Title:
Molecular Recognition sensor utilizing the modulation of the perpendicular magnetic anisotropy

Inventors: Vadym Zayets and Ivan Turkevych

Abstract: *The molecular recognition sensor detects a molecule or a biological object by measuring the change of perpendicular magnetic anisotropy (PMA) of a single-domain ferromagnetic metal (nanomagnet). The PMA is changed when the analyte molecule touches the ferromagnetic metal. When the molecule is close to surface of the ferromagnetic metal, the electron orbitals of the molecule and the surface atoms of the ferromagnetic metal interact with each other. As a result, the orbitals of the surface atoms of the ferromagnetic metal are deformed toward the analyte molecule and the PMA energy is changed. From the measurement of the PMA energy, the proximity, type and concentration of the analyte molecules are determined.*

Prior Art

The detection method, which is disclosed in the present invention, is based on the fact that the PMA energy of a ferromagnetic metal depends on the orbital deformation of the surface atoms, which is caused by their interaction with an analyte molecule. The following explains why the orbital deformation changes the strength of the spin-orbit (SO) interaction for the electrons of the surface atoms of the ferromagnetic metal. Next, it explains why the change of the SO interaction causes the change of the PMA of the ferromagnetic metal.

1. Prior Art. The spin-orbit interaction and the orbital deformation

The Einstein theory of relativity states that an electron moving in a static electric field experiences an effective magnetic field, which is called the effective magnetic field of the spin-orbit (SO) interaction H_{SO} [1]. The electric field of atomic nucleus may induce a substantial H_{SO}, because the electron moves with a very high speed on its atomic orbital in close proximity to the atomic nucleus. However, the value of the H_{SO} substantially depends on the orbital symmetry. It is because the electron experiences different directions of the H_{SO} on different parts of the orbit that may compensate each other. For example, in the case of a spherical orbital the contributions to the H_{SO} are equal and opposite in sign and the resulting $H_{SO}=0$. In the case of a deformed orbital, when the orbital is elliptical or/and the orbital center is shifted from the nuclear position, the H_{SO} becomes substantial and proportional to the degree of the orbital

deformation. Also, the H_{SO} is linearly proportional to an external magnetic field H_{ext}. Figure 1 demonstrates how the H_{SO} changes depending on the direction of the orbital deformation and the direction of the external magnetic field. When the orbital is spherical (Fig.1a), the H_{SO} equals to zero independently on the direction of the H_{ext}. When the orbital is deformed and the H_{ext} is applied perpendicularly the orbital deformation (see Fig.1b), the H_{SO} is also zero, because the orbital is symmetrical along the direction of the H_{ext}. For the cases of Figs. 1a and 1b, the magnetic energy of the electron E_{mag} is equal to:

$$E_{mag} = -H_{ext} \cdot S \cdot \mu_B \tag{1}$$

where S is the electron spin and μ_B is the Bohr magneton. When the orbital is deformed and the H_{ext} applied along the orbital deformation (Fig.1c), the H_{SO} becomes a non-zero and proportional to the H_{ext}. In this case the E_{mag} equals to:

$$E_{mag} = -(H_{ext} + H_{SO}) \cdot S \cdot \mu_B \tag{2}$$

The absolute value of the electron magnetic energy is larger in the case shown in the Fig. 1c and smaller in the cases shown in the Figs. 1a and 1b. Therefore, the orbital deformation substantially changes the electron magnetic energy and therefore magnetic properties of the ferromagnetic film.

[1]   Landau and Lifshitz, The classical theory of fields. Third Revised English Edition. Course of Theoretical Physics. Volume 2

2. Prior Art. Perpendicular magnetic anisotropy (PMA)

The equilibrium magnetization of an isotropic ferromagnetic thin film can be either in-plane or perpendicular-to-plane depending on the deformation of the electron orbitals at the film interface and the thickness of the film. The interaction of analyte molecules with interface electrons of the ferromagnetic film leads to the orbital deformation of the interface electrons and consequently to a change of the PMA. Consequently, the change of magnetization direction of the ferromagnetic film due to the change of the PMA is used as the molecular detection mechanism in the disclosed invention.

