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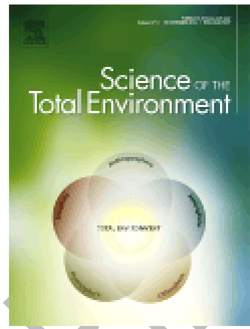

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GENERATION OF SYNTHETIC INFLUENT DATA TO PERFORM (MICRO)POLLUTANT WASTEWATER TREATMENT MODELLING STUDIES

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The MATLAB/SIMULINK code presented in this paper is available upon request, including the original data set and the parameter estimation techniques. Using this code, interested readers will be able to reproduce the results summarised in this study. To express interest, please contact Prof. Krist V. Gernaey (kvg@kt.dtu.dk) or Dr. Xavier Flores-Alsina (xfa@kt.dtu.dk) at the Technical University of Denmark (Denmark).

ABSTRACT

The use of process models to simulate the fate of micropollutants in wastewater treatment plants is constantly growing. However, due to the high workload and cost of measuring campaigns, many simulation studies lack sufficiently long time series representing realistic wastewater influent dynamics. In this paper, the feasibility of the Benchmark Simulation Model No. 2 (*BSM2*) influent generator is tested to create realistic dynamic influent (micro)pollutant disturbance scenarios. The presented set of models is adjusted to describe the occurrence of three pharmaceutical compounds and one of each of its metabolites with samples taken every 2-4 hours: the anti-inflammatory drug ibuprofen (*IBU*), the antibiotic sulfamethoxazole (*SMX*) and the psychoactive carbamazepine (*CMZ*). Information about type of excretion and total consumption rates forms the basis for creating the data-defined profiles used to generate the dynamic time series. In addition, the traditional influent characteristics such as flow rate, ammonium, particulate chemical oxygen demand and temperature are also modelled using the same framework with high frequency data. The calibration is performed semi-automatically with two different methods depending on data availability. The ‘traditional’ variables are calibrated with the Bootstrap method while the pharmaceutical loads are estimated with a least squares approach. The simulation results demonstrate that the *BSM2* influent generator can describe the dynamics of both traditional variables and pharmaceuticals. Lastly, the study is complemented with: 1) the generation of longer time series for *IBU* following the same catchment principles; 2) the study of the impact of in-sewer *SMX* biotransformation when estimating the average daily load; and, 3) a critical discussion of the results, and the future opportunities of the presented approach balancing model structure/calibration procedure complexity versus predictive capabilities.

KEYWORDS

BSM2 influent generator, calibration, micropollutant occurrence, trace chemicals, xenobiotics

RESEARCH HIGHLIGHTS

- The feasibility of a phenomenological influent generator model is demonstrated.
- The influent model can describe the dynamics of traditional variables as well as pharmaceuticals.
- The influent generator can effectively extrapolate time series.
- The importance of in-sewer biotransformation is shown when estimating consumption loads of drugs.

NOMENCLATURE

A	Surface area of the variable volume tank, soil model block [m^2]
ASM	Activated Sludge Model
ASM1	Activated Sludge Model No. 1
ASM2	Activated Sludge Model No. 2
ASM2d	Activated Sludge Model No. 2d
ASM3	Activated Sludge Model No. 3
ASM-X	Activated Sludge Model for Xenobiotic trace chemical framework
BSM2	Benchmark Simulation Model No. 2
CMZ	Carbamazepine, antiepileptic drug
CMZ-2OH	Metabolite of carbamazepine, 2-hydroxy carbamazepine
$CMZ_{gperPEperd}$	Total average daily load of CMZ [g CMZ/(day.1000 PE)]
COD	Chemical Oxygen Demand [g COD/m^3]
CODpart	Particulate Chemical Oxygen Demand [g COD/m^3]
$CODpart_{gperPEperd}$	Total average daily load of COD particulates per day per PE [g CODpart/(day.PE)]
DS1	Long term dataset
DS2	Short term dataset
FFfraction	Fraction of suspended solids that can settle in the sewer, first flush effect model block [-]
G_{rain_Temp}	Proportional gain to adjust the temperature after a rain event, temperature model block [-]
HH	Households model block in influent generator
HRT	Hydraulic retention time [h]
IBU	Ibuprofen, non-steroidal anti-inflammatory compound
IBU-2OH	Metabolite of ibuprofen, 2-hydroxyibuprofen
$IBU_{gperPEperd}$	Total average daily load of IBU per day per 1000 PE [g IBU/(day.1000 PE)]

$IBU\text{-}2OH_{\mathrm{gperPEperd}}$	Total average daily load of IBU-2OH per day per 1000 PE [g IBU-2OH/(day.1000 PE)]
IndS	Industry model block in influent generator
K_{D}	Solid-water distribution coefficient [L/g SS]
K_{down}	Gain for adjusting the flow rate to downstream aquifers, soil model block [m^2/d]
K_{inf}	Infiltration gain, soil model block [$m^{2.5}$/d]
M_{max}	Maximum mass of stored sediment in the sewer system, first flush effect model block [kg]
NH_4^+	Ammonium concentration [g N/m^3]
$NH4_{\mathrm{gperPEperd}}$	Total average daily load of ammonium per day per PE [g NH_4-N/(day.PE)]
PE	Person equivalent
Q_{lim}	Flow rate limit triggering a first flush effect, first flush effect model block [m^3/d]
Qpermm	Flow rate per mm rain [m^3/mm]
QperPE	Wastewater flow rate per person equivalent [m^3/d]
SMX	Sulfamethoxazole, antibiotic drug
SMX-N4	Metabolite of sulfamethoxazole, N4-acetyl-sulfamethoxazole
$SMX_{\mathrm{gperPEperd}}$	Total average daily load of SMX [g SMX/(day.1000 PE)]
Subarea	A parameter that forms a measure of the size of the catchment area. It will determine the number of variable volume tanks in series that will be used for describing the sewer system, sewer model block [-]
T	Temperature [°C]
T_{Bias}	Seasonal temperature variation, average, temperature model block [°C]
T_{dAmp}	Daily temperature variation, amplitude, temperature model block [°C]
WWTP	Wastewater treatment plant

