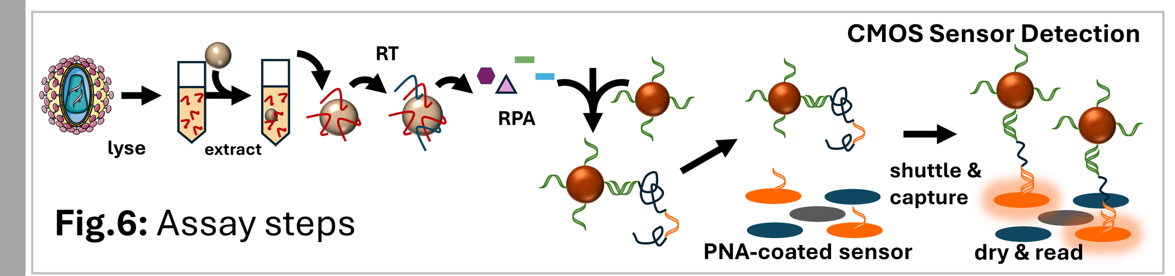
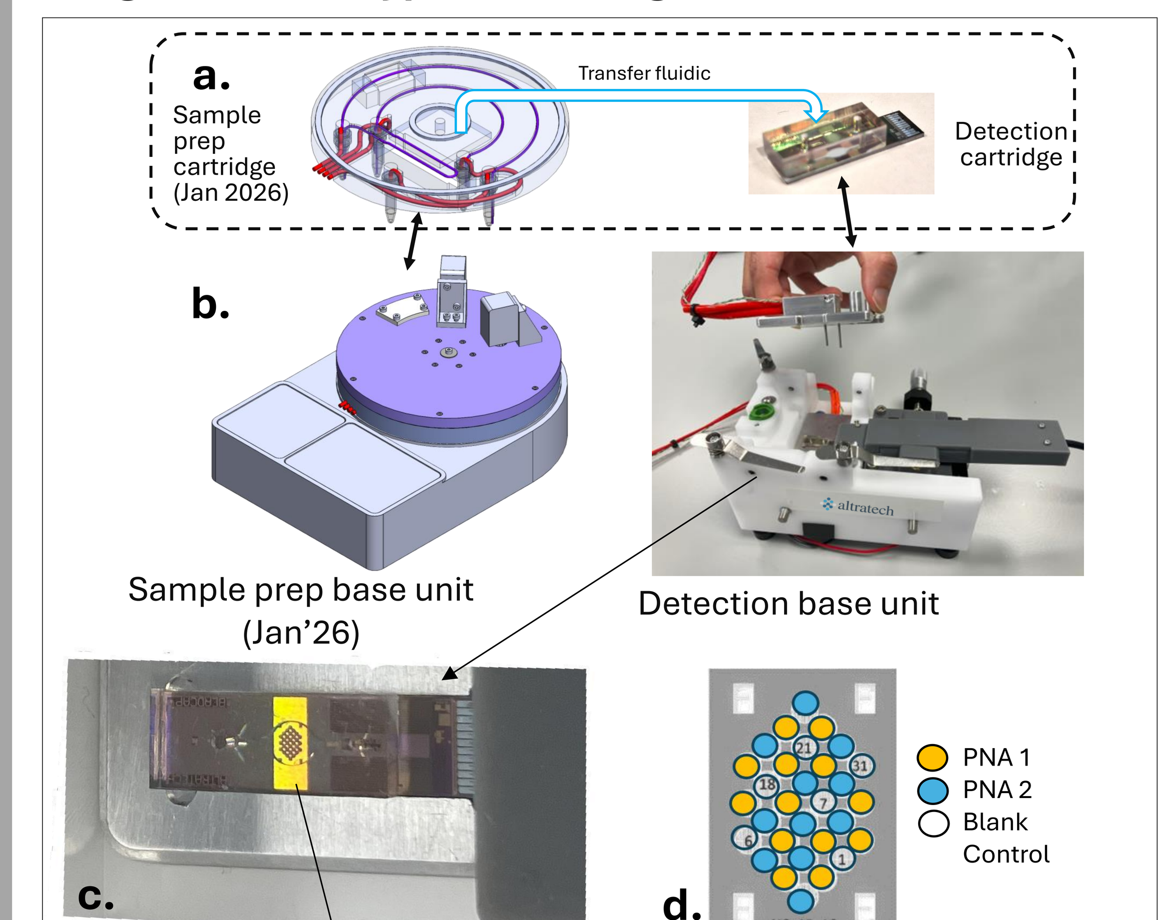