The physical phenomenon of the PMA and the reason, why the orbital deformation defines the strength of the PMA, are explained as follows. Figure 2 shows a cross-section of a nanomagnet as an array of its electronic orbitals. The magnetization of a thicker film (Fig. 2a) is in-plane, while the magnetization of a thinner film (Fig.2b) is perpendicular-to-plane. The PMA is the reason, why the magnetization changes its direction depending on the film thickness. The equilibrium magnetization direction is the direction of the smallest magnetic energy of the whole film. For the bulk electrons the magnetic energy is smallest when the magnetization is in-plane. For the interface electrons the magnetic energy is smallest when the magnetization is perpendicular-to-plane. In the case of a thicker film, the number of bulk electrons is larger and the total magnetic energy of the film is smaller when the magnetization is in-plane. In the case of a thinner film, the number of bulk electrons is smaller while the number of interface electrons remains the same. As a result, the magnetization becomes perpendicular-to-plane for the substantially thin film.

The reason why the dependence of the magnetic energy on the magnetization direction is different for the bulk and interface electrons, is their orbital shape. The orbital of the bulk electrons is spherical. They do

not experience any H_{SO}. The magnetic energy $E_{\parallel,b}$ and $E_{\perp,b}$ of a bulk electron for the case of in-plane and perpendicular-to-plane magnetization can be calculated as

$$E_{\parallel,b} = -H_M \cdot S \cdot \mu_B$$
$$E_{\perp,b} = -(H_M - H_D) \cdot S \cdot \mu_B \qquad (3)$$
$$\Delta E_B = E_{\parallel,b} - E_{\perp,b} = -H_D \cdot S \cdot \mu_B$$

where S is electron spin, μ_B is the Bohr magneton, H_M is the intrinsic magnetic field induced by the magnetization, H_D is the demagnetization field, which is directed perpendicular-to-plane and proportional to the perpendicular component of the H_M. ΔE_B is the difference of the magnetic energy for two magnetization directions. For the bulk electron, the ΔE_B is negative.

The interface electrons experience the SO field H_{SO}, additionally to H_M and H_D, because their orbitals are deformed. The H_{SO} is a non-zero only when the magnetization direction is along the deformation and therefore perpendicular-to-plane. For an interface electron, the magnetic energies $E_{\parallel,i}$ and $E_{\perp,i}$ for the in-plane and perpendicular-to-plane magnetizations, respectively, and their difference ΔE_i can be calculated as

$$E_{\parallel,i} = -H_M \cdot S \cdot \mu_B$$
$$E_{\perp,i} = -(H_M - H_D + H_{SO}) \cdot S \cdot \mu_B \qquad (4)$$
$$\Delta E_i = E_{\parallel,i} - E_{\perp,i} = (H_{SO} - H_D) \cdot S \cdot \mu_B$$

The H_{SO} is proportional to the degree of the orbital deformation. Even when the deformation is small, $H_{SO} > H_D$ and the ΔE_i is positive.

The difference of the magnetic energy for the $\parallel$ and $\perp$ magnetization directions is called the PMA energy (E_{PMA}) and it can be calculated as

$$E_{PMA} = \Delta E_i \cdot N_i + \Delta E_B \cdot N_B \qquad (5)$$

where N_B and N_i are the numbers of the bulk and surface electrons, correspondingly. Since ΔE_B is negative, Eq. (5) can be simplified as $\frac{E_{PMA}}{N_i} = \Delta E_i - t \cdot \beta \cdot |\Delta E_B|$

$$(6)$$

where t is the film thickness, while the constant β depends on the symmetry of crystal lattice and in the simplest case of a cubic lattice with the lattice constant a, the $\beta = (1/a) \cdot N_i/N_B$.

Figure 3 shows the energy of the perpendicular magnetic anisotropy E_{PMA} of a FeB thin film as function of its thickness for two cases of different orbital deformation at the interface with the interface magnetization ΔE_i of 1.15 and 0.85 mJ/m^2. The magnetization of the thinner film is perpendicular-to-plane. The magnetization of the thicker film is in-plane. The thickness of the film at which the magnetization changes direction depends on the degree of orbital deformation at the interface and therefore on the value of interface magnetization energy ΔE_i. For example, at the thickness of 1 nm, the magnetization can be switched between the in-plane and perpendicular-to-plane directions by the

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modulation of the orbital deformation.