1. INTRODUCTION

It has been more than 25 years since the publication of the Activated Sludge Model No. 1 (ASM1) (Henze et al., 1987). The ASM1 describes organic carbon and nitrogen removal processes in activated sludge systems and has been successfully applied to a large number of wastewater treatment plants (WWTPs). The successful results obtained in the early years have resulted in the further expansion of the number of phenomena included in activated sludge models (ASMs), e.g. by including the description of bacterial storage, 2-step nitrification, 4-step denitrification and phosphorus removal. In this way, ASM1 evolved to ASM2, ASM2d and finally ASM3 as well as many other versions of ASM inspired models. As a consequence, the use of ASMs (Henze et al., 2000) is constantly growing and practitioners in both industry and academia are increasingly applying these tools when performing WWTP engineering studies. Numerous publications demonstrate the usefulness of ASMs for benchmarking (Copp, 2002; Jeppsson et al., 2007; Gernaey et al., 2014), diagnosis (Rodriguez-Roda et al., 2002; Olsson, 2012), design (Flores et al., 2007; Rieger et al., 2012), teaching (Hug et al., 2009) and optimisation (Rivas et al., 2008) of WWTPs.

The potential adverse effects of xenobiotics in aquatic environments (e.g. Ternes, 1998) have promoted a substantial amount of research regarding the extension of ASMs to describe micropollutants (Clouzot et al., 2013; Plósz et al., 2013b). By micropollutants we mean compounds such as pharmaceuticals, personal care products, and biocides which are found in the environment in low concentrations (μg/L or ng/L). In many cases, these pollutants can pose a significant risk to the environment and human health. On aquatic life, such adverse effects can be characterised as spread and maintenance of antibacterial resistance (Baquero et al., 2008), sex reversal and/or intersexuality (Lange et al., 2009) or reduction of the reproductive behaviour (Coe et al., 2008).

Most models describing the fate of micropollutants in a WWTP include among others: volatilization (Lee et al., 1998), sorption/desorption (Joss et al., 2006; Lindblom et al., 2009), and biotransformation (Plósz et al., 2010; Suarez et al., 2010; Delgadillo-Mirquez et al., 2011).

These models are used as decision support tools to help understand the underlying mechanisms of micropollutant fate in the WWTP, and thus they provide a prediction of the efficiency of different treatment technologies (Lindblom et al., 2006; Snip et al., 2014; Vezzaro et al., 2014). In essence, the performance of WWTP modelling studies depends heavily on the availability of influent time series as these are the main disturbance of a typical WWTP (Rieger et al., 2012). These influent time series should represent the inherent natural variability of the traditional and/or micropollutant dynamics as accurately as possible (Ráduly et al., 2007). However, obtaining sufficiently long and qualitatively adequate time series for micropollutant modelling projects is costly and requires a high workload. This is because micropollutant analysis requires expensive analytical equipment, complex analytical procedures with costly consumable supplies and analysis methods requiring significant knowledge about the matrix effects in order to be successful (Richardson, 2012). Along this line of thinking, we believe that synthetic data generation is a promising tool since it can: 1) significantly reduce the cost and workload of measuring campaigns by inter- and extrapolating the obtained data; 2) fill gaps due to missing data in influent flow rate/pollution/temperature profiles; and, 3) create additional disturbance time series for scenario analysis following the same catchment principles.

There are several published studies that try to describe mathematically how these compounds appear at the inlet of the WWTP as reviewed by Martin and Vanrolleghem (2014) and the more recent studies of Talebizadeh et al. (2016) and Saagi et al. (2016). For example, Ort et al. (2005) developed a stochastic model, describing short-term variations of benzotriazole concentrations (a chemical contained in dishwasher detergents). On the other hand, De Keyser et al. (2010) developed within the framework of the European Research Project Score-PP, a model that generates time series of micropollutant occurrences according to specific (phenomenological/stochastic) release patterns. Gernaey et al. (2011) presented a phenomenological influent model capable to reproduce daily, weekly, and seasonal influent variation as well as dry and wet weather episodes for the Benchmark Simulation Model No. 2 (BSM2) platform. This influent model was calibrated and validated using data from two large

Scandinavian WWTPs for a period of 2 years (Flores-Alsina et al., 2014) and one large plant in Australia (Kazadi-Mbamba et al., 2016).

The same framework was upgraded with toxic/inhibitory compounds (Rosen et al., 2008) and more recently with pharmaceuticals (Snip et al., 2014). However, most of the previous studies were focused on model development rather than on practical applications. In addition, as far as we know, there is no (validated) tool described in the literature that is capable of describing the dynamics of traditional and non-traditional pollutants simultaneously using the same framework.

