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Electrochemical Amperometric Biosensor Applications of Nanostructured Metal Oxides: A Review

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Abstract

Biological sensors have been extensively investigated during the last few decades. Among the diverse facets of biosensing research, nanostructured metal oxides (NMOs) offer a plethora of potential benefits. In this article, we provide a thorough review on the sensor applications of NMOs such as glucose, cholesterol, urea, and uric acid. A detailed analysis of the literature is presented with organized tables elaborating the fundamental characteristics of sensors including the sensitivity, limit of detection, detection range, and stability parameters such as duration, relative standard deviation, and retention. Further analysis was provided through an innovative way of displaying the sensitivity and linear range of sensors in figures. As the unique properties of NMOs offer potential applications to various research fields, we believe this review is both timely and provides a comprehensive analysis of the current state of NMO applications.

Keywords: Metal oxides, Biosensor, Glucose, Urea, Cholesterol

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Contents

1. Introduction

As the need for portable and low-cost analytical instruments increased, biological sensors have been employed extensively for selective analyte detection [1-3]. Biosensors, in general, require a sensing layer designed to react with a specific biomarker or biomolecule. This sensing information is transformed into either optical, electrochemical, electrical, or other physical signals [4-7]. This article focused specifically on amperometric sensors as a subset of electrical detection of analytes.

In the case of amperometric sensing, current output of the sensor with sensor analyte is measured and used as the parameter for sensing performance. Current values from different concentrations of analyte are gathered to determine the sensitivity of the device. Comparing to other sensing types, amperometric sensing uses only current measurements rather than utilizing sensitive equipment such as optical and electrochemical measurement devices. Current measurements can simply obtained by using two electrodes to apply voltage and measure current through the device, allowing

a true surface sensitivity measurements particularly for nanostructure based amperometric sensors, which is the focus of this review article.

Nanostructures, contrary to their bulk counterparts, have a high surface-to-volume ratio and surface free energy due to their respective size to volume ratios. This unique property leads to stronger enzyme absorption, which is critical for enzymatic sensors [8,9]. As the size of a particle goes to nano-scale, physical properties of the materials change drastically due to quantum confinement effects [9,10]. Therefore, the conductivity of nanostructures found in nanorods, nanowires, nanotubes, and nanofibers are much higher than their bulk counterparts. The higher conductivity results in an increased signal-to-noise ratio and corresponding sensitivity. The band-gap of a nanostructure structure differs from bulk materials mainly because grains are now essentially defined as a single particle rather than large crystals [10-12]. Nanostructures allow large number of enzyme biomolecules to be immobilized on the electrode surface with increased free energy of nanostructures.

Sensitivity for biosensors is particularly important in clinical diagnostics because giving an accurate reading to clinicians and physicians would be vital. Nanostructures make an excellent candidate as the sensing material in terms of sensitivity for variety of reasons: (1) An increased surface area leads to enhanced sensitivity for particularly small analytes where the size of nanoparticles become comparable to those analytes [13, 14]. (2) Improved direct electron transfer yields an increased sensitivity and an enhanced detection limit [12]. (3) The size of nanostructure particles is close to the Debye length which is known to increase sensor sensitivity [15].

While nanostructures can be synthesized using variety of advanced materials, nanostructured metal oxides (NMOs) were chosen as the focus of this review article since NMOs in biosensors has drawn significant attention in the last decade. In the case of NMO materials, the above mentioned advantages of nanostructures directly apply. Furthermore, the surface morphology and the shape of nanostructures can simplify modification of NMO-related fabrication processes. These processes include but not limited to SILAR (Successive Ionic Layer Adsorption and Reaction) [16], chemical bath deposition (CBD) [17], chemical vapor deposition (CVD) [18], sol–gel [19], and pulsed layer deposition (PLD) [20]. This variety of fabrication methods allow easy changes to the nanostructure shape and geometry making NMOs very attractive materials for biosensing devices [21].

The bandgap value of NMOs falls within the semiconducting region, allowing them to be used in sensors [22, 23]. The sensing properties of NMOs depend on their semiconductor type. n-type and p-type semiconductors behave differently in terms of receptor functions, conduction paths, and sensing mechanisms due to different types of majority charge carriers. Common p-type metal oxide semiconductors include copper oxide (CuO), cuprous oxide (Cu_2O), nickel oxide (NiO), cobalt oxide (CoxOx), and manganese oxides (Mn_xO_y) whereas n-type NMOs include tin oxide (SnO_2), zinc oxide (ZnO), titanium oxide (TiO_2), and iron oxides (Fe_xO_y) [24, 25]. One of the biggest challenges remaining in the application of NMOs is the high tendency of adhesion and aggregation of NMOs due to high surface energy [26].

In this review paper, we have focused on particularly glucose, urea and uric acid, and cholesterol sensors that utilize NMOs. We have summarized each sensor in tables by categorizing them with the NMOS types. Furthermore, we devised a method of visual representation of the summarized table using figures where sensitivity and linear range were presented. Each section of the review offers extensive literature review and a quality discussion on different applications and NMOS types.

2. Applications of NMOs in Biosensors

This current review focuses on NMOs that are utilized in electrochemical biosensing applications. We have organized this review by having separate sections for glucose, urea/uric acid, and cholesterol sensors in sections 2.1, 2.2, and 2.3, respectively. Furthermore, we have combined some other types of sensing applications in section 2.4 which included hydrogen peroxide, DNA, and some unconventional sensing approaches. We have summarized the articles in respective tables where we listed their sensing properties such as sensitivity, limit of detection, detection range, and Michaelis–Menten Constant (Kmapp) value. We have also included stability parameters in tables such as duration, relative standard deviation (RSD), and long term stability. An alternative way of presenting the tables was devised where sensitivity and linear range were plotted.