The orbital deformation at interface can be of two types. The orbital can be elongated or shortened along the interface normal. Both types of the orbital deformation lead to the increase of the H_{SO} and the PMA energy.

[2]   M.T. Johnson, P.J.H. Blomen, F.J.A. den Broeder, and J.J. de Vries, Reports Prog. Phys. 59, 1409 (1996).

3. Prior Art. Similar effect in different patents

In the disclosed patent, the tested (analyte) molecule changes the PMA energy of a nanomagnet by deforming the interface orbital. In the previous patent of one of authors (V. Zayets) "全金属型トランジスタとその方法" V. Zayets,T. Nozaki, A.Fukushima, S. Yuasa, Patent application 2017-226503, H29/06/06 (made by **Koboyashi-san**), the PMA and magnetic properties of a nanomagnet are modulated by a gate voltage. The operational principle is similar. The gate voltage deforms electron orbitals at the interface of the nanomagnet. As a result, the gate voltage modulates the PMA.

4. Prior Art. Experimental demonstration of the PMA modulation

(a)   Modulation of the PMA by changing of amount of oxygen at the interface of a nanomagnet.
In the Ref. [3], it was demonstrated that the increase of amount of oxygen at the Co/MOx interface in Pt/Co/MOx stack (where M=Al, Mg, Ta) increases the PMA and changes the magnetization of a thin Co film from in-plane to perpendicular-to-plane direction [3]. The amount of oxygen at the interface was modulated by varying the plasma oxidation time. In the Ref. [4], the increase of the PMA and the change of the magnetization of a thin FeCo film from in-plane to perpendicular-to-plane direction was observed in a Pt/FeCo/Al thin film as a function of the degree of Al oxidation in oxygen plasma.

(b)   Modulation of the PMA by adding graphene molecules *on top of a nanomagnet*
In the Ref. [5] the PMA of the CoFeB films in Pd/CoFeB/MgAlOx/Pd stacks was strongly enhanced after deposition of graphene oxide GO layers over the stacks, which was attributed to the hybridization of 3d orbitals of Co with C and O orbitals of the graphene oxide.

(c)   Modulation of the PMA by a gate voltage [6]
(d)   Modulation of the PMA by adding of a small amount of heavy elements at the interface of FeB nanomagnet [7]

[3]   A. Manchon, C. Ducruet, L. Lombard, S. Auffret, B. Rodmacq, B. Dieny, S. Pizzini, J. Vogel, V. Uhlíř, M. Hochstrasser, and G. Panaccione, J. Appl. Phys. 104, (2008).
[4]   S. Monso, B. Rodmacq, S. Auffret, G. Casali, F. Fettar, B. Gilles, B. Dieny, and P. Boyer, Appl. Phys. Lett. 80, 4157 (2002).
[5]   K. Ning, H. Liu, L. Li, H. Li, J. Feng, B. Yang, X. Liu, Y. Li, Y. Chen, H. Wei, X. Han, S. Mao, X. Zhang, Y. Yangab and T. Ren, RSC Adv. 7, 52938 (2017).
[6]   T. Nozaki, A. Kozioł-Rachwał, W. Skowroński, V. Zayets, Y.Shiota, S. Tamaru, H. Kubota, A. Fukushima, S. Yuasa, and Y.Suzuki, " Large Voltage-Induced Changes in the Perpendicular Magnetic Anisotropy of an MgO-Based Tunnel Junction with an Ultrathin Fe Layer" , Phys. Rev. Applied 5, 044006 (2016);

[7]   T. Nozaki, T. Yamamoto, S. Tamaru, H. Kubota, A. Fukushima, Y. Suzuki, and S. Yuasa, APL Mater. 6, 026101 (2018).

Claims

Claim 1. (detection method).
A device for molecular detection and recognition, which consists of a ferromagnetic metal, which magnetization is perpendicular-to-plane and its top interface is open for a tested molecule to reach. A bias magnetic field is applied in the in-plane direction of the ferromagnetic metal. Under the bias magnetic field the magnetization of ferromagnetic metal is inclined toward the in-plane direction and has an angle between 10 and 80 degrees with respect to the in-plane direction. When the tested molecule touches the surface of the ferromagnetic metal, the PMA energy of the ferromagnetic metal is changed and consequentiality the magnetization angle is changed. By the detection of the change of the magnetization angle, the presence of the molecule is detected and its type is recognized.

