***Supplementary information***

**Instrumentation: High Resolution Differential-Surface Plasmon Resonance (SPR).** The SPR setup was described elsewhere.[1, 2] Briefly, it is based on the Kretschmann configuration, in which a p-polarized laser beam ($\lambda$= 635 nm) is focused through a prism onto a metal film placed on the prism. At the so-called resonance angle, the incident light is absorbed by the surface plasmon and the reflection drops to a minimum, which results in a dark thin line known as the SPR dip (Fig. 1). We use a gold film that is divided into a sensing area and a reference area. The dark lines from the two areas are simultaneously monitored by a quadrant cell photodetector, containing four nearly identical photocells (A, B, C and D). The resonance angles from the sensing and reference areas are detected by differential signals, (A-B)/(A+B) and (C-D)/(C+D), respectively which are recorded with a data acquisition unit (LabJack U12). Prior to each measurement, the prism is rotated to bring the dark lines to the center of the reflected beam spot, and the quadrant photodetector is adjusted to balance not only A and B for the sensing signal but also C and D for the reference signal (Fig. 1). When the analyte is injected into the cell, the index of refraction of the solution changes which causes a shift in the SPR resonance angle. However, since the sensing area is modified with *Arachis Hypogaea* Lectin (Peanut Agglutinin, PNA), the binding of disaccharides onto the sensing area causes an additional resonance angle shift. The differential signal, (A-B)/(A+B) - (C-D)/(C+D) eliminates the effect due to the solution refractive index change, which allows us to detect the disaccharide binding with an accuracy of ~$6\times10^{-5}$ degrees (Fig. 1). Because the four photocells (on a single chip) are nearly identical, thermal drift and mechanical noises are also subtracted out, thus providing a simple and accurate method to detect the small concentrations (pM, nM) of low molecular weight molecules such as heavy metal ions,[2] oxoanions[3] and disaccharides.

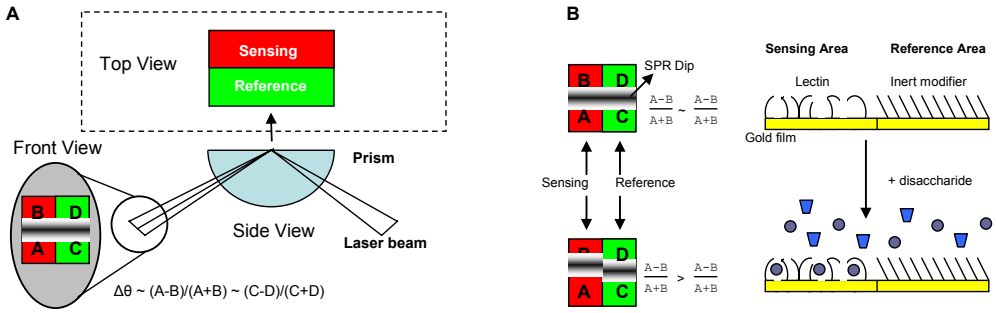


**Figure 1.** Schematic representation of the SPR setup. (A) A diode laser is focused with a cylindrical lens through a prism onto the gold film supported on the prism (not shown for clarity). The gold film is divided into a sensing area and a reference area. The reflected beams from the two areas have dark lines (SPR dips), corresponding to resonance of the surface plasmon, when the incident angle is appropriately adjusted. A quadrant cell photodetector simultaneously measures the SPR dips from the reference (C, D) and sensing (A, B) areas. (B) Prior to each measurement, the quadrant photodetector is adjusted to balance A, B, C and D, so that [(A-B)/(A+B)] – [(C-D)/(C+D)] ~ 0. When the analyte is injected into the cell, the specific adsorption onto the sensing area causes a shift in the SPR dip position, which is detected by the differential signal [(A-B)/(A+B)] – [(C-D)/(C+D)].

**Reagents.** Pure *Arachis Hypogaea* Lectin (Peanut Agglutinin, PNA) was obtained from EY Laboratories, Inc. (San Mateo, CA). All stock and buffer solutions were prepared using deionized water (18.2 MΩ. cm). Galacto-N-biose (T-antigen), N-Acetyl-D-lactosamine (control disaccharide), Anti-Arachis hypogaea Lectin antibody produced in rabbit (anti PNA), IgG from human serum, Anti-Human IgG (γ-chain specific)−(anti IgG), mercaptopropionic acid (MPA), phosphate salts, Tris, NaCl, 2-(morpholino)ethanesulfonic acid (MES), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) were of analytical reagent grade and purchased from Sigma-Aldrich (St. Louis, MO). The experiments were conducted at room temperature (22 $^{o}$C).

