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A biosensored spatial data infrastructure for the dynamic monitoring of the presence and the activity of endocrine disrupting chemicals in water

[Domenico Vito]

***Abstract*— Endocrine disrupting chemicals (EDCs) are a subset of environmental contaminants that can produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. EDCs have been reported to have a ubiquitous presence in the environment and in particular aquatic ecosystems. Many EDCs, in fact are not completely removed with conventional wastewater treatment systems. Due to their harmfulness and ubiquity, since the 1990's a number of countries, multinational governments such as the European Union and inter-government organizations (Organization for Economic Cooperation and Development, OECD) have initiated or amended programs to integrate EDCs into current strategies to assess chemical safety. These programs has been mainly focused on regulate exposure to EDCs, neglecting the issues about monitoring. Conventional water monitoring processes involves the collection of water samples that only provide snapshots of the situation at the sampling site and time, rather than information on spatio-temporal variations in water characteristics. Biosensors indeed, - defined by IUPAC as a "self-contained integrated device that is capable of providing specific analytical information using a biological recognition element" - offer the possibility for a faster and timely measurement for pollutants in water.**

Biosensors can be combined with remote communication technology like GPS and GPRS, resulting in networks of distributed elements able to gather spatial and temporal information. These sensing networks can be integrated with spatial data infrastructures. Spatial data infrastructures (SDI) are a framework of technologies, policies, and institutional arrangements includes all the technologies like Geographical Information Systems (GIS), geoportals and diffuse georeferred tools that enable the sharing of geospatial information on a national, regional or global level. SDI can be useful for water monitoring because can handle data and models providing spatial and temporal information on pollutant distribution and toxicity.

This work proposes a main framework of and SDI for monitoring the dynamic activity of endocrine disrupting chemicals in water. The proposed SDI is based on multiple remote sensing stations equipped by a set of impedentiometric immunobiosensors coated with ER-α receptor on an ArduinoMEGA® microcontroller-board.

The remote sensings are designed to gather spatial and temporal information on the type and the concentration of different EDCs compound in the sampled water.

The remote sensing stations are also fitted to communicate the measured data by GPS to a central server-side, thanks to the ArduinoGSMShield®. On the server side a QSAR model is installed to estimate EDCs activity, on the basis of 2 datasets on androgen and estrogen receptor binding. The two dataset are extracted from the Endocrine Disruptor Knowledge Base (EDKB). The outputs on activity and toxicity from the QSAR model and the data gathered from the on-field measurement about the types of EDCs and its on-situ concentration, can be georeferred on geographical maps by a GIS based Web Map Service. Thanks to the time and space dependence of the measured parameter, the produced maps will offer a visual and numerical representation of the dynamic presence of EDCs and toxicity risks in the monitored points.

On this view, the proposed SDI represents a useful tool to support decision-makers on regulatory policies that are inclusive of monitoring strategies.

Keywords*— *endocrine disrupting chemicals, biosensors, spatial data infrastructure, monitoring, water

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I. Introduction

The protection of water resources and the secure delivery of clean water to consumers are important tasks for human communities in the near future. Water directly impacts food, energy and economic growth security. This is a challenge that, world economy will face in the future. Furthermore, to achieve the MDG goals for water, proper management and use of water resources are essential [1].

Pollution of water sources, aquifers and wetland systems caused by industry, agriculture, and municipally treated wastewater is a worldwide problem. Rivers, channels, lakes, oceans, and ground water are often contaminated by a variety of organic substances that can have adverse effects on aquatic life and pose risks to human health. Current monitoring process uses conventional analytical methods as liquid chromatography (HPLC) and gas chromatography (GC) in combination with different detection principles.

These methods involves the collection of water samples followed by laboratory-based instrumental analysis and such analyses only provide snapshots of the situation at the sampling site and time rather than more realistic information on spatio-temporal variations in water characteristics [2]

One of the possibilities for a faster and timely measurement for pollutants in water, lies in the use of biosensors.

Biosensor starts to become an essential instrument for rapid and cost-effective environmental monitoring. They are in fact capable of measuring pollutants in complex matrices and with minimal sample preparation.