The objective of this paper is to test the feasibility of the BSM2 influent generator model, upgraded according to the principles stated in Snip et al. (2014), thereby creating realistic dynamic influent (micro)pollutant disturbance scenarios using data from an intensive measuring campaign. The occurrence of three pharmaceutical compounds (one anti-inflammatory, one antibiotic and one psychoactive drug) and one of each of its metabolites together with traditional influent characteristics (flow rate, ammonium, particulate chemical oxygen demand and temperature) will be (synthetically) modelled based on the available data. Information about excretion pathways and total consumption rates form the basis for generating the diurnal profiles of pharmaceuticals in wastewater at the discharge point of a real urban catchment. Automatic calibration is performed using: 1) a least-squares approach for the calibration of the pharmaceutical loads; and, 2) the Bootstrap method (Efron, 1979; Joshi et al., 2006) for the calibration of the traditional variables. Finally, the study includes a scenario analysis and a critical discussion of the results.

2. METHODS

2.1. WWTP and catchment under study

The WWTP under study is located in the North-East of Spain in Puigcerdà (**Fig. 1**). It serves around 16,000 PE (person equivalent) from both Spain and France and has a high seasonal load variation with fluctuating average flows in the range of 4,100 to 8,300 m^3/day depending on the season. Moreover, the organic load varies between 595 and 1,785 kg BOD/day and the nitrogen load between 123 and 349 kg N/day also depending on the season. This seasonal load variation is due to the touristic activities in the area during the winter time. There is also a significant increase in population during the weekends as many people living in larger cities have their second house located in the catchment area. The catchment is sparsely populated while covering a large area (approximately 100 km^2) and contains urban and agricultural areas. The WWTP is located close to the largest town in the area (Puigcerdà). Therefore, the majority of the flow and pollutant loads received by the WWTP (60%) are expected to originate from nearby (distance <1.5 km).

2.2. Compounds under study

The occurrence of a specific type of micropollutant, namely pharmaceuticals, will be described in this study. These pharmaceuticals are one non-steroidal anti-inflammatory compound - ibuprofen (*IBU*), one antibiotic - sulfamethoxazole (*SMX*), and one mood stabilising drug - carbamazepine (*CMZ*). These three compounds are selected because their occurrence and removal in wastewater have been extensively studied during the past years (e.g., *IBU*: Buser et al., 1999; Collado et al., 2012, *SMX*: Göbel et al., 2005; Carballa et al., 2008, *CMZ*: Clara et al., 2004; Leclercq et al., 2009). For each pharmaceutical, a human metabolite (the chemical compound excreted after intake of the pharmaceutical) is additionally included since these chemicals can occur in comparable or even higher concentrations than their parent chemicals (Zhang et al., 2008). For *IBU*, the metabolite chosen was 2-hydroxyibuprofen (*IBU-2OH*); for *SMX*, N4-acetyl-sulfamethoxazole (*SMX-N4*), and for *CMZ*, 2-hydroxyl carbamazepine (*CMZ-*

2OH). In addition, the wastewater stream was characterised in terms of traditional pollutants, including flow rate, a soluble pollutant (NH_4^+), a particulate pollutant (*CODpart*), and the temperature (*T*) at the inlet of the WWTP.

2.3. Measuring campaign

A data set comprising two measuring campaigns (long: *DS1* / short: *DS2*) is used for the calibration of the BSM2 influent generator. More information on the measuring campaign can be found in Aymerich et al. (2016). The long term (*DS1*) online data was collected using S::CAN sensors (scan Messtechnik GmbH, Vienna, Austria) for organic matter (spectrolyzer) and nitrogen (ammolyzer) at 2 minute intervals (from 02/10/2012 at 6:00 to 31/10/2012 at 14:00). The flow rate was measured with an electromagnetic meter (ABB Kent-Taylor: MagMaster 400T Series) (data frequency: 1 min). Grab samples, taken at the influent of the WWTP, were used to compare with the online data. Rainfall data was retrieved from a weather station (Queixans), which had a rain gauge in Queixans (4.1 aerial km from WWTP).

The short term data set (*DS2*) comprises an intensive three day measuring campaign (from Monday 08/10/2012 at 10:00 to Thursday 11/10/2012 at 8:00). The sampling interval was four hours during periods with low flow rates (between 12 and 8 in the night and midday) and two hours during periods with high flow rates resulting in 8 samples per day. Grab samples were collected after the pumping station and the grids and just before the biological treatment (there is no primary treatment). All samples were transferred into amber glass bottles and filtered with 0.7/0.45/0.22 μm Nylon filters (Whatman, Maidstone, UK) and were afterwards kept at 4°C in darkness until analysis. All the analyses were carried out in triplicates.

2.4. Analytical methods

Analysis of pharmaceuticals was performed following the fully automated on-line methodology by García-Galán et al. (in prep.). Briefly, 1 mL of wastewater is loaded on the on-line chromatographic system (Thermo Scientific EQuanTM166, Franklin, MA, US) consisting of 2 quaternary pumps and 2 LC columns, one for pre-concentration of the sample and the second one for chromatographic separation. The sample is further eluted by means of the mobile phase into the coupled mass spectrometer (TSQ Vantage triple quadrupole; Thermo Scientific, Franklin, MA, US). Chromatographic separation was achieved using a Thermo Scientific Hypersil GoldTM (50 x 2.1 mm, 1.9 µm particle size) column. Target compounds were analysed under dual negative/positive electro-spray ionization in multiple reaction monitoring (MRM) mode, monitoring two transitions between the precursor ion and the most abundant fragment ions for each compound. Recoveries of the compounds ranged between 51% and 139% (*CMZ-2OH* and *IBU*, respectively), whereas limits of detection ranged from 0.5 ng/L to 150 ng/L for *CBZ* and *IBU-2OH*, respectively.

