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Ali Kemal Yetisen

Holographic Sensors

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Author
Dr. Ali Kemal Yetisen
Department of Chemical Engineering
and Biotechnology
University of Cambridge
Cambridge
UK

Supervisor
Prof. Christopher R. Lowe
Department of Chemical Engineering
and Biotechnology
University of Cambridge
Cambridge
UK

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2. Yetisen AK, Montelongo Y, da Cruz Vasconcellos F, Martinez-Hurtado JL, Neupane S, Butt H, Qasim MM, Blyth J, Burling K, Carmody JB, Evans M, Wilkinson TD, Kubota LT, Monteiro MJ, Lowe CR (2014) Reusable, robust, and accurate laser-generated photonic nanosensor. Nano Lett 14 (6):3587–3593
3. Yetisen AK, Butt H, da Cruz Vasconcellos F, Montelongo Y, Davidson CAB, Blyth J, Chan L, Carmody JB, Vignolini S, Steiner U, Baumberg JJ, Wilkinson TD, Lowe CR (2014) Light-Directed Writing of Chemically Tunable Narrow-Band Holographic Sensors. Adv Opt Mater 2 (3):250–254
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6. Tsangarides CP, Yetisen AK, da Cruz Vasconcellos F, Montelongo Y, Qasim MM, Wilkinson TD, Lowe CR, Butt H (2014) Computational modelling and characterisation of nanoparticle-based tuneable photonic crystal sensors. RSC Adv 4 (21):10454–10461
7. Yetisen AK, Akram MS, Lowe CR (2013) Paper-based microfluidic point-of-care diagnostic devices. Lab Chip 13 (12):2210–2251

Supervisor's Foreword

As the world's population surpasses 7 billion, healthcare systems around the word face unique challenges. North America, Western Europe and Japan have ageing populations, which are a growing concern due to the increasing demand for long-term care limited by the shortages in healthcare workers. On the contrary, the developing world is populated with younger inhabitants; however, 55 % of the inhabitants of the developing world live in rural regions, where infrastructure is scarce and healthcare equipment is outdated. Unsurprisingly, the developing world countries face healthcare challenges to protect their population from infectious and non-communicable diseases. Hence, these global healthcare trends require efficient medical services and technologies that can meet the unfulfilled demand of ever-growing populations.

At the heart of the healthcare systems is screening large populations to monitor high-risk individuals and develop epidemiological strategies to timely mitigate emerging epidemics. When diseases are diagnosed at an early stage, the treatment is often simpler and more likely to be effective. Hence, the innovation in rapid, accurate diagnostic devices with connectivity has the potential to reduce the burden on the healthcare systems and patients worldwide. In their development, point-of-care diagnostic devices play a unique role since they are lightweight, portable and can be made readily available to healthcare workers and patients. Monitoring conditions and diseases rapidly at point-of-care offers unique opportunities in personalised medicine, which may allow optimisation of therapies, and subsequently produce improved treatment options. Such portable diagnostics can also allow efficient management of chronic diseases, where frequent measurements and treatments are required. In the developing world, low-cost diagnostics can reach underserved regions and reduce the poverty-related diseases to empower communities.

The development of point-of-care diagnostic devices concerns both the study of sensors and readout devices, and their clinical evaluation and the social context of use. These devices need to be user-friendly, fool-proof, lightweight, have a long shelf life and offer connectivity with emerging mobile devices. However, commercial sensors are complicated by the power-consuming electronics and custom readout devices, which increase the cost per diagnosis. Many colorimetric tests result in erroneous results due to subjective interpretation and have limitations in colorimetric range, in which the colour code differs from one assay to another. The development of an easy-to-interpret, colorimetric and quantitative sensing platform can standardise the readouts for visual interpretation, and facilitate simultaneous detection of conditions and diseases while also offering the possibility to quantify the assay by smartphones and wearable devices.

Ali Yetisen is a polymath whose research spans both physical and social sciences including point-of-care diagnostics, micro/nanofabrication, optical devices, microfluidics, smartphone apps, commercialisation, entrepreneurship, patent law and FDA regulations. His doctoral thesis makes a contribution to the development of reusable colorimetric optical sensors for applications in point-of-care diagnostics. His thesis harnesses laser-light writing in functionalised hydrogels for the production of holograms that allow quantification of analytes in aqueous solutions. Holographic sensor development approaches outlined include silver-halide chemistry, laser ablation and photopolymerisation. The fabricated sensors allow quantification of pH, organic solvents, metal ions and glucose. The present work is supplemented with computational simulations to lay a foundation for the laser writing techniques and principle of operation of the sensors to enhance our knowledge of how hydrogel-based sensing materials function. For example, the thesis describes the development of a kinetic theory for the hydrogel-based sensors in order to reduce the readout time. The work also shows a clinical trial to test the performance of the holographic sensors for the analysis of glucose in the urine samples of diabetic patients. In the development of readout technologies, the thesis demonstrates a smartphone application for the quantitative analysis of various colorimetric pH, protein and glucose assays. The final chapter of the thesis critically reviews the efforts in holographic sensor development, points out the limitations and draws guidelines for the future work.