Even though biosensors can't yet measure chemical compounds as accurately as conventional analytical methods, they can be useful particularly in situations when continuous and spatial data are needed.

Thanks to remote communication technologies as GPS and GPRS, biosensors can definitely be utilized to provide a network of distributed electronic devices in even very remote places.

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Such networks will contribute enormously towards continuous environmental monitoring especially in difficult situations live river sides and water basins.

Thus, biosensors used in networking can be particularly fitted for monitor the ubiquitous presence of pollutants like endocrine disrupting chemicals (EDCs). Furthermore distributed network of biosensors can also be integrated with spatial data infrastructures.

A spatial data infrastructure (SDI) is usually defined as an interaction of the technology, policies, standards, human resources, and related activities necessary to acquire, process, distribute, use, maintain, and preserve spatial and geographical data [17].

Combining geographical information from SDIs like satellite imagery with ground biosensor measurements in spatial models and time can result in a helpful tool to support decision making in pollutants monitoring programs. This could be the case for the EDCs.

Standing to their nature of electric sensors, biosensors offer the possibility to have continuous remote geo-localized and time variant inputs, that could be used also for numerical models on pollutant toxicity in water.

This work proposes the main framework of a spatial data infrastructure to monitor dynamically the presence and activity of EDCs in water for a toxicity assessment.

The proposed SDI is based on remote sensing stations equipped by a set of impedentiometric immunobiosensors, in connection by GPS with a central server side containing QSAR model, for the prediction of the activity, and thus the toxicity of the EDCs.

The QSAR model is associated with two datasets on androgen and estrogen receptor binding, that are extracted from the Endocrine Disruptor Knowledge Base (EDKB) – a databank of knowledge on EDCs developed by the U.S. FDA’s National Center for Toxicological Research (NCTR). for the prediction of the activity of the EDCs.

The main elements of the SDI and the whole integration in a unique platform will be exposed and discussed.

II. Endocrine disrupting chemicals (EDCs)

Endocrine disrupting chemicals (EDCs) are a subset of environmental contaminants that interfere with the normal development and functioning of endocrine systems.

EDCs are a threat to both humans and wildlife species because they can mimic, block, or alter the actions of natural endogenous hormones.

According to the definition adopted by the European Union " an endocrine disruptor is a exogenous substance or mixture that alters the function of the endocrine system , causing effects adverse health of an organism , or its progeny, or (sub) population " [5].

On the one hand, there is evidence from various laboratory experiments that estrogenic or estrogen-like compounds have the potential of affecting development of the reproductive and nervous systems [7].

Even if the full mechanism is still unclear, there a common position on the fact that endocrine disruption is related to interferences on hormone reception. Some EDCs can act directly on hormone receptors as hormone mimics or antagonists. Others can act directly on any number of proteins that control the delivery of a hormone to its normal target cell or tissue [4].

Endocrine disrupting compounds encompass a variety of chemical classes, including drugs, pesticides, compounds used in the plastics industry and in consumer products, industrial by-products and pollutants, and even some naturally produced botanical chemicals.

From a total of 564 chemicals that had been suggested on literature to be suspected EDCs, 147 were considered likely to be either persistent in the environment or to be produced at high volumes[7]:their disrupting activity can persist at very low doses in nanomolar (nM) to picomolar (pM) concentrations[5].

The origin of EDCs comes from a very wide number of sources.(industry,agriculture, households, air deposition,…), that contribute to the pollution of freshwater and groundwater systems. Moreover due to the specific chemical nature, the time of permanence of these compounds in river water could vary: many EDCs such as the natural and synthetic estrogens like 17b-estradiol and 17a-ethinylestradiol, respectively, are not completely removed with conventional wastewater treatment systems[7] and could persist on polluting since time.

Those outcomes, results in a simultaneous presence of different EDC in river water, with different concentration in time and space. Due to their harmfulness and ubiquity, since the 1990’s several states, and multinational government as the European Union and the Organization for Economic Cooperation and Development, (OECD) integrated EDCs regulation policies into current strategies for chemical safety [8]. The main problems of these policies stand in the fact that they more focused to reduce exposure to EDCs, rather than perform diffuse monitoring actions.

