Viewpoint

Community Sewage Sensors for Monitoring Public Health

Zhugen Yang[1,2*], Barbara Kasprzyk-Hordern[1], Christopher G. Frost[1*], Pedro Estrela[2], Kevin V. Thomas[3]

[1]*Department of Chemistry, University of Bath, Claverton Down, BA2 7AY, Bath, UK*
[2]*Department of Electronic and Electrical Engineering, University of Bath, Claverton Down, BA2 7AY, Bath, UK*
[3]*Norwegian Institute for Water Research (NIVA), Gaustadalléen 21, 0349 Oslo, Norway*

Corresponding authors: Dr Z. Yang (zhugen.yang@gmail.com) Tel.: +44 (0)1225 386 071; fax: +44 (0)1225 386 231 and Prof C.G. Frost (c.g.frost@bath.ac.uk) Tel.: +44 (0)1225 386 142; fax: +44 (0)1225 386 231

Wastewater-based epidemiology (WBE) has been shown to be an innovative approach for monitoring drug use in communities by quantifying drug residues (so-called "drug biomarkers") in sewage[1, 2]. WBE has thus far been validated by assessing illicit drug use trends across Europe, with the evaluation of spatial differences and temporal changes in the levels of specific biomarkers in sewage from 42 cities in 21 European countries (total population 24.74 million)[1]. It is hypothesized that sewage contains additional information on the lifestyle, health and pollutant exposure of a community which could also be obtained by the analysis of sewage biomarkers[2]. In fact, feces and urine from either humans or animals carry many biomarkers and pathogens, which could and enter the sewer system from a carrier of the disease in the community, e.g. patients at hospitals. Those pathogens such as bacteria, viruses and parasites in wastewater are hazardous to humans because they might cause epidemics in population. However, human hazards can be minimized if those pathogens could be monitored at an early stage in the community. Unlike illicit drug use trends, infectious diseases require rapid or even real-time detection to assess whether there is a need for the containment of the disease carriers to certain areas and prevent the development of an epidemic. To this end, there is a need to develop novel analytical tools that are able to accurately and rapidly monitor low levels of biomarkers/pathogens with minimal sample processing by unskilled personnel at the site of sample collection. Emerging biosensing technology will play a key role in the in situ quantitative analysis of biomarkers and pathogens in sewage due to rapid response times, low cost, minimal sample processing, high data resolution and ability to operate remotely. Community sewage sensors employed to detect biomarkers of health and diseases at a population-level have therefore the clear potential to provide real-time data for the assessment of community-wide health.

Biosensors have emerged as powerful tools for the detection of disease biomarkers for both healthcare and environmental monitoring. A biosensor is a small device with a biological receptor (DNA, antibody, protein etc.) that generates a signal (electrochemical, optical, piezoelectric, nanomechanical, mass sensitive etc.) in the presence of an analytical target (analyte). Compared to conventional analytical tools, biosensors can provide rapid response times, ultra-sensitive detection of biomolecules, and the potential to be miniaturized for portable assays requiring minimal sample processing. Moreover, this approach could be employed, not only for the detection of pathogens, but also for the monitoring of more general public health indicators such as obesity, diabetes, high blood pressure and sexually transmitted infections. For example, a recent report demonstrates that the level of an American city's obesity could be predicted by analyzing the bacterial community structure found in sewage[3]. Such an approach providing near real-time and continuous data would serve as an early warning sensing system to help agencies, such as the "Centre for Disease Control and Prevention" (CDC) in the United States, to make effective interventions to prevent the spread of epidemics, evaluate the effects of interventions and in turn increase the effectiveness of their policies and use of valuable resources. For example, in 2003 the effective interventions of CDC in the United States helped reduced spread of severe acute respiratory syndrome (SARS) to a minimum level.

