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A dynamic pharmaceuticals loads source generator *

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Abstract: As pharmaceuticals and metabolites are assumed to reach the environment after human consumption and excretion, it is important to model their discharge in wastewater. Due to the difficulty to collect detailed data on pharmaceuticals sales and the diversity of processes influencing the fate of pharmaceuticals, modelling pharmaceutical fate is difficult and models in the literature struggle to accurately and reliably predict pharmaceutical loads. In such a context, a new stochastic model is proposed. Pharmaceuticals loads in wastewater are predicted by modelling the discharge from sick persons in a catchment at a minute time step. Posology, time-use, metabolism and excretions are generated using different distributions. The model is tested for 9 molecules on an urban catchment (16 000 inhabitants), using monthly sales data. 24 h average samples and 24 consecutives 1 h average samples campaigns are used to assess the model performance. Results show that the model can predict with reasonable accuracy and reliability daily and hourly loads for an urban catchment.

Keywords: Stochastic modelling; Individual behaviour; Pharmaceuticals sales

1. INTRODUCTION

Pharmaceuticals in the environment are an important field of study and a great concern in terms of environmental and public health risks. Their modelling is paramount to fully understand their fate. However monitoring pharmaceuticals with analytical chemistry is difficult and costly. A significant part of pharmaceuticals reach the environment through human consumption and excretion (Heberer, 2002; Qian *et al.*, 2015) and pharmaceuticals fate models almost always include a source model in which loads discharged into wastewater are proportional to sales data (Kümmerer *et al.*, 1997; Heberer and Feldmann, 2005; Singer *et al.*, 2016). The results of such models are difficult to interpret since, from one molecule to another and from one study to another, pharmaceuticals loads may be greatly over- or under- estimated (de Garcia *et al.*, 2013). However, they are widely used because they are quick and easy to use and do not require detailed data, compared to other more elaborated models (e.g. Coutu *et al.*, 2016). In this context, we propose and assess a new pharmaceuticals fate stochastic model in wastewater based on detailed pharmaceutical sales data and monitoring campaigns.

2. MATERIALS AND METHODS

2.1 Experimental site and data

The model is tested on the Bellecombe wastewater treatment plant (WWTP) (France) collecting effluents from 16 000 inhabitants through 230 km of sewers which were previously modelled (Pouzol *et al.*, 2015). Census data indicate that 14 500 inhabitants are active people and that only 7 000 jobs exist on the catchment; then other active people work out of the catchment during the day. Monthly pharmaceuticals sales over 2.5 years were collected. Nine molecules were monitored with state-of-the-art sampling strategy, method (materials and handling) and analyses (LC-MS/MS). Twenty 24 h average samples and four 24 consecutives 1 h average samples campaigns were performed between 2012 and 2016.

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2.2 Model

The successive processes leading to the discharge of pharmaceuticals in sewers are stochastic by nature. The model thus aims generating discharges of sick persons over the catchment, who can be either inhabitants or outside persons who work in the catchment. Their number is determined by i) the total mass M of pharmaceuticals consumed in one day that is randomly picked according to sales data and ii) the standard individual posology. For each sick person, the model follows 4 steps:

Posology. It is determined according to pharmaceutical data and websites and consists of time consumption pattern, number of intakes, mass for each intake and duration between intakes. The last three values are randomly picked from literature distributions. The time consumption pattern consists of generic descriptions, e.g. “Awake and not out from household” for presence or “33% chance for each meal” for intakes time.

Time-Use. Periods of time when the person is asleep, out of household and eating are generated according to time-use survey data. These periods are weighted according to the time consumption pattern and then all intakes are randomly picked.

Metabolism. Pharmaceuticals intakes are transformed into a mass of pharmaceutical stored in the bladder over time, according to medical literature. Fractions of pharmaceuticals are transferred through three “boxes” (gastro-intestinal system, blood and bladder) at certain rates (exponential decay). All parameters are randomly picked from medical literature distributions (e.g. www.eurekasante.vidal.fr, <https://pubchem.ncbi.nlm.nih.gov/>).

Excretion. When persons excrete urine in toilets, pharmaceuticals stored in the bladder are discharged. The times of toilet uses are randomly picked using the time-use generated in step 2 (see Pouzol *et al.*, 2015 for details). For local inhabitants, it is assumed that excretion during “out of household” times are made outside the catchment. Conversely, for outside persons working in the catchment, these excretions are the only ones considered.

3. RESULTS AND DISCUSSION

3.1 Daily loads

Measured and modelled daily loads are compared using the ratio average modelled over average measured daily loads (R). The results of the model for one molecule are considered satisfactory whenever the ratio R is between 0.5 and 2. Also, the model is considered reliable if it has satisfactory results for every molecule.

Eight out of the nine molecules show satisfactory ratios R (average: 1.3, min: 0.5, max: 2.19). Ketoprofen is the only molecule with an unsatisfactory ratio R . However, its metabolic parameters are not well defined (wide range of excretion) and it is not sold solely as oral forms (Ketoprofen: 17 % dermal forms), as such the fraction directly discharged into the sewer is not well known and approximated by the model (from 25 to 75 %). This leads to an over-estimation of its daily loads.

The ratios between the coefficients of variation of the modelled over the measured daily loads indicate that the model underestimates the dispersion of the daily loads (averagely 0.28). This seems to be mainly the result of the temporal scale used for the pharmaceutical sales. Indeed, daily sales derived from monthly data are understandably unable to represent daily sales and so daily consumption and loads in wastewater.