III. Modelling the EDCs activity in water systems

In order to have clear understanding and mapping of the evolution of the presence of EDCs in water systems, is important to represent their evolution in time and space through valid evaluation models, that allows for an integrated representation of the effects of EDCs. Furthermore, is important to have information about EDCs in a continuous, reliable and timely way. Today, in fact river quality assessment is mainly based on discrete monitoring campaigns, with time intervals of several hours, weeks, months or even years.

For the study of highly dynamical processes such sampling schemes are often insufficient to make a reliable assessment of the EDCs presence within rivers.

Moreover, the lack of high rated information transmission reflects in a worsening of the temporal misfits, by which environmental policy making is affected.

This is particularly true in the case of EU regulation for EDCs, operatively within European Union’s Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH); a case with amplified temporal challenges[5].

The challenge of regulating EDCs involves temporally aligning the chemicals and their impacts on living beings with the institutions that are set out to control them.

So to make a step further from the current researches upon EDCs is important to consider two dimensions, that are not fully covered in the present studies.

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The two dimensions are:

- *a spatial one*: which lies the concurrent presence of different EDCs in a complex mixture, and the related toxicity strictly related to the mutual interaction between different compounds
- *a temporal one*: related to the time temporal misfit between institutions and biophysical systems, related to the time mismatches about the communication of scientific knowledge on EDCs distribution

To face this goals is important to implement:

- a robust and timely system of on line and real time relevation systems
- a robust data management system connected to a mathematical model to predict EDCs activity and assess toxicity.

These features can be address by a spatial data Infrastructure based on a knowledge base repository and connected with on-field sensing elements, like biosensors.

IV. Spatial Data Infrastructures

The term spatial data infrastructure was coined in 1993 by the U.S. National Research Council to denote a framework of technologies, policies, and institutional arrangements that together facilitate the creation, exchange, and use of geospatial data and related information resources across an information-sharing community [19].

Such a framework includes all the technologies like Geographical Information Systems (GIS), geoportals and diffuse georeferred infrastructures that enable the sharing of geospatial information within an organization or more broadly for use a national, regional or global level.

These technologies support both geospatial and time-series data. It enables users to handle data and to visualize it as interactive maps or graphs.

. So, finally integration between geographical, bio-data banks and real-time on field measurements could be possible in order to furnish spatial and temporal information about EDCs. This data could underlie to predictive data-models, finalized to realize an effective SDI system.

V. The EDKB Database

One of the main bio-data banks containing information on EDCs is Endocrine Disruptor Knowledge Base.

The Endocrine Disruptor Knowledge Base (EDKB) project, developed by the FDA's National Center for Toxicological Research (NCTR), is a databank focused on aggregating knowledge of EDCs with experimental results relevant to estrogenic, androgenic, and other EDCs data in a unique accessible location [20] .

The EDKB database currently contains 3,257 records of over 1,800 EDCs from different assays including estrogen receptor binding, androgen receptor binding, uterotropic activity, cell proliferation, and reporter gene assays in addition to a wide range of FDA-regulated products including drugs, food, and cosmetics as well as EPA-regulated products such as pesticides, chemical waste, and toxic metals[20]. It is a client-server application consisting of a Java front-end and an ORACLE® database serving as the data repository. The database can by queried by a user-friendly interface and the results can be cross-linked to other publicly available and related databases including TOXNET, ChemIDplus, Chem Finder, and NCI DTP.

A major element of the EDKB program has been the development of computer-based predictive models to predict affinity for binding of compounds to the estrogen and androgen nuclear receptor proteins. with SAR and QSAR methods [22]. Different authors, in fact released open source dataset on androgen [23] and estrogen [24] receptor binding available on the EDKB web site.

This information can be used for example to relate information about a monitored substance within a biosensored spatial data infrastructure.

VI. Biosensor for EDCs

A of the possibility to have a fast and timely measurement for the presence of pollutants like EDCs in water, is the use of biosensors.