2.1. Glucose Sensors

Glucose sensing has been studied since late 1970s in order to help monitor glucose levels of diabetic patients. Most chemical glucose sensing technologies rely on enzymatic reactions in which enzymes catalyze glucose oxide (GOx) generating reactions [27,28]. This method is considered a gold standard but suffers from degraded readings due to pH and temperature changes. Recently, non-enzymatic glucose sensors were developed and metal oxides proved to be one of the promising materials in the use of glucose sensing [29]. Particularly, CuO, ZnO, TiO_2, SnO_2, Cerium Oxide (CeO_2), NiO, and MnO_x have been studied for potential integration into glucose sensors [30-35]. Amperometric glucose sensors are mainly characterized through cyclic voltammograms (CVs) and electrochemical impedance spectroscopy (EIS). The main characterization parameter of the amperometric glucose sensors is the sensitivity to the glucose concentration, which is generally given in current change per mM in a square centimeter; $\mu A\ mM^{-1}\ cm^{-2}$. Sensitivity ranges between 1-5000 $\mu A\ mM^{-1}\ cm^{-2}$. Also, the detection range is one of the important parameters which determines the lower and upper glucose concentrations that the sensor can detect. It is known that the clinical blood glucose levels are between 4.4 mM and 6.6 mM.

CuO stands out among all the other NMOs due to its intrinsic p-type semiconductor property, high stability, capability for electron transfer, and nontoxicity [36,37]. CuO based glucose sensing applications has focused primarily on synthesis and fabrication methods. The main goal is to control the physical properties of CuO nanostructures which directly affect the sensitivity and response/recovery time of glucose analytes. Utilizing Cu foil as the electrode and the substrate, Li et. al. developed flower-like CuO nanostructures for non-enzymatic glucose sensing [38]. The sensitivity for particularly dandelion-like structures reached above 5,000 $\mu A\ mM^{-1}\ cm^{-2}$ which is much higher than traditional NMO glucose sensors. Additionally, with its wide detection range (5 µM to 1.6 mM), the sensor was tested with human serum samples and measurements agreed with hospital-used blood sugar instruments [38]. An enzymatic CuO glucose sensor was fabricated where nanostructured CuO wires, platelets, and spindles were synthesized by using one precursor. Sensor performance was tested by using carbon electrodes as the substrate and resulted in relatively low sensitivity values (62 $\mu A\ mM^{-1}\ cm^{-2}$) for a limited detection range (1 µM – 80 µM) [39]. Li et. al. produced crystallized leaf-like CuO nanostructures for the development of an amperometric glucose sensor with a sensitivity of 246 $\mu A\ mM^{-1}\ cm^{-2}$ [40]. Although the detection range was relatively narrow (1 µM – 170 µM), sensor responded the human serum levels (up to 40 µM) well and it was stable for 90 days. A wide linear detection range (4 µM to 8 mM) was achieved by Wang

et. al. through CuO nanorods and flowers [41]. The sensitivity values for flowers like CuO structures reached up to 709.52 μA mM^{-1} cm^{-2}. Kim et. al.'s proposed rose-like CuO nanostructures reached even higher glucose detection range (0.78 μM to 100 mM) with a high sensitivity (4640 μA mM^{-1} cm^{-2}) [42]. These structures remained stable as long as 42 days.

Cu_2O nanostructures were also used for glucose sensing. Cu_2O has a cubic structure rather than a monoclinic crystal structure as CuO which affects its sensing performances significantly. Khan et. al.'s shuriken-like Cu_2O nanostructures exhibited a 6 decades wide range of sensitivity (0.01 μM to 11.0 mM) with an extremely low detection limit (35 nM) [43]. Moreover, they performed rigorous selectivity analysis of glucose to lactose, fructose, mannose, ascorbic acid, and uric acid, which makes Cu_2O a very promising NMO for glucose sensing.

Zinc oxide (ZnO) is an important member of II-VI group semiconductors. Nanostructured ZnO structures are nontoxic, chemically stable and biocompatible in most cases, which made them attractive for biomedical research, particularly for sensors. An early study on ZnO based glucose sensors explored using ZnO nanocomb structures functionalized with glucose oxidase that exhibited a more than 2 decades of linear range (0.02 mM – 4.5 mM) with a sensitivity of 15.33 μA mM−1cm−2 [44]. However, selectivity or stability analysis were not performed. Similarly, glucose oxidase adsorbed ZnO nanorods and nanoplates showed about 2 decades of linear sensitivity range (0.1 mM – 9 mM) with good selectivity to absorbic acid, dopamine, and fructose [45]. Tarlani et. al. obtained different morphologies of nanostructured ZnO such as rod, powder, particle, cube, rock candy-like, sheet, sphere, brain-like, groundnut-like and pussy willow-like by utilizing aminoacids [46]. All these structures formulated by multi-walled carbon nanotubes on glassy carbon electrode and were used to detect glucose. The best sensitivity was obtained from the spherical ZnO nanostructures (64.29 μA mM^{-1} cm^{-2}) with a relatively short linear range (1 mM – 10 mM). The selectivity against dopamine, uric acid and fructose were found to be satisfactory and the sensors were stable over 30 days. Au nanostructures were functionalized using three-dimensional hierarchical ZnO nano-architectures by Fang et. al. which resulted a short linear range (1 mM – 20 mM) [47]. Selectivity was studied with good results against dopamine, uric acid and fructose. The stability of sensors was tested for 15 days. Also, human serum samples were tested with satisfactory results. ZnO hexagonal prisms with nickel nanostructures were used for non-

enzymatic glucose sensing by Yang et. al. with close to 3 decades of linear range (10 μM to 8.1mM) [48]. Selectivity to distracter chemicals were good and the sensors were stable over 30 days. In order to detect glucose levels from sweat, Munje et. al. developed a wearable, flexible electrochemical glucose sensor based on sputtered ZnO electrodes [49]. Although the linear range was not very wide, sensors were able to detect as low as 0.6 μM of glucose (sweat glucose levels are much lower than blood glucose levels).