2.5. Model-based influent generator

The phenomenological modelling approach proposed by Gernaey et al. (2011), which generates influent pollutant disturbance scenarios, is upgraded to describe pharmaceuticals according to the principles stated by Snip et al. (2014) (**Fig. 2** and **Table A1**). The flow rate dynamics are generated by combining the contributions of households (*HH*), industries (*IndS*), rainfall and infiltration from the *soil model* (FLOW RATE model block). In a similar way, *HH* and *IndS* (POLLUTANTS model block) are assumed to be the source of *COD* and *N*. Finally, daily and seasonal variations for temperature are generated (TEMPERATURE model block). Concentrations are calculated by combining the outputs from the FLOW RATE and POLLUTANTS blocks. The length of the sewer system can be incorporated in the influent dynamics: the larger the simulated sewer network, the smoother the simulated diurnal flow rate and concentration profiles, which is achieved by increasing the number of variable volume tanks in series used to model the sewer system. In addition, the dry weather model can be extended with rain and storm weather events, where the proposed approach can also mimic the "first-flush" effect from the sewer network and the influent dilution phenomena that are typically observed at full-scale WWTPs following a rain event. These two elements comprise the TRANSPORT model block. More information on the model blocks is given in the Appendix (**Table A1**).

Data profiles are sampled cyclically at different time scales and the resulting signal is obtained by multiplication. The pollutant fluxes are transformed into g/PE, by multiplying the values of the input files – containing normalised information on the dynamics – with their loads (normally given in mg/(day.1000 PE)) and PE, the number of person equivalents in the catchment. Zero-mean white noise can be added to provide more realism to the generated series using the variance of the noise as a tuning parameter. A schematic representation of the whole calculation procedure is presented in **Fig. 2**. Further information can be found in Snip et al. (2014).

2.6. Calibration technique

The calibration is performed using a pseudo-automatic approach with two different steps. In the first step, the catchment characteristics and some of the features in the *soil model* are manually adjusted based on the information available using a step-wise procedure (Flores-Alsina et al., 2014). This previous study identified the most sensitive parameters of the influent generator at different time scales (hours, days, months) and different weather conditions (dry/wet). Therefore, firstly the flow rate per PE was calibrated along with the parameters related to the soil model: 1) the gain to adjust the flow rate to the downstream aquifers (*Kdown*); and, 2) the infiltration gain, a measure of the quality of the sewer system pipes (Kinf) under dry weather conditions. Secondly, the parameters related to wet weather conditions (*Qpermm*) and first flush effects were calibrated. Thirdly, the peak values of the different components were adjusted to match the correct hourly dynamics found in the data.

During the second step, the model parameters such as the average daily loads are estimated with automatic calibration techniques (**Table 1** and **2**). The parameter estimation is carried out using a least squares approach, minimising the errors between the model prediction and the measurement data. These optimisations are performed in Matlab R2014b with the `lsqnonlin` function, which uses the sum of squares of relative errors as objective function. This function has the advantage that it allows a definition of lower and upper bounds of the parameters to be estimated, and therefore negative parameter values can be avoided. The automatic calibration of the flow rate, temperature, particulate COD and ammonium are also included in the Bootstrap method (**Table 1**) (Efron, 1979; Joshi et al., 2006). This method uses the initial set of data to replicate additional data sets through resampling (100 additional data sets in this study). For all these additional data sets the parameters are estimated again, resulting in a range of different parameter estimates. Therefore, a confidence interval of the estimated parameters can be obtained. To create the additional data sets, a comparably high number of data points are needed. As this high number of data points is not available for the pharmaceuticals (*DS2* has only 24 data points), no additional data sets are created for pharmaceuticals and the parameter estimation is only performed once. The accuracy of the calibration was tested with different qualitative and quantitative evaluation methods which are mentioned in the Appendix.

3. RESULTS

3.1. Dynamic modelling of traditional influent characteristics

In this section, the BSM2 influent generator is used to describe the dataset comprised in *DS1*. Parameters concerning the traditional variables (*QperPE, Qpermm, CODpartgperdperPE, SNHgperdperPE,* T_{Bias}, T_{dAmp} and $G_{\mathrm{rain\_Temp}}$) are estimated using the Bootstrap method (Efron, 1979; Joshi et al., 2006). Other parameters are adjusted using a manual procedure (see Section 2.6) based on the information available. The calibration of the traditional variables is evaluated with quantitative and qualitative criteria, which are described in the Appendix.