A biosensor is defined by IUPAC as a "self-contained integrated device that is capable of providing specific quantitative or semi-quantitative analytical information using a biological recognition element (biochemical receptor) which is retained in direct spatial contact with the transduction element"[3]. Biosensors start to become an essential instrument for rapid an cost-effective environmental monitoring: they are in fact capable of measuring pollutants in complex matrices and with minimal sample preparation. Even though biosensors can't yet measure analytes as accurately as conventional analytical methods, they can be useful particularly in situations when continuous and spatial data are needed.

The monitoring process using conventional analytical methods in facts, involves the collection of water samples followed by laboratory-based instrumental analysis. Such analyses only provide snapshots of the situation at the sampling site and time rather than more realistic information on spatio-temporal variations in water characteristics [2].

Further, a biosensor can not only determine chemicals of concern but can record their biological effects (toxicity, cytotoxicity, genotoxicity or endocrine disrupting effects). Often, information on biological effects is more relevant than the chemical composition.

For this reasons biosensor technology has been considered as a key tool for the complete implementation of the new European Union directives, such as Water Framework Directive (WFD – 2000/60/CE) [11] and can be highly considered to monitor the presence and the toxicity of EDCs in water [13].

A. *Structure of a biosensor measurement system*

Biosensor technology is based on a specific biological recognition element, called biochemical converter (BCC), which selectively recognizes analytes and binds them into the specific binding layers (Figure 1).

This binding creates a change Φ in a physicochemical property of the BCC that can be optical, mass, thermal or electrochemical. The change is perceived by the measuring converter (MC), which traduce it into a corresponding electrical signal [13]. According to the biological nature of

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BCC biosensors can be classified in enzymatic, non-enzimatic, immunochemical, whole-cells or DNA-based.

On the basis of the transducing element indeed, biosensors can be categorized in electrochemical (amperometric or potentiometric), optical, fluorescence, piezoelectric or micromechanical and thermometric [11].

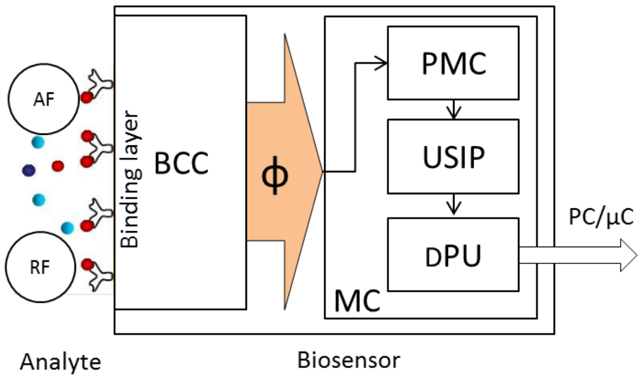

Figure 1. Structure of a Biosensor measurement system

In a test specimen the signal captured by the biological recognition element is the sum of two components:

- *the action factor (AF)*, results from the presence of the analyte we want to measure
- *the random factors (RF)*, related to the interference of other compounds and the surrounding environment.

In order to obtain measurable information from the BCC reaction MC generally includes

- *a primary measuring converter (PMC)*, that traduces into an electrical signal at the first stage
- *a unit for separating information parameters (USIP)*, that filters the AF from the background noise and the RF
- *a data processing unit (DPU)*, for the statistical and frequency analysis of the data coming from USIP, using mathematical algorithms to extract the desired information about the analyte from the sensed signal.

Further processing can be obtained connecting the biosensor to a PC or a microcontroller.

B. *Biosensors for EDCs sensing*

During ongoing research several biosensors to detect EDCs have been developed. They exploited different transduction method addressing different EDC compounds (Table 1).

Among the different types of developed biosensors, immunosensors represent a very attractive technique for ECDs monitoring. Immunosensors are widely used for the detection of an analyte where an enzyme is labelled with a specific antigen [12].

But the main drawback of the classic immunosensor techniques is that, enzyme labelling is a time consuming and complicated procedure.