The ferromagnetic film that constitutes the molecular recognition sensor of the disclosed invention can consist of, but not limited to, Fe, Co, Ni, FeCo, FeB, FeCoB with the thickness of 0.5-2 nm.

The ferromagnetic film that constitutes the molecular recognition sensor of the disclosed invention can be covered with multilayers of magnetic and non-magnetic materials consisting of, but not limited to, Fe, Co, Ni, FeCo, FeB, FeCoB, Pt, Pd, W, MgO_{1+x}, $MgAlO_{2+2x}$ with the thickness of 0.5-5 nm, where x is varied from -0.1 to 0.1, two dimensional materials such as graphene, graphene oxide, MoS_2, MXenes.

Claim 2. (MTJ).
A device for molecular detection and recognition, which consists of "free" layer, "pin" layer and tunneling layer. The "free" layer consists of a ferromagnetic metal, which magnetization is perpendicular-to-plain. The features of the "free" layer are disclosed in Claim 1. The "pin" layer consists of a ferromagnetic metal, which magnetization direction is in-plane. The tunneling layer is fabricated between the "free" and the "pin" layers and is made of a non-conductive material, through which a tunneling current can flow.

A bias magnetic field is applied in the in-plane direction. Under the bias magnetic field, the magnetization of the "pin" layer is in-plane and the magnetization of the "free" layer is inclined toward the in-plane direction. The tunneling current and the tunneling magnetic resistance (TMR) of the magnetic tunnel junction (MTJ) depend on mutual magnetization directions of the "free" and the "pin" layers.

When the tested molecule touches the surface of the "free" layer, the magnetization angle of the "free" layer is changed and consequentiality the TMR is changed.   By monitoring the resistance of the MTJ, the presence of the molecule is detected and its type is recognized.

The tunneling layer can consist of, but not limited to, MgO and AlO_x with the thickness of 0.5-2 nm.

Claim 3. (mask).

A device for molecular detection and recognition described in Claims 1 and 2, in which the detection surface of ferromagnetic metal is cover by a non-magnetic material (mask) with openings. The geometrical shape of the openings corresponds to the shape of the detectable molecule. The mask provides the molecular recognition function.

Only a molecule, which shape corresponds to the shape of the opining in the mask, can fit to the opining, reach the surface of the ferromagnetic metal and be detected. A molecule of a different shape cannot fit the opining and cannot be detected.

Molecular ligands can be used as a mask. The molecular ligands restrict access of all molecules to the surface of the ferromagnetic metal. Only specific molecules can bind to the ligands and deform electron orbitals of the ligand. As a result of the bonding of the analyte molecule to the ligand, the interaction of the ligand with the underlying surface of the ferromagnetic metal is changed and the PMA energy of the ferromagnetic metal is changed. Therefore, only the molecules which can specifically bind to the ligands are detected and recognized.

The molecular mask that specifically controls the interaction of analyte molecules with the ferromagnetic thin film can consist of, but not limited to, metal-organic framework (MOF) materials (such as HKUST-1, ZIF-5, etc.), covalent organic framework (COF) materials (such as TPB-DMTP, etc.), molecular sieve materials (such as zeolites, aluminosilicate minerals, porous glasses, active carbons, etc.), nanoporous materials (such as nonporous aluminum oxide, etc.).

The molecular ligands that specifically mediate the interaction of analyte molecules with the ferromagnetic thin film can consist of, but not limited to, coordination metal complexes, porphyrins, phthalocyanines, oligonucleotides and the like.

Main Figure

Fig.4.

Detailed explanation of Figures

Figure 4. The detection method. Figure 4 explains the detection principle of the disclosed invention. When the analyte molecule is far from the interface of the ferromagnetic film, the deformation of interface orbitals is small, magnetic field of spin-orbit interaction (H_{SO}) is small and the interface PMA is small (Fig. 4a). When the molecule approaches the interface, the electron orbitals on the surface of the ferromagnetic metal deform toward the analyte molecule. The orbital deformation leads to an increase of the effective H_{SO} and consequently to the increase of the PMA energy E_{PMA}. By measuring the change

of the E_{PMA}, the approach of the analyte molecule can be detected and the type of the analyte molecule can be recognized. Additionally, the concentration of the analyte molecules can be measured.