A large number of biosensors have been developed for the detection of disease biomarkers and pathogens in samples such as urine, sera and saliva (Table 1). Although sewage is a complex matrix, spurious effects, such as nonspecific interactions can be minimized provided that an ultra-high affinity probe such as an aptamer is used to target specific analytes, as well as by calculating the differential response of a probe and a reference chip. As an example, a macrocantilever-based label-free biosensor can quantitatively detect a prostate cancer biomarker (α-methylacyl-CoA racemase; AMACR) directly in patients' urine without any sample preparation[4]. Hence, there is the clear potential to develop a wider range of innovative community sensors to quantitatively assess sewage profiles and patterns of factors related to health and illness within populations using WBE. Additionally, biosensors have the potential to be miniaturized to a handheld device for point-of-care analysis that may facilitate the monitoring of infectious diseases in developing countries where the occurring rate (such as malaria, acquired immune deficiency syndrome (AIDS) and tuberculosis) is extremely high. For instance, a plasmonic enzyme-linked immunosorbent assay (ELISA) has been developed to ultra-sensitively detect an HIV-1 capsid antigen p24 at concentrations as low as 1 attogram per millilitre in serum of HIV-infected patients with the naked eye[5]. In this sensor, the ELISA enzyme controls the aggregation of nanoparticles, rising a blue colour if a target protein is present otherwise a red colour if no target. All of these biosensors can potentially be used in sewage matrices as community sensors to assess urinary and fecal biomarkers/pathogens for the monitoring of public health using WBE, while also providing a means of collecting data for epidemiological and socio-economic studies. Community sewage sensors arrays can be customized designed for the monitoring of different biomarkers/pathogens in a single assay. Their use could be of considerable economic and societal impact especially in resource-constrained areas. More importantly, biosensing technology platforms can be utilized to collect information on community-wide health in order to report to health agencies as an early prevention measurement and effective interventions. Although the selectivity and long-term stability of community sensors as well as environmental susceptibility to deterioration of bio-recognition are yet to be addressed, we envisage that the rapid and real-time monitoring of health in communities will soon be possible.

Table 1 Examples of biosensors used for the detection of infectious diseases and pathogens

Infectious diseases	Biosensors and its transducers	Biomarkers/pathogens
HIV	Plasmonic ELISA	protein biomarkers
	Impedimetric, voltammetric and amperometric proteins biosensors	HIV virus lysate, HIV-1 protease
	Mechanical sensors	HIV CD4 T cell number
Tuberculosis	Electrochemical PCR-free mycobacterium tuberculosis (MTB) genomic sensors	PCR-free MTB nucleic acid or cells
Others diseases	Fluorescent peptides sensors	Drug resistant chronic myelogenous leukemia
Pathogens	Fluorescent array, evanescent wave fibre-optic, laser cytometry, electrochemical and mass sensitive DNA/antibodies sensors	Pathogenic Bacillus species like Bacillus anthracis and bacillus cereus
	Optical, electrochemical and mass sensitive DNA/ aptamers/antibodies biosensors	campylobacter species for campylobacteriosis
	Fluorescent, electrochemical and piezoelectric antibody/lectin/ganglioside biosensors	cholera toxin from bacterium Vibrio cholera
	Optical, electrochemical, mass sensitive antibodies/antimicrobial peptides/aptamers/bacteriophages biosensors	Escherichia coli, like E coli O157:H7; Listeria moncytogenes,; Salmonella; Shigella spp, Staphylococcus aureus; viral threats (smallpox viral hemorrhagic fevers, viral encephalitis etc.)

Funding to support SEWPROF MC ITN entitled 'A new paradigm in drug use and human health risk assessment: Sewage profiling at the community level' from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement [317205] is greatly acknowledged. P.E. and C.G.F. acknowledge support from the European Commission FP7 Programme through the Marie Curie Initial Training Network PROSENSE (grant no. 317420, 2012-2016). K.V.T. acknowledges the support of NIVAs Strategic Institute Initiative on Contaminants of Emerging Concern.

References

1. Ort, C.; van Nuijs, A. L. N.; Berset, J.-D.; Bijlsma, L.; Castiglioni, S.; Covaci, A.; de Voogt, P.; Emke, E.; Fatta-Kassinos, D.; Griffiths, P.; Hernandez, F.; Gonzalez-Marino, I.; Grabic, R.; Kasprzyk-Hordern, B.; Mastroianni, N.; Meierjohann, A.; Nefau, T.; Oestman, M.; Pico, Y.; Racamonde, I.; Reid, M.; Slobodnik, J.; Terzic, S.; Thomaidis, N.; Thomas, K. V., Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis. *Addiction* **2014,** *109*, (8), 1338-1352.

2. Thomas, K. V.; Reid, M. J., What Else Can the Analysis of Sewage for Urinary Biomarkers Reveal About Communities? *Environ Sci Technol* **2011,** *45*, (18), 7611-7612.

3. Newton, R. J.; McLellan, S. L.; Dila, D. K.; Vineis, J. H.; Morrison, H. G.; Eren, A. M.; Sogin, M. L., Sewage reflects the microbiomes of human populations. *MBio* **2015,** *6*, (2), 1-9.

4. Maraldo, D.; Garcia, F. U.; Mutharasan, R., Method for quantification of a prostate cancer biomarker in urine without sample preparation. *Anal Chem* **2007,** *79*, (20), 7683-7690.

5. de la Rica, R.; Stevens, M. M., Plasmonic ELISA for the ultrasensitive detection of disease biomarkers with the naked eye. *Nat Nanotechnol* **2012,** *7*, (12), 821-824.