This thesis not only shows a viable strategy for the fabrication and optimisation of holographic sensors in the entire visible spectrum, but it also demonstrates new insights into their functioning. The findings of this thesis provide a sound basis for the development of optimised holographic sensors as a step towards producing multiplexed diagnostic devices that can meet user requirements at point-of-care.

Cambridge, UK, November 2014 Prof. Christopher R. Lowe

Abstract

Developing non-invasive and accurate diagnostics that are easily manufactured, robust and reusable will provide monitoring of high-risk individuals in any clinical or point-of-care environment, particularly in the developing world. There is currently no rapid, low-cost and generic sensor fabrication technique capable of producing narrow-band, uniform, reversible colorimetric readouts with a high-tunability range. This thesis presents a theoretical and experimental basis for the rapid fabrication, optimisation and testing of holographic sensors for the quantification of pH, organic solvents, metal cations and glucose. The sensing mechanism was computationally modelled to optimise its optical characteristics and predict the readouts. A single pulse of a laser (6 ns, 532 nm, 350 mJ) in holographic "Denisyuk" reflection mode allowed rapid production of sensors through silver-halide chemistry, in situ particle size reduction and photopolymerisation. The fabricated sensors consisted of off-axis Bragg diffraction gratings of ordered silver nanoparticles and localised refractive index changes in poly(2-hydroxyethyl methacrylate) and polyacrylamide films. The sensors exhibited reversible Bragg peak shifts, and diffracted the spectrum of narrow-band light over the wavelength range $\lambda_{peak} \approx 500$–1,100 nm. The application of the holographic sensors was demonstrated by sensing pH in artificial urine over the physiological range (4.5–9.0), with a sensitivity of 48 nm/pH unit between pH 5.0 and 6.0. For sensing metal cations, a porphyrin derivative was synthesised to act as the crosslinker, the light absorbing material, the component of a diffraction grating as well as the cation chelating agent. The sensor allowed reversible quantification of Cu^{2+} and Fe^{2+} ions (50 mM–1 M) with a response time within 50 s. Clinical trials of a glucose sensor in the urine samples of diabetic patients demonstrated that the glucose sensor has an improved performance compared to a commercial high-throughput urinalysis device. The experimental sensitivity of the glucose sensor exhibited a limit of detection of 90 μM, and permitted diagnosis of glucosuria up to 350 mM. The sensor response was achieved within 5 min and the sensor could be reused about 400 times without compromising its accuracy. Holographic sensors were also tested in flake form, and integrated with paper-iron oxide composites, dyed filter and chromatography papers, and nitrocellulose-based test strips. Finally, a generic smartphone application was developed and tested to quantify colorimetric tests for both Android and iOS operating systems. The developed sensing platform and the smartphone application have implications for the development of low-cost, reusable and equipment-free point-of-care diagnostic devices.

Abbreviations

Å	Angstrom
AAm	Acrylamide
Ag^+	Silver ion
Ag^0	Silver metal
$AgNO_3$	Silver nitrate
$AgClO_4$	Silver perchlorate
AgBr	Silver bromide
Au^0	Gold metal
ATP	Adenosine-5′-triphosphate
ADP	Adenosine diphosphate
A^-	Conjugate base of the acid
ATMA	(3-Acrylamidopropyl)trimethylammonium chloride
3-APB	3-(Acrylamido)phenylboronic acid
2-APB	2-Acrylamidophenylboronate
5-F-2-MAPBA	2-Acrylamido-5-fluorophenylboronic acid
a.u.	Arbitrary units
~	Approximately
°C	Celsius
CL	Chemiluminescence
CCD	Charge-coupled device
CH_4N_2O	Urea
CI_{low}	Lower confidence bound
CI_{high}	Upper confidence bound
CH_3CN	Acetonitrile
CMOS	Complementary metal-oxide-semiconductor
CIE	International Commission on Illumination
CVD	Chemical vapour deposition
ø	Diameter
Λ or d	Lattice spacing between the two consecutive layers
d_{ks} and d_{kss}	Shortest distances to the sample point