**Sensor chip modification.** The sensor chips were 47-nm gold films sputtered on BK7 glass slides by an ion beam coater (Model 681, Gatan Inc.). The film was separated in two parts with a gap of 100-200 μm. One part was modified as reference area with a layer of anti IgG / IgG and the second part was designated as sensing area and modified with a layer of anti PNA / PNA (Fig. 2). The gold film was initially functionalized with a ~1 mg

$mL^{-1}$ thiol-modified carboxylated dextran (CD) solution overnight. This polymer produced a highly hydrophilic surface minimizing non-specific binding interactions[4] (step 1). After that, the carboxylated dextran-modified surface was rinsed with water and incubated with 10 mM MPA for 30 min to ensure full surface coverage with anchoring carboxylic groups. Then, the surface was thoroughly rinsed with water and dried with nitrogen. The sensing area modification was performed by setting a 10 uL drop of anti PNA-EDC solution (2.5 mg $mL^{-1}$ anti-PNA + 100 mM EDC in 0.1 MES buffer, pH = 5.5) underneath a previously oxidized (hydrophilic) polydimethylsiloxane (PDMS) stamp for 30 min (step 2). After that, the anti-PNA solution was washed out by through rinsing with 0.1 MES buffer, pH 7, and water (step 3). The reference area of the chip was subsequently modified with 10-20 uL of anti IgG- EDC solution, final pH = 6 (prepared from 50 uL of the commercial anti-IgG solution in PBS, pH = 7.4, and 71 mM EDC in 0.1 MES, pH = 5.0) for 30 min (step 4). In this case, there was no need of use PDMS to locate the modifying solution on reference area since the difference in surface tension between sensing and reference area resulting after sensing area modification was large enough to contain the solution on the reference area. After anti-IgG binding on reference area, anti-IgG / EDC solution was washed out by treating the whole surface with 0.1 M MES buffer, pH = 7, for 15 min and subsequent through rinsing. Then, activated-carboxylic groups were inactivated by 30-min. incubation in 25 mM TRIS buffer, pH = 7.

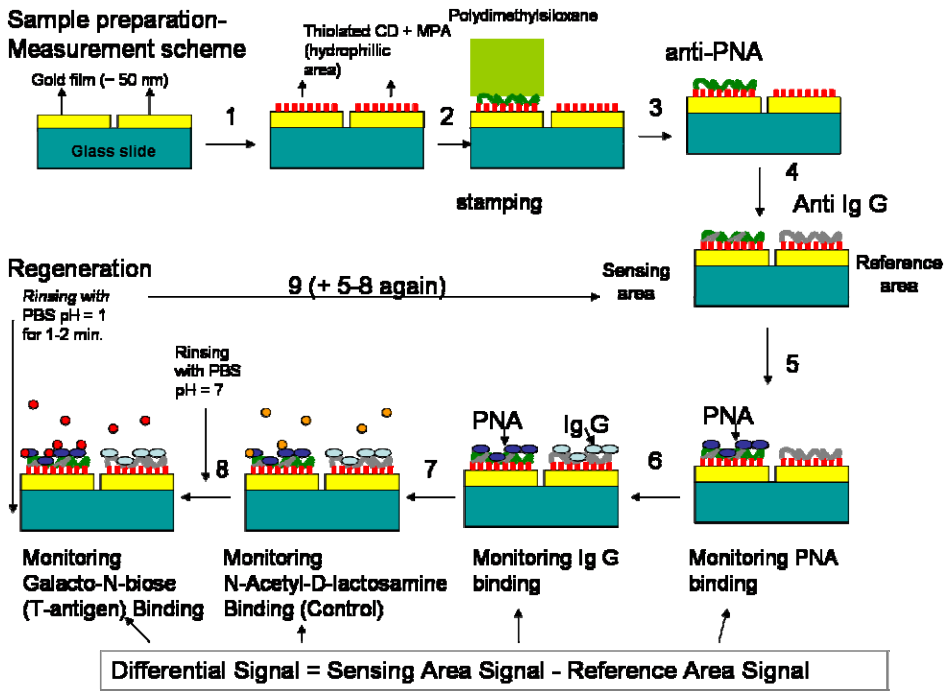


**Figure 2.** Schematic representation of modification and use of a sugar sensor SPR chip (see experimental section for details).

**Detection of binding interactions.** The response of the SPR sensors was performed in PBS buffer: 0.01 M phosphate, 0.15 M NaCl, pH 7.2-7.4. Binding of PNA onto anti-PNA (sensing area) as well as IgG onto anti-IgG (reference area) was monitored to characterize the protein amounts bonded to each sensor area (steps 5 and 6) as well as to evaluate reusability of the sensor chip (step 9). After PNA and IgG adsorption on sensing and reference area, respectively; the direct binding of the disaccharides: T-antigen and N-Acetyl-D-lactosamine onto PNA was measured (steps 7 and 8). Successive injections of different concentrations of disaccharide solutions prepared in the same buffer were added after 2-4 additions of PBS buffer. The injections of PBS buffer allowed quantification of the differential SPR signal drift due to mechanical perturbation of solution from sample injections as well as baseline correction and accurate evaluation of the total SPR differential signal change in presence of the analyte molecule. All the solutions were prepared in Eppendorf ultracentrifuge plastic tubes thoroughly washed with ultrapure water. The SPR cell was a Teflon® cylinder of 400 µL capacity washed with piranha

solution (98% $H_2SO_4$: 30% $H_2O_2$ = 3:1, V/V) and then sonicated in 18.2 MΩ.cm water three times before use (Caution: piranha solution reacts violently with most organic materials and must be handled with extreme care). 5-10 μL sample volumes were injected into 320-340 μL of PBS buffer.

After one cycle use (steps 5-8) the chip surface was fully regenerated by incubation of PBS, pH =1, for 1-2 min. and thorough rinsing (step 9).

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## References

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