Fig.6: Assay steps

Integrated Prototype & Cartridge Fig.7:



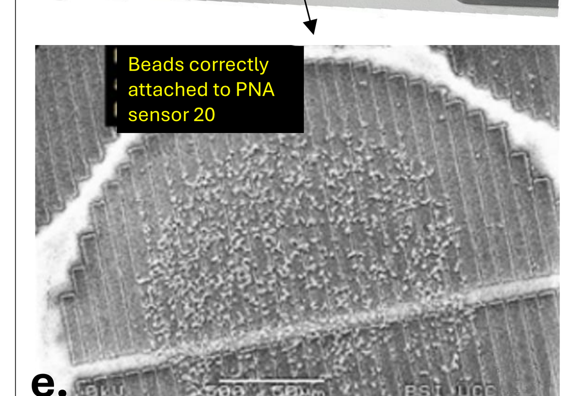


Fig.7:
a. Sample Prep and Detection cartridges
b. The Sample prep and Detection base units.
c. The digital CMOS chip in the microfluidic channel.
d. The 30 Sensor spotting pattern.
e. SEM photo of one sensor with specifically captured beads.

QUANTIFICATION DATA (DIRECT ASSAY)

Fig. 8:
Quantification of synthetic SARS-CoV-2 **RNA** (Twist Bio-sciences), captured from human saliva (bioIVT). LOD=1E6.

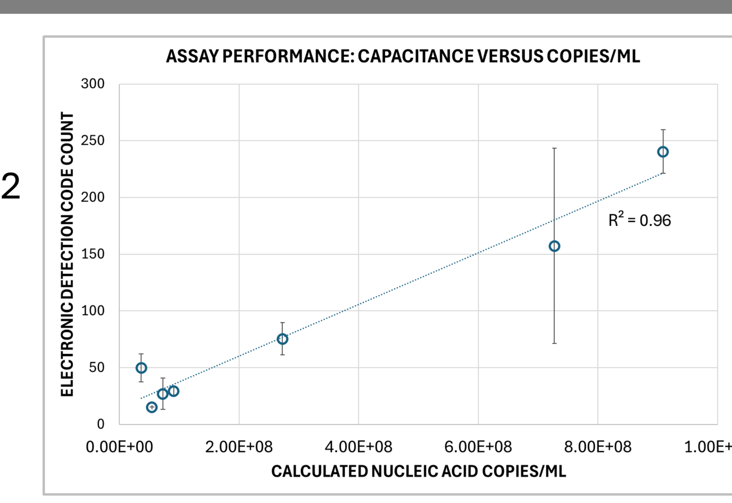
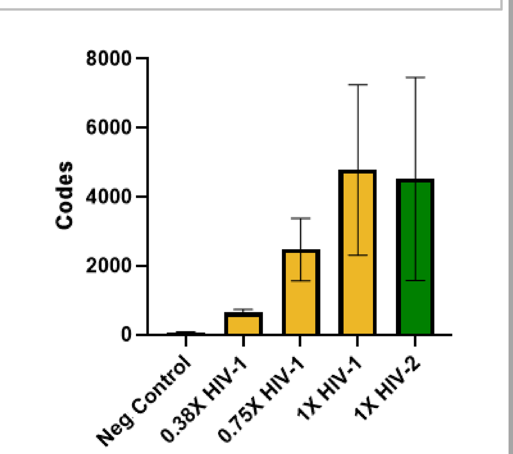


Fig.9:
Capacitance-vs-HIV1 & HIV2 immuno-assay **Antibodies** (n=2).

→Detection and quantification of HIV 1 & 2 antibodies in HIV-positive-patient plasma (NIBSC):



In this Fig.9 experiment, the enzyme in a commercially-available HIV antibody test was replaced with a superparamagnetic PNA-coated reporter bead, allowing detection and quantification on specific sensors on our proprietary CMOS silicon chip.