Titanium Oxide (TiO_2), a wide bandgap (Eg = 3.2 eV) and intrinsically n-type semiconductor, has been extensively investigated as a glucose biosensor. Luo et. al. investigated the glucose sensing properties of highly dispersed titanium dioxide nanoclusters synthesized on reduced graphene oxide [50]. Sensitivity levels of 35.8 μA mM^{-1} cm^{-2} were observed. Selectivity experiments were carried out with no apparent interference effects and the response time of the sensor was also measured to be less than 10 seconds. Jang et. al. built a glucose biosensor based on the adsorption of glucose oxidase at a TiO_2-Graphene nanocomposite electrode with relatively low sensitivity (6.2 μA mM^{-1} cm^{-2}) and a short linear range (1 mM – 8 mM) [51]. However, their synthesis of electrodes (colloid dispersion) was simple and easy to repeat. A non-enzymatic glucose sensor was built by depositing cobalt rich cobalt–copper alloy nanostructures on vertically aligned TiO_2 nanotube arrays that resulted quite high sensitivity values (4651.0 μA mM^{-1} cm^{-2}) [52]. The linear range was up to 12 mM (lower limit was not mentioned in the article). A wide range of interferents and real human serum were tested with good results.

Nickel Oxide (NiO), a p-type semiconductor, was also studied as a biosensing material. Liu et. al. produced vertically aligned 3D porous NiO nanosheets on graphite disks by using chemical bath deposition method [53]. This non-enzymatic glucose sensor had good anti-interference performance against Uric Acid and Absorbic Acid and a fast response time (<1 s). Linear range was up to 10 mM with a moderate sensitivity value (36.13 μA mM^{-1} cm^{-2}) and the sensors were stable up to 14 days. Blood serum tests were also conducted with satisfactory results. Another non-enzymatic NiO glucose sensor was produced by Prasad et. al. based on NiO nanostructures decorated multi-walled carbon nanotubes [54]. Their sensor demonstrated moderate sensitivity levels (122.15 μA mM^{-1} cm^{-2}) up to 9 mM and higher sensitivity levels for lower concentration ranges (122.15 μA mM^{-1} cm^{-2} for 1-200 μM). Sensors anti-interference and human serum response were tested successfully. A relatively high sensitive (1138 μA mM^{-1} cm^{-2}) NiO nanosheets were

prepared with graphene oxide films for non-enzymatic glucose sensing by Zhang et. al [55]. The detection limit was found to be 0.18 µM but the linear range was too low (1 µM - 0.4 mM) to be used for human glucose testing even though it showed good anti-interference and stability performance. NiO thin films were magnetron sputtered on ITO substrates by Garcia et. al. that exhibited high sensitivity (1680 µA mM^{-1} cm^{-2}), stability over 2 months, and anti-interference performance against variety of interferents [56]. However, the linear range was relatively narrow (0 - 1.0 mM) that limits the real-life application of this sensor.

Other metal oxides were also experimented for the glucose sensing applications. A conductometric Tin Oxide (SnO_2) sensor with clinical linear range [57], an enzymatic, nanoporous Cerium oxide (CeO_2) again with a clinical range and more than 6 weeks of shelf life [58], and Manganese Oxide (Mn_xO_y) [59, 60] were experimented with some promise.

Table 1 shows representative glucose sensors with different metal oxide structure or types for glucose sensors. Limit of detection, on the other hand, can be considered as the resolution. Sensitivity values were also provided for comparison. Furthermore, in order to provide an insight on the stability of each device, duration in days, relative standard deviation in percentage, and the retention in percentage were also provided in Table 1.

In order to show the correlation between the linear range and the sensitivity with respect to different metal oxides, Figure 1 was created by using the values from Table 1. Each vertical line represents one particular article's performance in terms of linear range where the horizontal axis gives the sensitivity value that was obtained for that particular sensor. It is obvious that CuO and ZnO have higher sensitivity values with relatively wide linear range. TiO_2 sensors do not provide a wide linear range and ZnO seems to have low sensitivity values. Although limited samples, SnO_2 and Mn_xO_y did not show superior characteristics. However Cu_2O glucose sensor provided the best sensitivity for the given wide linear range.

It is important to note here that the full functionality of a glucose sensor needs to be evaluated by looking into anti-interference performance against lactose, fructose, mannose, ascorbic acid, uric acid. Also, testing the device for real human blood serum gives the sensor a direct application opportunities hence should be included in any research. Parameters such as stability and response time are also important to measure. The authors believe that CuO and NiO are the most promising metal oxides to be utilized in glucose sensing.

2.2. Urea and Uric Acid Sensors

Uric acid is a product of the metabolic breakdown of purines, which are found in cells and food products. Uric acid levels in blood are between 140 – 430 μM and abnormal uric acid values can lead to gout and kidney stones [61]. Traditionally, uric acid tests are conducted either via blood tests or through urine samples using color changing strips. There have been attempts to develop smaller scale uric acid sensing devices to lower the cost and applicability of uric acid measurements. Most designs focused on conductometric measurements using advanced materials to construct the electrodes in enzymatic or non-enzymatic sensors [62-64]. Urea, on the other hand, is a product of urea cycle occurring in human livers and kidneys where ammonia (NH_3) is dissolved into ureasol ($(NH_2)_2CO$) [65]. Urea is considered a waste product and excreted via urine and sweat. Urea levels are within 2.5 – 7.5 mM in blood and abnormal urea levels can lead to kidney and liver problems such as renal failures and uremia (excessive urea in blood) [66].

Urea sensors: Vertically aligned ZnO nanorods were used as urea sensors within the linear range of 0.001–24.0 mM but relatively low sensitivity (41.64 μA mM^{-1} cm^{-2}) [67]. However, sensors showed good anti-interference capability and stability. Highest sensitivity value for urea sensors was achieved by Tak et. al. by exploiting the large surface to volume ratio of flower-like ZnO nanostructures in a range of 1.65 mM to 16.50 mM [68]. Sensitivity value was determined to be 132 μA mM^{-1} cm^{-2} with a tested response time of 4 s. However, cross-sensitivity and durability tests were not performed. An electrochemically deposited nanostructured ZnO films showed similar linear range (1.7 - 13.6 mM) but a smaller sensitivity values (40 μA/$mM^{-1}cm^{-2}$ [69].

Besides ZnO, some other NMOs were also experimented towards urea sensing such as non-enzymatic SnO2 thin films [70], very stable (6 months) but less sensitive (3.7 μA mM^{-1} cm^{-2}) enzymatic CeO_2 thin films [71], enzymatic NiO nanostructures thin films with low sensitivity (21.3 μA mM^{-1} cm^{-2}) [72], and non-ezymatic Ni/CoO films with relatively good sensitivity of 166 μA $mM^{-1}cm^{-2}$ but for a limited linear range (0.06 mM – 0.30 mM) [73].