3.1.1. Influent flow rate, pollution loads and temperature

In dry weather conditions 28% of the influent flow rate is assumed to originate from *HH*. The *IndS* contribution to the flow rate is assumed to be negligible. The remaining 72% of the influent flow rate (dry weather conditions) originates from groundwater infiltration, which is due to the large catchment area compared to the number of inhabitants and the poor quality of the sewer pipes. Additionally, there is an irrigation channel connected to the sewer network resulting in higher flow rate. The dynamic (dry weather) flow rate pattern is obtained by repeating the default (daily, weekly and seasonal) data profiles in a cyclic manner (Gernaey et al., 2011). The generated signal is then multiplied with two gains corresponding to the flow rate per person equivalent (*QperPE* = 110 m^3/PE.day, **Table 1**) and the number of person equivalents in the catchment area (*PE* = 16,000). Finally, a continuous groundwater contribution due to infiltration processes is assumed. Thus, soil model parameter values (K_{down} = 400 m^2/d, K_{inf} = 4400 and A = 27,916 m^2) are adjusted to reach the pre-established flow rate due to infiltration. Wet-weather conditions are modelled by converting rainfall intensities into flow rate values using an empirical factor (*Qpermm* = 824 m^3/mm, **Table 1**). Finally, the sewer length is calibrated by adjusting the parameter subarea, which here corresponds to a HRT of 3 hours. A description of the rest of the FLOW RATE and TRANSPORT (sewer) model block parameters can be found in Gernaey et al. (2011).

In this study, we selected one soluble (NH_4^+) and one particulate compound (*CODpart*) to describe different types of traditional pollution dynamics. In dry weather conditions, the predefined data profiles are also sampled cyclically every 24 hours and multiplied by the pollution load and the number of person equivalents in the catchment (*PE* =16,000). Accordingly, the daily average ammonium and total *CODpart* loads in the *HH* block are 5.53 g N/(day.PE) ($NH4_{\mathrm{gperPEperd}}$) and 57.11 g CODpart/(day.PE) ($CODpart_{\mathrm{gperPEperd}}$), respectively (**Table 1**). The same assumptions as made in the previous paragraph apply here as well (industrial contribution is negligible). During wet-weather conditions, the parameters of the first-flush model should be adjusted (**Fig. 2**). Hence, the flow rate at which the particles will be flushed out of the sewer system (Q_{lim}) is set to 10,000 m^3/d. The maximum total mass of particles that can settle in the sewer (M_{Max}) is 700 kg SS, and the fraction (*FFfraction)* of particles capable of settling in the sewer network is 0.40. The same sewer length is assumed (HRT = 3 h). A description of the rest of the POLLUTANTS and TRANSPORT (first flush) model block parameters can be found in Gernaey et al. (2011).

Lastly, the wastewater temperature (*T*) is calibrated following the same dry/wet weather procedure. Dry weather temperature is modelled based on two sinus functions; one for the daily variation and another one for the seasonal variation. The daily variation is calibrated by adjusting the amplitude of the daily variation (T_{dAmp} = 0.38°C, **Table 1**). The seasonal variation can be obtained by shifting the sinus wave into the correct season and adjusting the average temperature (T_{Bias} = 17.7°C, **Table 1**). In order to describe how temperature decreases due to wet weather events, rain data is added to the influent generator as an additional input. Thus, rainfall data is multiplied with a gain ($G_{\mathrm{rain\_Temp}}$ = 0.14, **Table 1**) before subtracting it from the temperature. In order to correctly simulate the slow increase in the wastewater temperature following a rain event, a first-order transfer function is added. The rest of the TEMPERATURE model block parameters can be found in Gernaey et al. (2011). It is assumed that there will be no temperature decrease due to snow melting as the water will have warmed up to the surroundings when it reaches the WWTP due to the distance from the mountains to the WWTP.

The results of the calibrated parameters using the Bootstrap method are shown in **Table 1**. It is important to highlight that the estimations performed with the Bootstrap method are complemented by standard deviations of the calibrated parameters. These standard deviations are within the range of 0.03% to 3.8% of the calibrated value, indicating low variability on the assumed values. The standard deviations are the highest for the parameters related to the flow rate, which is due to the fact that these can compensate for each other to some extent (Weijers and Vanrolleghem, 1997). The standard deviations can also be used as inputs to run uncertainty analysis (see for example Flores-Alsina et al. (2008) and Belia et al. (2009), but this was not pursued here.

3.1.2. Simulation results

Simulation results show that the four model blocks can reproduce daily and weekly dry weather variations as is also demonstrated by the evaluation criteria shown in the **Appendix**. **Figs. 3** and **4** describe the daily flow rate and pollutant (NH_4^+, *CODpart*) profiles which represent a general behaviour, namely one morning peak, one evening peak, and late night and midday minima. The morning and evening peaks represent the increased activity of the residents just before going to work or after returning from work. The daily minimum flow rate corresponds to the night hours with reduced water consumption. The daytime flow rate shows a small decrease corresponding to the residents' working hours. When it comes to the daily variation of the wastewater influent temperature, the model describes the dynamics reflecting the differences between night and day (**Fig. 5**).

Figs. 3, **4** and **5** also demonstrate that the previously presented model blocks can predict reasonably well the wet-weather episodes. It is important to highlight that the flow rate model block was not able to reproduce all the peaks found in the measurements (**Fig. 3**, grey line). We are convinced that this is due to wet-weather episodes within the catchment that were not entirely captured by the rain gauge in Queixans (see **Fig. 1**, Section 2.3). We hypothesize that it is necessary to have additional data from rain gauges covering the entire geographical area in order to correctly describe the rain contribution to the influent flow rate, but such data are not available. We assume that the rainfall might come from a part of the catchment where data was not available (or not registered). Therefore, in order to represent all rainfall events a synthetic (rainfall) dataset had to be generated by subtracting the simulated dry weather flow from the measurements. Sewer HRT had to be accounted for to correctly describe the dynamics.