However with recent developments label-free electrochemical immunosensors started to be available, and they showed to have promising application for EDCs monitoring. In particular there are several works that reported the use of impedentiometric immunosensors for the detection of EDCs compound [14,15].

TABLE I. DIFFERENT BIOSENSORS DEVELOPED TO DETECT EDCS

Table Column Head			
Analyte	***Transduction method***	***Limit of detection***	***Reference***
Carbamates	Potentiometric	15-25µM	Ivanov et al. 2000
Bisphenol A	Amperometric	0,6 ng/ml	Mita et al. 2007
Progesterone	Amperometric	0,43 ng/ml	Carralero et al 2007
Estrogens	Total internal reflectance	0,05-0,15 ng/mL	Rodriuges-Mozaz et al 2006
Dioxins	Piezometric	15 ng/L	Kuosawa et al. 2006
Phenols	Electrochemical	0,8 µg/L	Nistor et al. 2002
Clorolphenols	Electrochemical	10 µg/L	Degiuli and Blum,2000

Source [14]

Impedance biosensing involves application of a small amplitude AC voltage to the sensor electrode and measurement of the in/ out-of-phase current response as a function of frequency. Impedance biosensors are fabricated by immobilizing a biorecognition molecule onto a conductive and biocompatible electrode and then detecting the change in the interfacial impedance upon analyte binding.

Radhakrishnan et al.(2014)[15] demonstrated the possibility of detection of two endocrine-disrupting chemicals (EDC), norfluoxetine and BDE-47, by gold a Ti-layered impedance biosensor coated with Peanut protein Arah 1 monoclonal antibody. They obtained detection limits of 8.5 and 1.3 ng/mL for norfluoxetine and BDE-47, respectively. It is interesting that the value for norfluoxetine is comparable to the detection limits reported from high pressure liquid chromatography (10 ng/mL) and gas chromatography (2 ng/mL) measurements. The study also pointed out that only few voltage frequencies are most sensitive to analyte binding. This reduced the detection time, allowing for real time impedance biosensing.

Other researches on impedance immunobiosensors explored the use of endocrine receptors as detection molecule.

For example, human estrogen receptor α (ER-α) group is capable of interacting with a large variety of chemicals (e.g., phytoestrogens, xenoestrogens, pesticides) that cause estrogenic effects in-vivo.

Le Blanc et al. (2009) [16] used this knowledge to get sensing information on the effects of EDCs on ERa receptors.

The signal obtained was comparable to the response of the organism which is exposed to EDCs, opening the way to the measurement of the toxicity of a mixture of EDCs by a biosensor.

In conclusion, due to their all-electrical nature free of optical or acoustic components, impedance immunochemical biosensors offers significant advantages for portable and remote environmental monitoring of EDCs.

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VII. A biosensored spatial data infrastructure for the dynamic monitoring of the presence and the activity of endocrine disrupting chemicals in water

Here is proposed a structure for a spatial data infrastructure to monitor EDCs presence and activity in water. The challenge is to provide an informative system with reliable information, based on integrated data and tools derived from both on field observations and scientific models.

This could be possible, using data streams from remote field sensors within water environments.

Figure 2 depicts the structure of spatial data infrastructure on discussion:

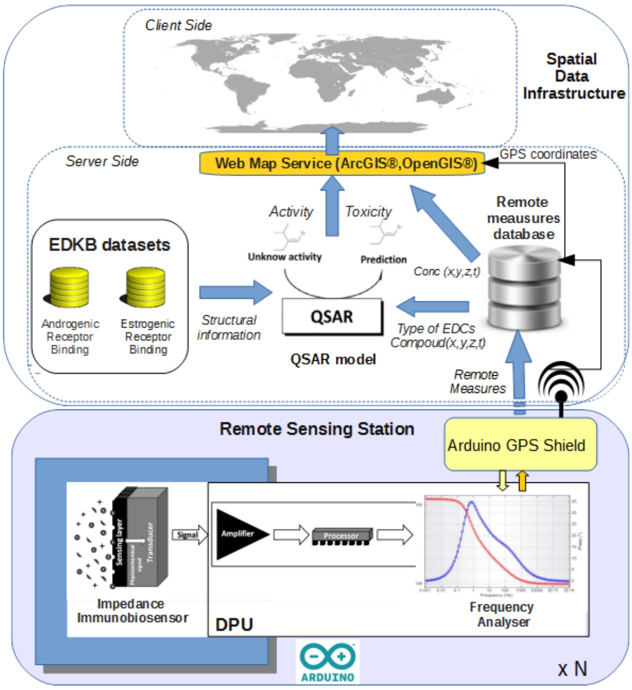

Figure 2. Structure of the Spatial Data Infrastructure for the EDCS monitoring

The whole system is composed by multiple remote sensing stations connected to the spatial data infrastructure by GPS communication channels on the server side.

Each remote sensing station carries a set of gold immunobiosensor coated with ER-α receptor. This solution will be capable to sense different classes of EDCs compounds, and their concentration [15,[16].

The raw electrical signal from the biosensor is filtered into a useful measure on the presence and concentration of EDCs compounds by a DPU unit.

The DPU unit, is composed by an amplification stage and a frequency analyser: this stage will be implemented on an embedded ArduinoMEGA® microcontroller-board[26].

In order to get a spatial distribution of EDCs, the remote stations should be installed in different strategic points along the lake and river side of the studied zone.

The continuous monitoring of the selected points will provide data in temporal series.

In particular, these data will offer information about the type and the concentration of different EDCs on the sampled water, both on dependence of geographical coordinates of the monitoring point and time.

Thanks to the GPS connection granted by the installation of the on-board ArduinoGSMShield® [26]; all the monitored data together with the GPS position of the station can be transmitted to the central server-side. Here the data are firstly stored in a remote measures database and secondly used for model simulations and georeferentiation.

In particular the data on the type of EDCs in combination with the information on the molecular structure available from the EDKB dataset on androgen and estrogen receptor binding, will furnish the inputs for the QSAR model installed on the server side.

The Quantitative Structure-Activity Relationship (QSAR) models QSAR models are computational models that predict the potential activity of a compound using information about its molecular structure.

QSAR models are frequently to provide reliable predictions of bioaccumulation and toxicity of pollutant for regulatory purposes in EU [21]. Thus, a QSAR model for EDCs [20] is a key element to be integrated into the SDI, in order to assess the toxicity of the sensed EDCs compounds.

Once generated, the outputs on activity and toxicity from the QSAR model together with the data gathered from the on-field measurement about the type of EDCs and its on-situ concentration, can be available to be georeferred on a map. This would be possible thanks to a Web Map Service based on a GIS software (ArcGIS®, OpenGIS®).

The final result of the system will be a set of maps on the client side that show the places on which EDCs are detected, together with information about the potential toxicity.

Thanks to the time and space dependence of the measured parameter, the produced maps will offer a visual and numerical representation of the dynamic presence of EDCs and toxicity risks in the monitored points.

VIII. Conclusions

The ubiquitous presences of EDCs in the environment and water basins have sparked scientific and political debates regarding the need for strategies to assess and regulate chemicals with endocrine disrupting properties to protect human and environmental health since the 90s.

This work places on a scenario where, even if several scientific and regulatory initiatives have been pursued to address the problem related to the high toxicity and environmental persistence of EDCs, a comprehensive and effective effort in monitoring actions still lacks.

The proposal is about a spatial data infrastructure based on a low cost open source biosensored remote station and reliable databanks connected to a QSAR simulation model.

The proposed SDI has as outputs georeferred that dynamically represent with time and space dependency, the presence and the activity of EDCs in the monitored points. These maps are thus, capable to provide an assessment of toxicity risks related to EDCs in a geographical and temporal way.

Standing to their web-based and interactive nature, the maps also reduce the time and knowledge misfits between the real state of the water ecosystems and decision-makers.

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On this view, the SDI for EDCs monitoring represents a useful tool to support future regulatory policies aimed to include also monitoring strategies.

The study is on a preliminary state, but it has given a proof of concept of the feasibility of the system.

Considering its modular structure the main framework can be also expanded to be a better usable scientific knowledge instrument.

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