Figure 5. The method of molecular recognition. Figure 5 shows a ferromagnetic film with a molecular mask on top of it. The mask is designed in such way that it allows only specific molecules to approach the interface of the film. Only molecules with a specific size, shape and chemical composition can pass through the openings of the molecular mask and can be detected by the disclosed sensor. Figure 5(a) shows the case when a molecule does not fit into the opening of the mask. Therefore, it cannot approach closely enough to the interface of the ferromagnetic metal. The orbitals on the surface of the ferromagnetic metals are unaffected by the molecule. As a result, the molecule is not detected by the sensor. Figure 5(a) shows the case when a molecule matches the opening of the mask. Therefore, it can fit into the opening and can approach to the interface of the ferromagnetic metal. The orbitals on the surface of the ferromagnetic metal are deformed. As a result, the molecule is detected by the sensor. By designing the shape of the openings and the material of the mask, only a specific type of molecules can reach the surface of the ferromagnetic metal and be detected. Therefore, the sensor is able to recognize this specific type of molecules.

Figure 6. The Hall-probe sensor.

Figure 6 shows the Hall-probe sensor, which consist of a nanomagnet (1) on the top of a nanowire (2) with an isolation layer (3). The nanomagnet is made of a ferromagnetic metal. The nanowire and the Hall probe are made of a non-magnetic metal. The equilibrium magnetization of the nanomagnet is perpendicular-to-plane. An external magnetic field *H* is applied along the wire. Under the magnetic field, the magnetization of the nanomagnet inclines towards the in-plane direction. The ball with arrow shows the magnetization direction of the nanomagnet. A bias current is passed along the nanowire. Two Hall probes are contacting the nanowire to detect the Hall voltage. The Hall voltage is linearly proportional to the perpendicular-to-plane component of the magnetization. The proximity, type and concentration of the analyte molecules are detected by measuring the Hall voltage.

Figure 6(a) shows the case when the analyte molecule is far from surface of the nanomagnet. The PMA energy is small. The magnetization of the nanomagnet is inclined more to the in-plane direction. As a result, the Hall voltage is small.

Figure 6(b) shows the case when the analyte molecule is near the surface of the nanomagnet. The PMA energy becomes larger. The magnetization of the nanomagnet is inclined more to the perpendicular-to-plane direction and the Hall voltage increases. As a result, the proximity, type and concentration of the analyte molecules are detected.

Figure 6. MTJ sensor. Figure 6 shows the molecular recognition sensor based on the magnetic tunnel junction (MTJ). It consists of (1) a thicker "pin" electrode, where the equilibrium magnetization is in-plane, a thinner "free" electrode, where equilibrium magnetization is perpendicular-to-plane and (3) a thin non-conductive layer between the "pin" and the "free" layers. The "pin" and the "free" layers are made of ferromagnetic metals. A bias voltage is applied between the "pin" and the "free" layers and a tunneling current flows between the layers.

The proximity of an analyte molecule is detected by monitoring the tunneling current. The tunneling current depends on the angle α between the magnetizations of the "pin" and the "free" layers. The tunneling current is largest when the magnetizations of the "free" and the "pin" layers are in the same direction. The tunneling current is smallest, when the magnetization of the "free" and the "pin" layers are in opposite directions.

An external magnetic field H_{ext} is applied in the in-plane direction. The magnetization of the "pin" layer (M_{pin}) remains in the in-plane direction while the magnetization of the "free" layer (M_{free}) inclines towards H_{ext}. The inclination angle of the M_{free} depends on the PMA energy of the "free" layer and strength of H_{ext}.

In the case when there are no analyte molecules in the proximity of the "free" layer, the PMA energy E_{PMA} of the "free" layer is small. The M_{free} inclines more to H_{ext} and M_{pin} direction and the tunneling current is large. When the analyte molecules touch the surface of the "free" layer, the PMA energy of the "free" layer becomes larger and the M_{free} inclines more towards perpendicular-to-plane direction. The angle between M_{free} and M_{pin} direction becomes larger. As a result, the tunneling current becomes smaller.