Uric acid sensors: 3D periodic mesoporous nickel oxide (NiO) particles with crystalline walls and a moderate sensitivity (756.26 μA mM^{-1} cm^{-2}) levels were achieved for uric acid detection up to 0.374 mM [74]. However, this work did not conduct and interference studies. NiO thin films were used on platinum coated glass substrates to uric acid lebels with a relatively high sensitivity (1278.48 μA/mM) that covered the clinical human uric acid levels (0.05 mM - 1.0mM) [75]. Same

group worked on growing CuO thin films on platinum coated glass substrates for uric acid measurements with a a relatively high sensitivity 2700 μA $mM^{-1}cm^{-2}$ [76]. The sensor was stable for more than 14 weeks and selective to glucose, cholesterol, urea, ascorbic acid, and lactic acid.

Table 2 summarizes the specifications of some urea sensors based on metal oxide structures. Similar to Table 1, limit of detection, detection range, sensitivity and K_{mapp} values were provided along with the specific metal oxide structures and stability parameters. Here, it must be noted that some values were converted from mg/dL to mM by using the molar mass of urea (60.056 g/mol).

Figure 2 shows the overall summary of each sensor's linear range and sensitivity. It can clearly be seen that uric acid sensors tend to have a higher sensitivity. Although the linear range seems limited, the devices are suitable for the clinical blood uric acid levels. Also, CuO and NiO films provide a better sensitivity. It must be noted here that all uric acid sensors based on NMOs were thin films. Urea sensors, on the other hand, are mostly achieved through enzymatic reactions and with low sensitivity values. Linear ranges are about the same for each sensor but a composite NiO/CoO film provided significantly higher sensitivity.

2.3. Cholesterol Sensors

Cholesterol is an organic molecule that is synthesized by the human body to maintain the cell membrane temperature. High levels of cholesterol can narrow the arteries and increase the risk of heart disease. ZnO was one of the most used materials for cholesterol sensing. ZnO nanorods on Silver electrodes for cholesterol sensing reached a sensitivity of 74.10 μA mM^{-1} cm^{-2} at a detection limit of 0.0015 μM [77]. Response time was less than 2 s and nanorods were stable for over 45 days. Flower-shaped ZnO nanorods were also fabricated with a sensitivity of 61.7 μAμM^{-1} cm^{-2} at a response time less than 5 s [78]. However, this structure was tested for only very low levels of cholesterol (1.0–15.0 μM), which would not make it suitable for human serum samples [78]. ZnO nanotube arrays on Si/Ag substrate were fabricated enzymatic cholesterol sensors [79]. The sensitivity value was 79.40 μA$mM^{-1}cm^{-2}$ and a linear range of 1.0 μM - 13.0 mM. A fast response time (~2 s) and a low detection limit (0.5 nM) were reported and the sensors were tested with human blood serum [79]. A solution-gated, enzymatic, field-effect-transistor by using vertically aligned ZnO nanorods were realized with reported selectivity to electroactive agents [80]. Linear

range was 0.001–45mM with a moderate sensitivity (10 μA mM^{-1} cm^{-2}), and a detection limit (0.05 mM) were obtained [80]. Wang et al aimed to use a novel method for the fabrication of gold/platinum hybrid functionalized ZnO nanorods and multi-walled carbon nanotubes. They achieved a moderate linear range (0.1 μM - 759.3 μM), a low detection limit (0.03 μM), but a low sensitivity (26.8 μA mM^{-1} cm^{-2}) values [81]. One alternative to increase the sensitivity of ZnO based cholesterol sensors is to create composite matrixes. One good candidate is CuO, which offers higher sensitivity with a drawback of lower stability values. A ZnO–CuO composite matrix on to indium tin oxide substrates via pulsed laser deposition resulted in a sensitivity of 760 μA mM^{-1} cm^{-2} and a 5 s response time [82]. The concentration range of the composite matrix fell between 0.5 mM to 12mM.

Different metal oxides were experimented in order to reach high sensitivity values. Ansari et al deposited a chitosan-tin oxide (SnO_2) nanobiocomposite film onto ITO substrates for enzymatic cholesterol detection that resulted in a high sensitivity value (1300 μA mM^{-1} cm^{-2}) [83]. The sensor retained 95% of its enzyme activity after 4 – 6 weeks. Chitosan was also used in CeO_2 NMOs to increase the stability. The physiosorption technique was utilized to obtain a linear detection range of 0.2 – 10.4 mM with a sensitivity of 1807 μA mM^{-1} cm^{-2} for Chitosan stabilized CeO_2 films, which were stable over 60 days and exhibited good selectivity [84]. Another CeO_2 films were fabricated using sol-gel method with a very high sensitivity (80000 μA mM^{-1} cm^{-2}) with a wide linear detection range (0.2 – 10.4 mM) [85]. NiO and MnO2 were also experimented to develop cholesterol sensors but the sensitivity values were quite low [86, 87].

Table 3 summarizes the limited literature on nanostructured metal oxide based cholesterol sensors in a similar fashion of Table 1 and 2. Similar to some urea sensors, some cholesterol sensors' units were converted from mg/dL to mM by using the molar mass of the cholesterol (386.65 g/mol). It can be seen from Table 3 that ZnO was the most experimented metal oxides. It is promising to create composite structures with CuO and ZnO to increase the sensitivity values. Although very high sensitivity values were obtained for CeO_2, it must be noted here that these sensors are rely on enzymatic reactions and would be affected by environmental conditions such as pH and temperature. Figure 3 also shows the summary of the sensitivity values for cholesterol sensors.

2.4. Other Sensor Applications

Although glucose, uric acid, and cholesterol are the most investigated biological sensors using metal oxide nanostructures as a platform, there were several other metal oxide-based sensing systems worth mentioning in this review article.