D	Dimension
DBAE	2-(Dibutylamino)-ethanol
$\Delta\lambda$	Changes in Bragg peak position
Δn_0	Changes in effective refractive index
$\Delta\Lambda$	Changes in grating period
$\Delta\theta$	Changes in the Bragg angle
DMPA	2,2-Dimethoxy-2-phenylacetophenone
DCC	*N,N′*-dicyclohexylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethyl sulphoxide
DCM	Dichloromethane
DI	Deionised
DNA	Deoxyribonucleic acid
$\eta(t)$	Number of molecules bound
Ery	Erythrocyte
Eq	Equation
ECL	Electrochemiluminescence
EDMA	Ethylene dimethacrylate
ESEM	Environmental scanning electron microscopy
FT-IR	Fourier transform infrared spectroscopy
FWHM	Full width at half maximum
g	Gram
GOx	Glucose oxidase
G-6-P	Glucose-6-phosphate
G-6-PDH	Glucose-6-phosphate dehydrogenase
h	Hour
hv	Incident light
H^+	Hydrogen ion
H_z	Magnetic field strength
H_{oz}	Initial magnetic field strength
HCl	Hydrochloric acid
HeNe	Helium Neon
HEMA	2-Hydroxyethyl methacrylate
'H NMR	Proton Nuclear Magnetic Resonance
HK	Hexokinase
HA	Protonated form of the acid
HL7	Health level seven
I	Normalised intensity distribution
I_{max}	Maximum intensity
IMCI	Integrated Management of Childhood Illness
iOS	Internet operating system
IDA	Iminodiacetic acid
k	Propagation constant or Integer (see context)
kV	Kilovolt
KOH	Potassium hydroxide

L	Litre or Free macrocyclic ligand (see context)
λ_{peak}	Bragg peak of the 1st order diffracted light in vacuo
λ_h	Change in the periodicity of the multilayer structure
λ_∞	Wavelength at the infinite
λ_{shift}	Step Bragg peak shift
$\Delta\lambda$	Bragg peak shift
λ_0	Initial wavelength
LASER	Light Amplification by Stimulated Emission of Radiation
LED	Light-emitting diode
LiBr	Lithium bromide
LDH	Lactate dehydrogenase
Lue	Leucocyte
LVDT	Linear variable differential transformer
m	Metre
M	Molar
min	Minute
mJ	Millijoule
MBAAm	*N,N'*-methylenebisacrylamide
MAA	Methacrylic acid
MHz	Megahertz
M^+	Solvated metal ion
M^+-L	Metal-macrocyclic ligand pair
M^+L	Contact pair
$(ML)^+$	Final complex
MP	Megapixel
n	Effective index of refraction of the recording medium
ns	Nanosecond
n	Sample size
N	Newton or Number of functional groups (see context)
$n(t)$	Rate of change of bound molecules
N_g	Total number of glucose molecules
N_f	Total number of boronic acid groups
NP	Nanoparticle
Na_2HPO_4	Sodium phosphate dibasic
$(NH_4)_2SO_4$	Ammonium sulphate
Nd:YAG	Nd-Yttrium-Aluminum-Garnet
$Na_2S_2O_3$	Sodium thiosulphate
Na_2CO_3	Sodium carbonate
Na_2HPO_4	Sodium phosphate dibasic
NaOH	Sodium hydroxide
NAD^+	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide hydride
$NaHCO_3$	Sodium bicarbonate
OD	Optical density
pK_a	Acid disassociation constant

Ph	Photochemistry
PBS	Phosphate buffered saline
PMMA	Poly(methyl methacrylate)
PVA	Poly(vinyl alcohol)
PBG	Photonic band gap
PDMS	Poly(dimethylsiloxane)
pHEMA	Poly(2-hydroxyethyl methacrylate)
pAAm	Poly(acrylamide)
R	Ratio of the intensities of the reference and the object
r	Position
RGB	Red, green, blue
R_c, G_c, B_c	Non-linear red, green and blue values
R_l, G_l, B_l	Linearised the red, green and blue values
R^2	Correlation coefficient
RCA	Rolling circle amplification
RI	Refractive index
rpm	Revolution per minute
s	Second
σ	Standard deviation (see context)
s_y	Standard of residuals
s_m	Standard of slope
s_b	Standard of intercept
Si	Silicon
SDK	Software development kit
SEM	Scanning electron microscopy
t	Thickness
θ	Angle of incidence of illumination or tilt angle (see context)
THF	Tetrahydrofuran
TEM	Transmission electron microscopy
TACPP	5,10,15,20-Tetrakis[4″-(3‴-(acryloyloxy) propoxy)phenyl-4′-carboxyphenyl] porphyrin
U	Uncertainties
UV	Ultra Violet
v	Volume
$v_{\pm}$	$\pm$Variation
4-VPBA	4-Vinylphenylboronic acid
W	Watt
WD	Working distance
WHO	World Health Organisation
x_m, y_m	2D chromaticity values
X, Y, Z	Tristimulus values
y	Constant position

Contents