Merits of the disclosed sensor

1) <u>Possibility of miniaturization and on-chip integration.</u> The size of the nanomagnet in the proposed sensor can be fabricated as a small as 20x20 nm^2. Nanomagnets of this size are currently used in magnetic random-access memory (MRAM). The integration of MRAM into a Si-chip is a well-established commercial technology. For example, a similar technology is used for the fabrication of an embedded MRAM. Therefore, the disclosed sensor is compatible with the CMOS technology and can be fabricated on a Si chip by using currently available MRAM technology. Since the sensor does not have any large bulk components, it can be integrated into a micro-devices, such as electronic medicines, for example electronic antibiotics providing drug release at the point of bacteria detection.

2) <u>Ability to detect a single molecule.</u> It is possible to detect the change of the PMA, when only 0.5% of interface orbitals of the nanomagnet are deformed [6]. Since the nanomagnet can be fabricated as small as 20x20 nm^2, a molecule with an effective area as small as 1x1 nm^2 can be detected.

3) <u>High specificity.</u> The reason of the high selectivity of the disclosed sensor is due to its high sensitivity to the interface orbitals deformation that depends on structure and composition of the analyte molecules. As a result, two slightly different molecules can be distinguished. Furthermore, the specificity of the sensor can be enhanced by using molecular masks and transduction ligands that allow interaction with only specific molecules.

4) <u>High sensitivity.</u> The PMA is essentially a surface phenomenon that is based on the deformation of electronic orbitals in only one monolayer at the surface, which in turn results in extraordinary

sensitivity of the disclosed sensor.

Comparison with designs of others patents

The type of the proposed sensor is new; its operational principal is new and there are no patents of similar design.

Most common types of chemical and biochemical sensors and their operational principles

Since our patent describes a new type of a sensor based on new operation principle, we describe the most-commonly-used sensors and their operational principles, including patent references.

Type 1. Sensors utilizing magnetic nanoparticles as magnetic markers or magnetic tags.

Main idea: detection of magnetic field of a magnetic marker

Operational principle:

Step 1: A magnetic nano-particle (a magnetic tag or a magnetic marker) is bonded to a biological molecule.

Step 2: A material, which can capture the biological molecule, is deposited on the surface of a magnetic probe. The magnetic probe uses the magneto-resistance effect.

Step 3: When the biological molecule is captured, the magnetic nano particle induces a magnetic field, which is detected by the magnetic probe.

Demerits:

(1)   Only bio-molecules, which are marked by a magnetic tag, can be detected

(2)   Difficulties to detect a very small change of magnetic field, because the magnetic field of the magnetic nano particle is very small. Additionally, the direction of the magnetic field may be different depending on the position, where the bio-molecule is captured by the sensor

(3)   Problem of magnetic noise of environment

(4)   Difficulties of detection of a single molecule

US5981297A   (1997). https://patents.google.com/patent/US5981297A

Title: Biosensor using magnetically-detected label. Claim: First usage of magnetic markers for bio-molecule

WO2012068139A1 (2012). https://patents.google.com/patent/WO2012068139A1/

Title: GMR sensor. Claim: GMR sensor

JP6043396B2 (2013). https://patents.google.com/patent/JP6043396B2/

Title: Magnetic nanoparticles, magnetic detector arrays, and methods for their use in the detection of biological molecules. Claim: Molecule influence the exchange coupling between two ferromagnetic films.

US20170097337A1 (2017). https://patents.google.com/patent/US20170097337A1/

Title: Method for detecting small molecule analytes using magnetoresistant sensors. Claim: Fabricated and tested sensor.

EP1469311A4. https://patents.google.com/patent/EP1469311A4/

Title: Biosensor, magnetic molecule measurement method, and measurement object measuring method. Claim: Use the semiconductor Hall sensor as a magnetic detector.

Type 2. Sensors utilizing surface plasmons

Main idea: the detection of a small change of the refractive index due to bonding of a bio molecule to a metal

Operational principle:

Step 1: A material, which can capture the biological molecule, is deposited on the surface of a metal.

Step 2: When the biological molecules are captured, the refractive index of a very thin layer on the top of the metal is changed.

Step 3: The resonance angle of a surface plasmon, which propagates on the top of the metal, is changed.

Step 4: The change of the resonance angle of the plasmonic resonance is detected by an optical method using a prism.

Demerits:

(1) The change of refractive index should be substantial due to the absorption of the bio-molecule.