Hydrogen peroxide (H_2O_2) sensing is another popular application of metal oxide nanostructures. Copper(II) oxide nanorod bundles modified by basal plane pyrolytic graphite electrode were developed by McAuley et al [88]. The limit of detection and sensitivity values were measured to be 0.2 μM with a sensitivity of 0.15 μA/μM [88]. Multi walled carbon nanotubes were combined with CuO nanoflower-modified electrodes by Zhang et al for H_2O_2 detection with detection range of 0.5 – 82 mM and sensitivity value 0.16 μM [89]. Gu et al produced gold electrodes modified three-dimensional (3D) CuO flower-like nanostructures for H_2O_2 sensing with a detection range of 50 - 750 μM and a sensitivity of 116·1 μA/mM [90]. ZnO micro-pompons were simultaneously deposited with gold electrodes by Zhou et. al. with a linear range of 0.2 - 3.4 mM, sensitivity of 1395.64 $\mu AmM^{-1}cm^{-2}$, and a response time of less than 4 s [91]. Chirizziet et.al. proposed an approach based on the immobilization of cupric/cuprous oxide core shell nanowires that resulted a sensitivity of 2.793 μA/mM with a detection limit of 0.35 μM [92]. Porous Cerium dioxide nanostructured films were also used by Yagati et al as H_2O_2 sensing with a limit of detection 0.6 μM and linearity up to 3mM [93]. The response time of the sensor was measured to be 8 s with a sensitivity of 5.4 $\mu AmM^{-1}cm^{-2}$ [193]. Gold nanoparticles aggregates were assembled with manganese dioxide (MnO_2) nanoparticles by Li et al for a hydrogen peroxide sensing range of 0.78 μM to 836 μM with a sensitivity of 53.5 $\mu A/cm^2$ and a detection limit of 46.8 nM [94]. Bracamonte et. al. used CeO_2 to detect H_2O_2. The sensitivity range was obtained as 160 $\mu A\ cm^{-2}\ mM^{-1}$ [95].

Sequence-specific target DNA detection was explored by Yuzhong et al by introducing gold nanoparticles onto the surface of CuO nanospindles deposited onto glassy carbon electrodes [96]. With a good selectivity, proposed DNA biosensor has a linear concentration range of 0.1 pM to 1 μM with a detection limit of 35 fM which could distinguish a single-mismatched target DNA [96]. Another DNA sensor was realized by using nanostructured zirconium oxide with Escherichia coli (*E. coli*) single stranded DNA with a detection range of 10^{-6} to 10^6 pM [97]. Another DNA type biosensor was developed for detection of bacterial meningitis by using flower-like ZnO nanostructures Pt/Si substrates, which exhibited a sensitivity of 168.64 $\mu A/ng/\mu l/cm^2$ with a detection limit of about 5ng/μl [98].

Vibrio cholera detection was employed by using nanostructured magnesium oxide films on ITO glass substrates [99]. Patel et al reported a cholera detection sensitivity of 16.80 nA/ng/cm^2, fast response time (less than 3s), and linearity between 100 to 500 ng/L that is stable for 120 days [99]. CuO nanoparticles were also explored for sweat electrolyte sensing via resistive measurement techniques by Sahin et al using artificial sweat as the analyte [100, 101]. Their work centered around sodium and potassium doping and annealing effects of CuO fabrication [101]. Roychoudhury et al developed a dopamine biosensor using nickel oxide nanoparticles demonstrating a sensitivity of 0.06 μA/μM in a linear range of 2 μM to 100 μM with a detection limit of 1.04 μM [102]. The sensor had a response time of 45 s with long shelf life of 45 days [102]. Azzouzi et al produced an amperometric biosensor based on graphene oxide for the detection of L-lactate tumor biomarker with a linear detection of 10 μM–5 mM, sensitivity of 154 μA/mM/cm^2, and a detection limit of 0.13 μM. [103].

3. Conclusion and future perspectives

In this review, we focused on most common sensing analytes such as glucose, urea and uric acid, and cholesterol by organizing each section with different types of NMOs. Corresponding tables for each section summarized the sensing parameters of the devices. Sensitivity, limit of detection, detection range, K_{mapp} value, stability duration, relative standard deviation, and retention, and the sensing type were provided for each article where available. Some other applications of NMOs such as hydrogen peroxide and DNA sensing were provided as well as some unconventional sensing approaches. Representative figures from literature were used to give a visual illustration of the data and nanostructures.

It can be seen from our extensive literature review that there is a wide variety of techniques utilized to incorporate NMOs in electrochemical biosensors. Those who are interested in working on NMOs should first decide on the technique to move forward. Like any biosensors, sensitivity, selectivity, response time, and stability are main characteristics to determine if the proposed approach is valuable. Although new advances in technology allow more sophisticated manufacturing methods, there is still some "art" in producing consistent films. One should be looking into more robust, repeatable manufacturing schemes. Biosensors are ultimately to be used in clinical applications.

Currently, NMOs have yet to be explored fully for their capabilities in real-life scenarios with application-specific issues such as durability, energy efficiency, and environmental conditions. Manufacturing NMO based biosensors should also be explored in terms of accuracy, calibration techniques, and robustness. Also, sample matrices that electrodes are applied to are very important and directly affects the sensing properties. Therefore, a detailed study should be carried out to investigate the effects of fabrication methodologies. It is also known that every time a film is used for sensing, the surface chemistry is altered. Therefore, a careful study of the sensors should be done by looking into the isoelectric point (IEP) of the surface to make sure the surface still stays active.