When it comes to the concentration dynamics of particulates, **Fig. 4** shows that the influent model can describe re-suspension of particulates (see days 12, 19 and 26) following a rain event (**Fig. 3**). The increase of *CODpart* load is mainly caused by the flush out of the particulate fraction that has settled in the sewer system during the preceding period with dry weather conditions. However, there are also increases in *CODpart* loads when there is no increase of flow rate (see days 7, 27 and 28), which explains the low scores on the evaluation criteria obtained for this variable. This could be due to the placement of the sensors, which are located in a tank into which the influent is pumped. The pumping of the influent could have an impact on the re-suspension of the solids. Unfortunately, it was not possible to place the sensor before this pump and therefore no conclusions could be drawn about the potential influence of re-suspension on the measured concentration dynamics.

Moreover, the NH_4^+ load is also increased during the same episodes as the *CODpart* load increases. Even though NH_4^+ is a soluble pollutant, this behaviour has been detected before during and after wet weather conditions (Wilén et al., 2006) and therefore could be an explanation for the increase in load demonstrated in the data.

Finally, **Fig. 5** demonstrates that temperature drops due to rain events (see day 15). The additional rain events that had to be included in order to correctly describe wet-weather flow rate in **Fig. 2** do not seem to have an effect on temperature dynamics (**Fig. 4**). This strengthens the hypothesis of a geographically separated rain episode not captured by the rain gauge situated close to the WWTP as the effect of cold rain water on the influent temperature is reduced during transport of the water through the sewer network.

3.2. Dynamic modelling of pharmaceutical compounds

The second part of the results details how the BSM2 influent generator describes the occurrence of a selected set of pharmaceuticals (*DS2*). For the calibration of the pharmaceuticals too few data points are available (24 data points) to use the Bootstrap method. Therefore, the automatic parameter estimation is only performed once on the available data and no standard deviation of the estimate is given (see **Table 2**).

3.2.1. Ibuprofen (IBU) and 2-hydroxyibuprofen (IBU-2OH)

Measurement data reveal a high correlation of both *IBU* and *IBU-2OH* with NH_4^+ measurements in the grab samples (r^2 of 0.69 and 0.79, respectively). These results are in agreement with Weigel et al. (2004), which state that *IBU* is mainly excreted in the urine. For this reason it was decided to use the same pre-defined data profile that was selected to describe NH_4^+ (morning peak, one evening peak, and late night and midday minima, **Table A2**). Similarly to the traditional pollutants, the generated signal (sampled cyclically) is multiplied by a gain that assumes the total *IBU* ($IBU_{\mathrm{gperPEperd}}$ = 3.71 g/(day.1000 PE)) and *IBU-2OH* ($IBU\text{-}2OH_{\mathrm{gperPEperd}}$ = 2.22 g/(day.1000 PE)) loads within the catchment (*PE* = 16,000). The average predicted loads of *IBU* and *IBU-2OH* are 59 and 35 g/day, respectively, which corresponds to concentrations at the inlet of the WWTP of 9.1 and 5.4 µg/L, respectively. The assumed hydraulic retention time was 3 hours (the same as in Section 3.1).

3.2.2. Sulfamethoxazole (SMX) and N4-acetyl-sulfamethoxazole (SMX-N4)

A correlation was found between *SMX* and its metabolite *SMX-N4* with NH_4^+ (r^2 of 0.63 and 0.58, respectively), which indicates again that these compounds are mainly excreted via urine. This correlation corresponds well with the theoretically expected distribution pattern, assuming a half-life of 10 h in the human body and a typically prescribed oral administration of twice a day (morning/evening). A similar observation was made by Göbel et al. (2005) and Plósz et al. (2010). Therefore, the ammonium data profile is also used to describe *SMX* and *SMX-N4* influent dynamics, even though the correlation is lower than that of *IBU* and *IBU-2OH* (**Table**

A2). The generation of the time series follows the same mechanisms as described in Section 3.2.1. The estimated total pollution load for *SMX* ($SMX_{gperPEperd}$) and *SMX-N4* ($SMX\text{-}N4_{gperPEperd}$) is 0.123 and 0.08 g/(day.1000 PE), respectively (**Table 2**). As a result, the quantity of compound arriving to the plant is 0.991 and 0.627 g/day (in terms of load) or 304 and 192 ng/L (in in terms of concentrations) for *SMX* and *SMX-N4*, respectively**.** It is important to highlight here that to describe the influent dynamics and the corresponding sharp pulses, the in-sewer HRT is reduced to an average of 1 hour by modifying the parameter *subarea* (see Section 3.2.4 for further discussion details).