(2) Difficulties with the precise control of the thickness uniformity of the absorbing layer. The plasmonic resonance significantly depends on the thickness of the absorbing layer, which variation generates substantial noise during detection.

(3) Difficulties to make a small integrated detector, because it consists of a laser, a prism and a CCD camera, which all are bulk components.

(4) Difficulties with a single molecule detection.

US5313264A (1988). https://patents.google.com/patent/US5313264A/

Title: Optical biosensor system. Claim: The first usage of a prism in plasmonic sensor.

US5485277A (1994). https://patents.google.com/patent/US5485277A/en

Title: Surface plasmon resonance sensor and methods for the utilization thereof. Claim: The first usage of plasmon resonance for sensing.

US20070065954A1 (2005). https://patents.google.com/patent/US20070065954A1/en

Title: Surface plasmon resonance biosensor system for detection of antigens and method for determining the presence of antigens.

Type 3. Sensors using surface acoustic waves

Main idea: the detection of a small mass change on the surface of a detector due to bonding of bio molecules.

Operational Principle:

Step 1: A material, which can capture the biological molecule, is deposited on the surface of an electro-acoustic film.

Step 2: When the biological molecules are captured, the mass of a very thin layer on the top of the film is changed.

Step 3: The resonance frequency of a surface acoustic wave, which propagates on the top of the electro-acoustic film, is changed.
Step 4: The resonance frequency of a surface acoustic wave is detected by a network analyzer.

Demerits:
(1) The change of the elastic properties should be substantial due to absorption of the bio-molecules.

(2) Difficulties to make a small integrated detector, because the sensor consists of a network analyzer and microwave components. Additionally, the size of the sensor and the detection area should be larger than the wavelength of the surface acoustic wave in order to get a reasonable sensitivity.

(3) Difficulties of a single molecule detection.

US8134278B2 (2009). https://patents.google.com/patent/US8134278
Title: Surface acoustic wave device and surface acoustic wave biosensor

JP2006313092A (2005). https://patents.google.com/patent/JP2006313092A/en
Title: Surface acoustic wave sensor and surface acoustic wave sensor system

JP2008224582A (2007). https://patents.google.com/patent/JP2008224582A/en
Title: Gas sensor

US20160313316A1. https://patents.google.com/patent/US20160313316
Title: Surface acoustic wave sensor for influenza detection

Type 4. Sensors utilizing floating-gate transistors

Main idea: the detected molecules change the charge and/or the Fermi level of the transistor gate. As a result, the transistor can switch the bias current on or off and detect the bio molecules
Operational Principle:
Step 1: A detectable bio-molecule is bound to the transistor gate
Step 2: The charge and/or the Fermi level of the gate is changed
Step 3: The bias current of the transistor is changed and the molecule is detected.

Demerits:
(1) Large noise due to environment electrical field and charging

(2) Difficulties to use in a liquid due to the electrolyte charge. The ions in the electrolyte makes a large noise.

(3) Difficulties of a single molecule detection.

US4881109A (1986)
Title: Sensor using a field effect transistor and method of fabricating the same

EP1464953A1 (2003). https://patents.google.com/patent/EP1464953A1/en
Title: Biosensor comprising an organic field effect transistor and method for the fabrication of the sensor organic transistors (OTFT)

EP2366994A1 (2010). https://patents.google.com/patent/EP2366994A1/en
Title: Biosensor on thin-film transistors

Type 5. Sensors utilizing fluorescent particles (fluorescent markers or fluorescent tags)

Main idea: the detection of light from a fluorescent marker
Operational Principle:
Step 1: A fluorescent nano-particle (a fluorescent tag or a fluorescent marker) is bonded to a biological molecule.
Step 2: Fluorescence from the particle is observed in an optical microscope

Demerits: The detection is limited by the resolution of an optical microscope (~1 um). A molecule can be detected and traced inside a cell structure (cell size 1-200 um), but the low resolution makes difficult to recognize different molecules, to distinguish them from each other and to distinguish their interaction.

US8043802B2 (2002). https://patents.google.com/patent/US8043802
Title: Fluorescence based biosensor

US5701012A   (1996). https://patents.google.com/patent/US5701012A/en
Title: Fluorescent biological particle detection system