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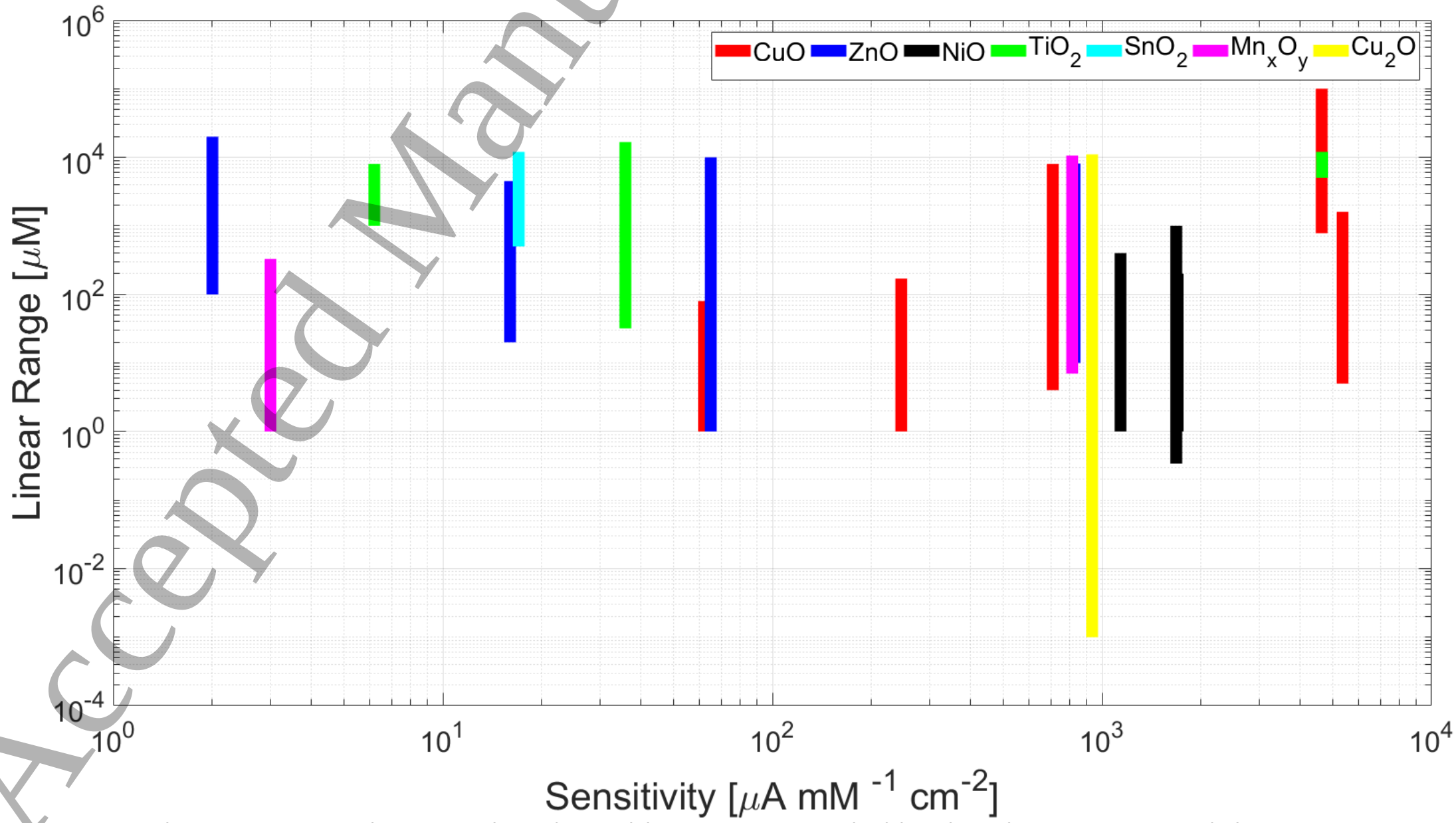

Figure 1: Glucose sensors that were listed in Table 1 were compiled by their linear range and the sensitivity. Each vertical line represents the linear range at a particular sensitivity that was reported for that particular work.