3.2.3. Carbamazepine (CMZ) and 2-hydroxy carbamazepine (CMZ-2OH)

In this particular case, the occurrence of *CMZ* is highly correlated with the occurrence of *CODpart* in the grab samples (r^2=0.82). On the other hand, the occurrence of *CMZ-2OH* is correlated with NH_4^+ (r^2=0.63), similar to the previous compounds. This is attributed to the fact that *CMZ* is excreted 28% in the faeces (Zhang et al., 2008), while *CMZ-2OH* is only present in urine. This is expected, as one way human metabolism would reject drugs is by making them more water soluble through modifying the molecular structure (addition of e.g., glucuronide, OH moieties). Consequently, a particulate data profile was used to describe the dynamics of *CMZ*, while the NH_4^+ data profile was selected for *CMZ-2OH* (**Table A2**). The main difference between the NH_4^+ and *CODpart* data pollution profiles is that particulates load dynamics lag slightly behind the soluble pollutant fluxes. This is mainly to introduce the delay in time in the influent model (see **Fig. 2**) (further information can be found in Gernaey et al. (2011)). The loads of $CMZ_{gperPEperd}$ and $CMZ\text{-}2OH_{gperPEperd}$ loads are 0.0886 and 0.1538 g/(day.1000 PE), respectively. The total quantity of *CMZ* and *CZM-2OH* arriving at the WWTP is 1.43 and 2.41 g/d, which in concentration terms equals 219 and 370 ng/L, respectively. The estimated HRT was 3 h (the same as used in Section 3.1).

3.2.4. Simulation results

Fig. 6 shows the influent data and the model simulation results for *IBU* (**Fig. 6a**) and *IBU-2OH* (**Fig. 6b**). These show that the set of models presented herein can describe the general (daily) variation of both compounds (parent/metabolite). This is also demonstrated by the high scores on the evaluation criteria obtained for *IBU* and *IBU-2OH*. For the two cases, a substantial increase in the pollutant load can be observed during the morning/evening combined with night minima. Even though *IBU* has an irregular administration pattern, a dynamic correlation with NH_4^+ is found (**Figs. 4** and **6a, b**) which depicts the impact of human urine. The ratio between the parent compound (*IBU*) and the metabolite (*IBU-2OH*) at the inlet of the WWTP was lower (1:0.6) than a typical human excretion ratio (1:1.7) (Weigel et al., 2004). The ratio between these compounds varies from study to study (Ferrando-Climent et al., 2012; Verlicchi et al., 2012). It is well known that different *IBU* administrations (i.e. oral and topical) might introduce active, unmetabolised compounds to the sewer (Daughton and Ruhoy, 2009). The lower *IBU* ratio could also indicate a waste of ibuprofen pills (these could have been flushed). Another influencing factor in the *IBU-OH/IBU-2OH* ratio could be biotransformation within the sewer. However, there are experimental evidences that state the contrary (Jelic et al., 2015). In addition, it cannot be excluded that there is a bias in the data (Johnson et al., 2008). It is however important to note that the concentrations reported in this study are within the ranges summarised in the review by Verlicchi et al. (2012).

The comparison of the predicted behaviour with the experimental data of *SMX* and *SMX-N4* is shown in **Figs. 6c, d**. Again, the modified BSM2 influent model was capable of reproducing the behaviour of both compounds using the calibrated NH_4^+ profiles. The ratio between the parent compound (*SMX*) and its metabolite (*SMX-N4*) is 1:0.65 although the excretion ratio is 1:3 (Vree et al., 1995). This indicates a possible in-sewer re-transformation of *SMX-N4* to S*MX* as reported by numerous studies (Göbel et al., 2005; Plósz et al., 2010; Jelic et al., 2015) (this aspect will be further analysed in Section 4.2). It is important to highlight that the parameter *subarea*, which characterizes the length of the sewer and thus influences the HRT, had to be modified. We hypothesise two possible explanations for this situation. Firstly, one must notice that *SMX* is several orders of magnitude lower in load than *IBU* and consequently more sensitive to errors related to the sampling method (Ort and Gujer, 2006). This could lead to missing toilet flushes that contain *SMX* when sampling, which would also explain the different times of the occurrence of peaks during the day. Secondly, due to the sparsely distributed catchment (Section 2.1), we assume that most of the detected compound is consumed and excreted in an urban area close to the sampling point. Hence, the shorter HRT prevents complete mixing of *SMX* and therefore the concentrations remain above detection limits. Indeed, the sources of NH_4^+ and *IBU* are higher and seem to point more plausible towards a wide geographical distribution. Again, when calculating the concentrations of *SMX* and *SMX-N4* at the inlet of the WWTP, they are within the ranges summarised by Verlicchi et al. (2012).

Figs. 6e, f show a good prediction of the pollutant occurrence achieved by the modified BSM2 influent generator. Simulation and experimental results demonstrate the time difference in the different *CMZ* and *CMZ-2OH* peaks and the need to use different input data profiles to correctly describe their dynamics. The close link between *CMZ* and *CODpart* dynamics could be associated to desorption during filtering. The ratio between parent compound (*CMZ*) and metabolite (*CMZ-2OH*) in the wastewater is 1:2.9, which is similar to the one estimated by Plósz et al. (2012) in wastewater. However, these ratios differ from the theoretical excretion rate of 1:4 (Zhang et al., 2008). As *CMZ* is reported to be persistent and even suggested as an anthropogenic marker (Clara et al., 2004), biotransformation in the sewer seems unlikely to occur. However, the retransformation of metabolites of *CMZ* back into its parent compound has been reported (Vieno et al., 2007). Nevertheless, the possibility of desorption of excreted *CMZ* or the retransformation of metabolites should be further investigated. The ranges reported by Verlicchi et al. (2012) agree with the obtained concentrations in this study.