RNA DETECTION (INDIRECT ASSAY)

Fig.10:
'Sample-to-Result' capture & detection of HIV (spiked) RNA from human plasma and human whole blood, at five dilutions to 1000 cp/mL:

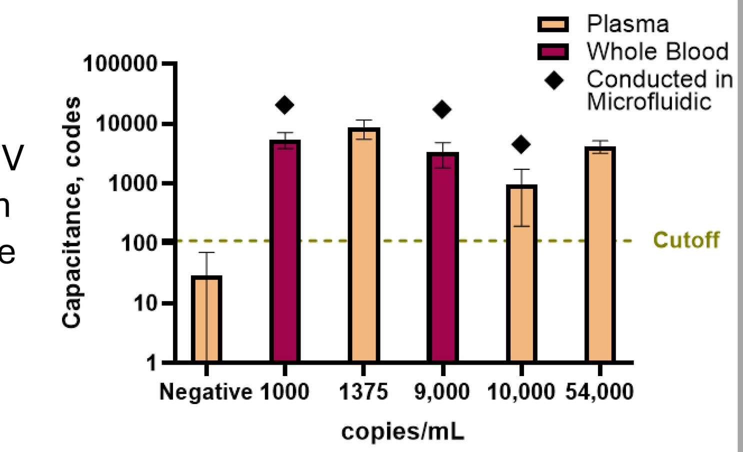


Fig.11:
'Sample-to-Result' capture & detection of HIV (spiked) RNA @1000 cp/mL from 100uL human whole blood, filtered via a commercial finger-pressure membrane filter device[5].

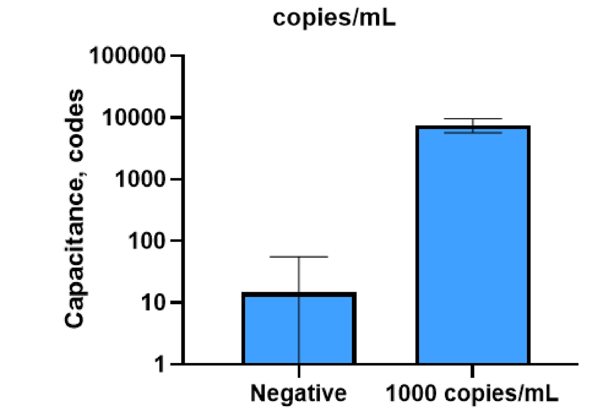
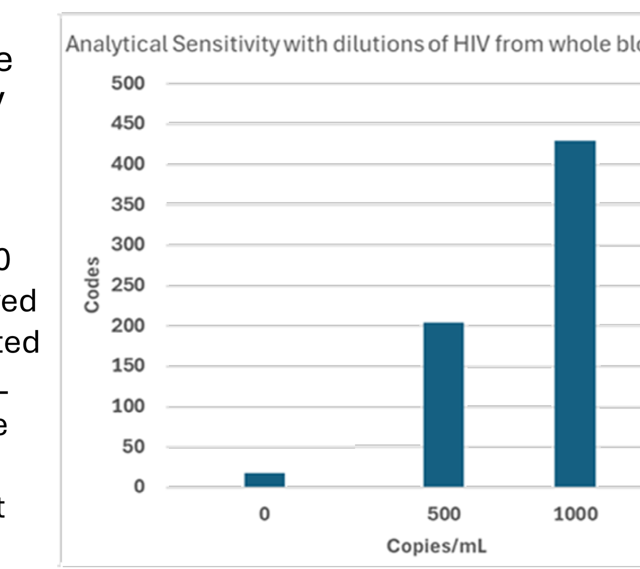


Fig.12:
'Sample-to-Result' capture & detection of Accurun HIV RNA virions from 200uL bioIVT human plasma:

These experiments were 1,000 copies/mL (n=5 chips) contrived HIV samples; some were diluted down to equivalent 500 cp/mL (n=3). Significance levels were p=0.0000, p=0.0000 and p=0.0004 when tested against the negative sample chips.



Discussion:

This data demonstrates 'sample-to-result' detection of HIV virus from contrived human whole blood samples at ≤1,000 cp/mL, and with further dilution of the extracted RNA. at 500 cp/mL These performance levels are similar to leading HIV sample-to-result POC device[6] (400 cp/mL LOD) and to recent portable respiratory RNA products[7,8] (667 & 400 cp/mL resp). Further LOD reduction is now underway.

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9. Altratech patents US11274291/10738348/11796498, US11459601 and EU/CN/JP equivalent granted patents. **(Altratech Ltd owns an extensive patent portfolio covering all aspects of this product & technology).**

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