3.2 Hourly loads

Usually, measured and modelled hourly dynamics are compared using the Nash-Sutcliffe efficiency (NSE) indicator. However, as only 4 hourly loads campaigns are available, average normalized measured hourly loads time series are not sufficiently representative of the dynamics. As an alternative, it is proposed to apply a modified NSE indicator, named NSE_{fuzzy} , for each measured time series

accounting for the distribution of all modelled time series. NSE_{fuzzy} is calculated as follows and is interpreted like the usual NSE (satisfactory model performance if above 0.5):

$$NSE_{fuzzy} = 1 - \frac{\sum_{t=1}^T (\tilde{L}_{measured}(t) - \tilde{L}_{fuzzy}(t))^2}{\sum_{t=1}^T (\tilde{L}_{measured}(t) - \bar{\tilde{L}}_{measured})^2} \quad (1)$$

if $Q_1(\tilde{L}_{modelled}(t)) \leq \tilde{L}_{measured}(t)$ then $\tilde{L}_{fuzzy}(t) = Q_1(\tilde{L}_{modelled}(t))$
if $Q_3(\tilde{L}_{modelled}(t)) \leq \tilde{L}_{measured}(t)$ then $\tilde{L}_{fuzzy}(t) = Q_3(\tilde{L}_{modelled}(t))$
else $\tilde{L}_{fuzzy}(t) = \tilde{L}_{measured}(t)$

with:

t : time

$\tilde{L}_{measured}(t)$: normalized measured pharmaceutical hourly load at time t

$\tilde{L}_{fuzzy}(t)$: normalized modelled hourly load at time t for NSE_{fuzzy}

$\bar{\tilde{L}}_{measured}$: average normalized measured hourly load at time t

$Q_1(X)$, $Q_3(X)$: first and third quartiles of a list of values X

$\tilde{L}_{modelled}(t)$: distribution of the normalized modelled hourly loads at time t .

The model is considered reliable if it gives satisfactory results for every molecule.

Seven out of the nine molecules show satisfactory NSE_{fuzzy} values (average: 0.5, min: 0.18, max: 0.72). Results for Ibuprofen are displayed in Figure 1. The low NSE_{fuzzy} values for Atenolol (0.18) and Carbamazepine (0.19) can be explained by the combination of i) stochastic nature of pharmaceutical consumption and ii) low consumption levels (only a few patients per day for Carbamazepine in the entire catchment). More hourly campaigns would help to determine the average dynamics of hourly loads with more confidence. Assessing the model performance would then be less sensitive to random peaks in measured hourly loads which do reflect the average dynamics.

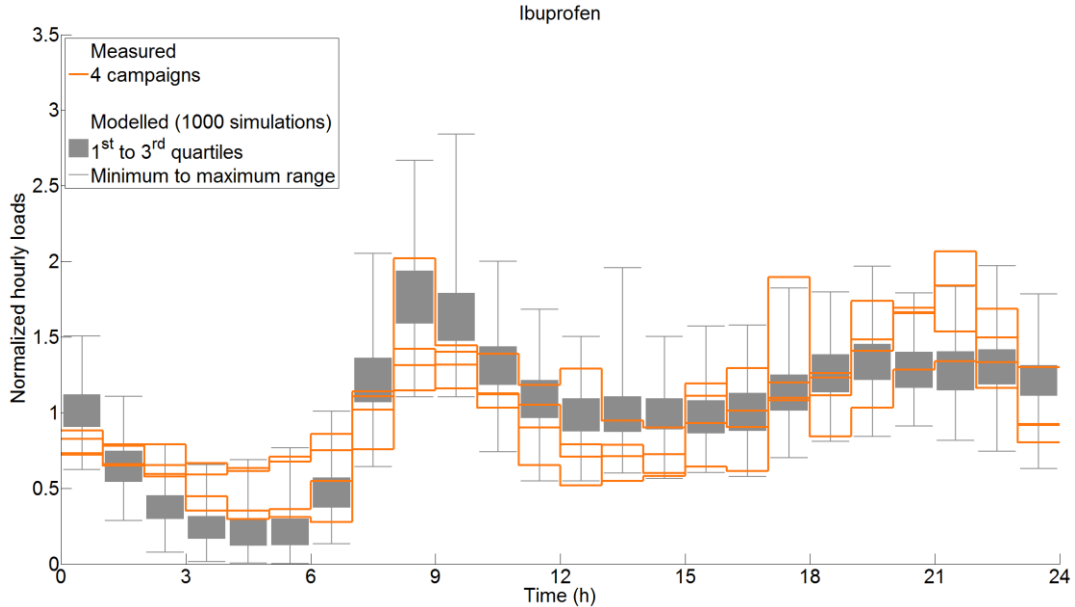


Figure 1. Comparison of the measured and modelled hourly loads.

CONCLUSIONS

The proposed model is able to predict reliably both the daily and hourly loads of pharmaceuticals at the WWTP inlet with an acceptable accuracy considering the available data and the analytical uncertainties. Daily loads are either over or underestimated depending on the molecule. The variability of the daily loads is under-estimated. Hourly loads are sensitive to random peaks due to the stochastic nature of the processes.

Future works should focus on: i) measuring more hourly loads in order to better determine the average dynamics of pharmaceuticals, ii) testing the model on other catchments and for more molecules and iii) simplifying the model structure in order to facilitate its implementation and use.

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