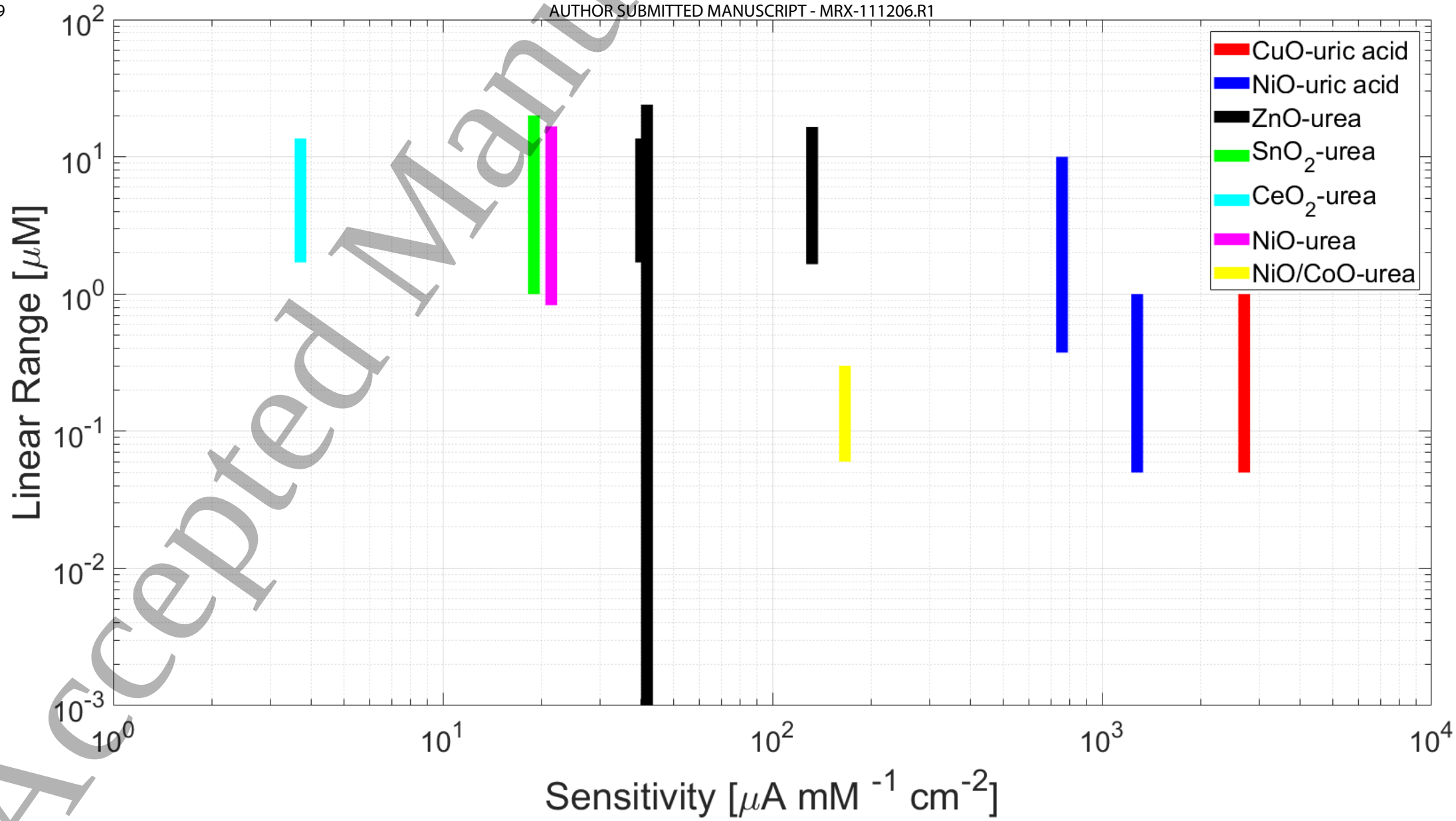

Figure 2: Urea and uric acid sensors that were listed in Table 2 were compiled by their linear range and the sensitivity. Each vertical line represents the linear range at a particular sensitivity that was reported for that particular work.

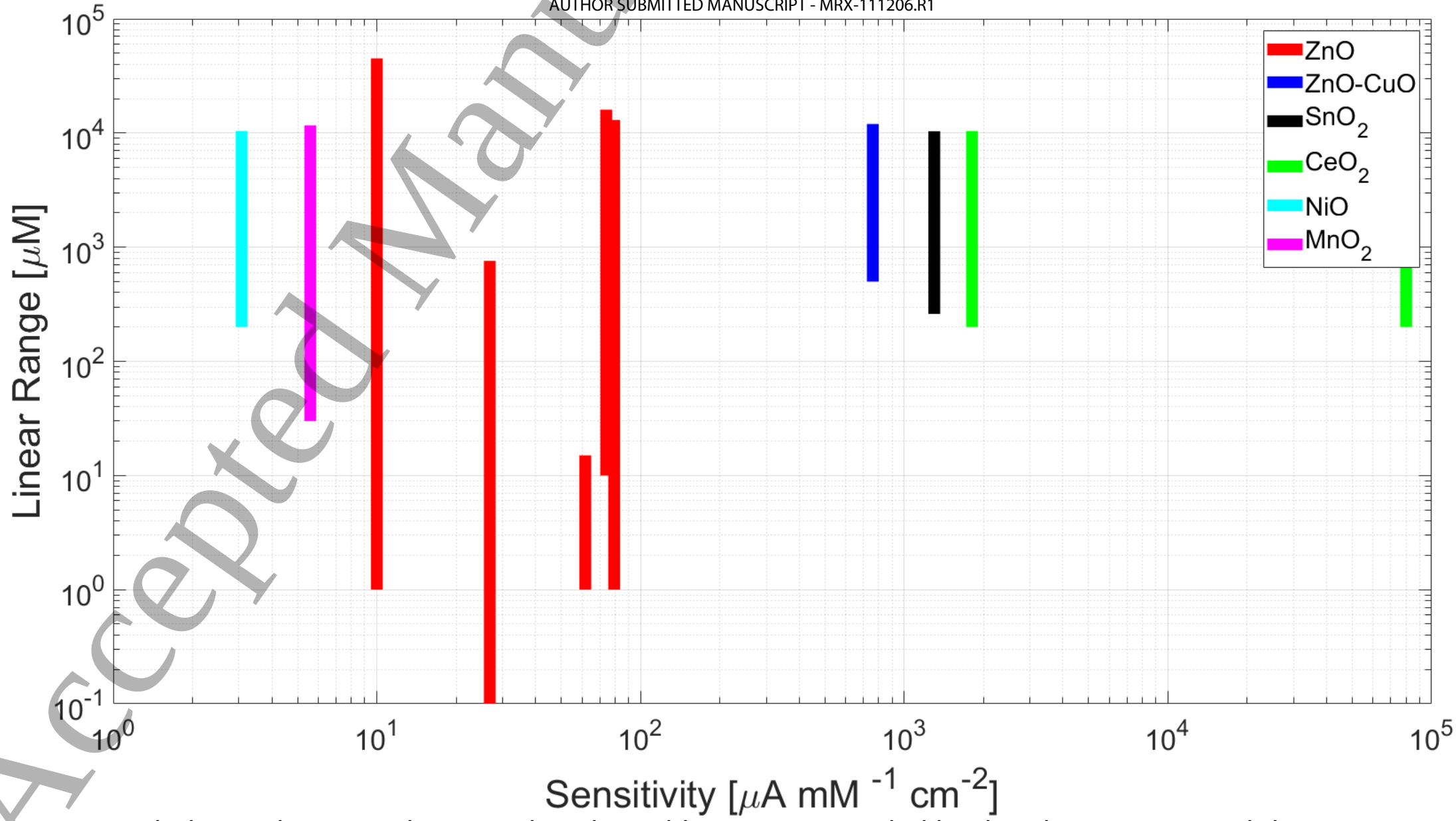

Figure 3: Cholesterol sensors that were listed in Table 3 were compiled by their linear range and the sensitivity. Each vertical line represents the linear range at a particular sensitivity that was reported for that particular work.

Structure Name	Type	Detection Range	Limit of Detection (LOD)(µM)	Michaelis–Menten Constant (K_{Mapp}) (mM)	Sensitivity value (µA $mM^{-1}cm^{-2}$)	Stability Duration (Day)	Stability RSD (%)	Medium	Human Serum	References
CuO	Chrysanthemum-like, candock-like, and dandelion-like	0.005 – 1.6 mM (for dandelion-like)	1.2 (for dandelion-like)		5368 (for dandelion-like)	30	3.5	NaOH	Yes	[38]
CuO	Nanospindles	1.0 - 80 µM	1		62			Phosphate buffer solution (PBS)	No	[39]
CuO	Leaf like	1.0 - 170 µM	0.91	0.29	246	90	3.28	PBS	Yes	[40]
CuO	Nanorods and flowers like	4 µM to 8 mM	4		709 (Flowers like) 371 (Nanorods)			NaOH	No	[41]
CuO	Rose like	0.78 - 100 mM	390		4640	42		PBS	No	[42]
Cu_2O	Shuriken-like	0.01 µM - 11.0 mM	0.035		933	80	2.7	NaOH	Yes	[43]
ZnO	Nanocombs	0.02 – 4.5 mM	20	2.19	15.33			PBS	No	[44]
ZnO	Nanorods, nanoplates	0.1 to 9 mM	1.94	3.12	1.94			PBS	No	[45]
ZnO	rod, powder, particle, cube, rock candy-like, sheet, sphere, brain-like, groundnut-like and pussy willow like	1 to 10 mM	820		64.29 (for spherical)	30	0.39	PBS	No	[46]
ZnO	Three-dimensional hierarchical	1.0 - 20 mM	20		1.4	15	5.3	PBS	Yes	[47]
ZnO	Hexagonal prisms	0.01 to 8.1mM	0.28		824.34	30	1.32	KOH	Yes	[48]
ZnO	Sputtered electrodes	0.6 µM to 11 mM*	6 µM*		14.50			PBS	Yes	[49]
TiO_2	Nanocluster	0.032 mM – 1.67 mM	4.8	0.81	35.80		5.6	PBS	No	[50]
TiO_2	TiO_2- GR nanocomposite	1 mM – 8 mM			6.2		5.6	PBS	No	[51]
TiO_2	Nanotube arrays	1 – 12 mM	0.60		4651.0	90	8	NaOH	Yes	[52]
NiO	3D porous nanosheets	Up to 10 mM	0.90		36.13	14	6	NaOH	No	[53]
NiO	Decorated multi-walled carbon nanotubes	1 - 200 µM Up to 9 mM	0.011 31		1696 122.15	21	3.5	NaOH	Yes	[54]
NiO	Nanosheets	1 µM - 0.4 mM			1138	10	3.8	NaOH	No	[55]

NiO	Thin film	0 - 1.0 mM	0.34		1680	61	2.37	NaOH	Yes	[56]
SnO_2	Nanostructured	0.5–12 mM.			16.90	10	10	PBS	No	[57]
CeO_2	Nanoporous	1.39 - 8.33 mM*		1.01		70		PBS	No	[58]
MnO_x	Nanorod	0.007 - 10.6 mM	2.7		811.8	36	5.5	NaOH	Yes	[59]
Mn_3O_4	Nanostructures	1.0 - 329.5 µM	0.50		2.6		5.4	NaOH	No	[60]

Table 1: Representative glucose sensors implemented using nanostructured metal oxides.

Structure Name	**Type**	**Detection Range**	**Limit of Detection (LOD)(µM)**	**Michaelis–Menten Constant (KMapp) (mM)**	**Sensitivity value (µA $mM^{-1}cm^{-2}$)**	**Stability Duration (Day)**	**Stability RSD (%)**	**Medium**	**Human Serum**	**References**
ZnO	Nanorods	0.001 - 24.0 mM	10.0	0.3280	41.64	14	2	PBS	No	[67]
ZnO	Flower-like	1.65 - 16.50 mM	7590	0.190	131.98	84	1.2	PBS	Yes	[68]
ZnO	Nanostructure	1.7 to 13.6 mM*	2300*	1.02*	40 *			PBS	No	[69]
SnO2	Thin film	1 - 20 mM	600		18.90			PBS	No	[70]
CeO2	Thin film	1.7 to 13.6 mM*	16.7*	1.04*	3.7*	180 *		PBS	No	[71]
NiO	Nanostructure	0.83 – 16.65 mM	880	0.34*	21.33	140		PBS	No	[72]
Nickel/cobalt oxide	3D graphene nanocomposite	0.06 mM – 0.30 mM*	5 mM*		166*			NaOH	No	[73]
NiO	Nanostructure	0.374 mM-10.0 mM.	0.005		756.26			NaOH	No	[74]
NiO	Thin film	0.05 mM - 1.0mM	110	0.17	1278.48	120		PBS	Yes	[75]
CuO	Thin film	0.05 - 1.0 mM.		0.12	2700	98		PBS	Yes	[76]

* Original units (mg/dL) were converted to molarity using the molar mass of glucose (180.156 g/mol).

Table 2: Representative urea and uric acid sensors implemented using nanostructured metal oxides.

* Original units (mg/dL) were converted to molarity using the molar mass of urea (60.056 g/mol).

Structure Name	Type	Detection Range	Limit of Detection (LOD) (μM)	Michaelis–Menten Constant (K_{Mapp}) (mM)	Sensitivity Value (μA $mM^{-1}cm^{-2}$)	Stability Duration (Day)	Stability RSD (%)	Stability Retention (%)	Medium	Human Serum	References
ZnO	Nanorods	0.01-16 mM	0.0015	0.16	74.10	45		95.0	PBS	No	[77]
ZnO	Flower-shaped	1.0 - 15.0 μM	0.012	2.57	61.7	32		83.7	PBS	No	[78]
ZnO	Nanotube	1 μM - 13 mM	0.0005		79.40	60		93	PBS	Yes	[79]
ZnO	FET	0.001 - 45mM	50		10	30		95	PBS	Yes	[80]
ZnO	Nanorods	0.1 - 759.3 μM	0.03	1.84	26.8	90		90	PBS	No	[81]
CuO-ZnO	Composite matrix	0.5-12 mM		1.8	760	98	1.4		PBS	Yes	[82]
SnO_2	Nanobicomposite	0.26 – 10.36 mM	129.3*	3.8	1300*	56		90	PBS	No	[83]
CeO_2	Nanocomposite	0.2 – 10.4 mM*	129.3*	0.09*	1807 *	70		65	PBS	No	[84]
CeO_2	Nano-structured	0.2 – 10.4 mM *	258.6*	2.08	80000*				PBS	No	[85]
NiO	Nanostructured	0.2 – 10.4 mM*	1128*	0.67	3.07*				NaOH	No	[86]
MnO_2	Nanorods	0.03 - 11.66 mM	2.07		5.59	90		65	NaOH	No	[87]

Table 3: Representative cholesterol sensors implemented using metal oxides.

* Original units (mg/dL) were converted to molarity using the molar mass of cholesterol (386.65 g/mol).