4. SCENARIO ANALYSIS

The scenario analysis presented in this section of the paper demonstrates some of the benefits of using the modified BSM2 influent generator when performing WWTP (micro)pollutant modelling studies. Therefore, for exemplary purposes, we make use of the calibrated model to study how the results are affected by changes in some settings in the two different scenarios investigated here. In *scenario 1* we show how the workload related to the measuring campaign can be reduced by synthetically generating additional high frequency data. In *scenario 2* we demonstrate the effect of including biotransformation when estimating *SMX* and its metabolite loadings at the influent of a WWTP.

4.1 Generation long-term (micropollutant) time series

Data frequency is critical in any dynamic modelling exercise (Rieger et al., 2012). This first scenario will demonstrate how the modified BSM2 influent generator can increase the length of the *IBU* time series on the basis of the available data. These extrapolated time series could replace expensive measuring campaigns based on: 1) the model predictions; and, 2) well-educated guesses obtained during the study. The extrapolation is achieved by combining calibrated outputs from the FLOW RATE model block (Section 3.1.1) and *IBU* (3.2.1). The generation of these extended time series for *IBU* (normalised) profiles is based on assuming: 1) a weekly household flow pattern including the weekend effect; and, 2) a yearly pattern including the holiday effect. The weekly pattern supposes an additional 10-25% load on Friday, Saturday and Sunday, because the area is a touristic area. Finally, the holiday period (seasonal variation) leads to a higher consumption during winter time due to an increase in the number of tourists (25%) in that period of the year. In addition, we also assume that more people get sick during winter and this also increases the consumption of *IBU*. Moreover, also the influent flow rate time series have to be extended to calculate *IBU* concentrations (FLOW RATE model block). The latter involves the generation of a seasonal infiltration profile and yearly rainfall data based on four seasons (winter, spring, summer, autumn). Further information about the model blocks and how to create these profiles can be found in Gernaey et al. (2011). **Fig. 7** depicts the extended dynamic *IBU* profile generated with the influent model. The assumed (increased) weekly variation and the effect on the total *IBU* concentration profile are shown in **Fig. 7a**. There is also a higher concentration visible during the winter (beginning and end of the time series). During the generation of a yearly profile, the rainfall has an effect (dilution) on the *IBU* concentration especially during spring, when more rain is expected in the catchment compared to other seasons (**Fig. 7b**).

4.2. Reactive sewer modelling

Previous simulation results showed that the size of the sewer system can be incorporated in the influent dynamics by increasing or decreasing the parameter s*ubarea* and consequently the HRT (Gernaey et al., 2011). The basic assumption behind this is that the larger the sewer system, the smoother the simulated diurnal flow rate and concentration variations should be. In addition, different reports have demonstrated the importance of considering biotransformation processes within the sewer systems (Hvitved-Jacobsen et al., 1998; Ashley et al., 2005). This has been shown for traditional pollutants (Sharma et al., 2008) but also for micropollutants (Jelic et al., 2015). The effect of such in-sewer reactions should especially be taken into account in the field of sewage epidemiology where estimations of illicit drug consumptions are made (Zuccato et al., 2005; van Nuijs et al., 2012; Plósz et al., 2013a). To demonstrate the impact of sorption, desorption, biotransformation and biodegradation processes on the estimated average daily load, the sewer model is upgraded with the Activated Sludge Model for Xenobiotic trace chemical framework (ASM-X) (Plósz et al., 2010; 2012). Further details about the ASM-X implementation in the sewer system are described in Snip et al. (2014). The estimation of the loads is performed with the least squares approach mentioned in Section 2.6. The estimated loads without assuming any reactions are taken from the results in Section 3.2.2.

Table 3 summarizes the estimated loads for *SMX* and *SMX-N4* when reactions in the sewer are assumed. The estimated consumptions are calculated assuming an excretion ratio of 14% of *SMX* (Vree et al., 1995). Simulation results show that there are substantial differences in both *SMX* and *SMX-N4* (calculated) loads. Specifically, a lower load of *SMX* and a higher load of *SMX-N4* should be assumed at the beginning of the TRANSPORT model block in order to take into account re-transformation of *SMX-N4* (metabolite) to *SMX* (parent compound). The ratio of *SMX:SMX-N4* obtained with the in-sewer reactions activated (1:1.17) is closer to the excretion ratio of 1:3 (Vree et al., 1995) than the ratio without reactions (1:0.69). This indicates that it is likely that *SMX-N4* is retransformed into *SMX* in this study. The re-transformation of this metabolite to sulfamethoxazole was observed during wastewater treatment (Göbel et al., 2005) and sewer transportation (Jelic et al., 2015). Even though we made some assumptions during this exercise (see Section 5.6), our aim has been to make the reader aware that accounting for reactions within the sewer system can have an important effect on the estimation of consumption rates (van Nuijs et al., 2012). The common approach used in wastewater engineering is to back-calculate the daily consumption of a micropollutant normalised per 1000 inhabitants in a given catchment from the measurements taken at the inlet of the WWTP. Depending on the analysed data, several corrections can be included to consider weekly or seasonal variations. The set of models presented here can be helpful in improving those estimates by accounting for some of the drainage phenomena occurring at the catchment level and the activation of reactions.

5. DISCUSSION

This study has demonstrated that generation of synthetic influent data with the modified BSM2 influent generator is a promising tool to improve model-based (micro)pollutant simulation studies in WWTPs since they can: 1) significantly reduce the cost and workload of measuring campaigns; 2) fill gaps due to missing data in influent flow rate/pollution/temperature profiles; and, 3) create additional disturbance scenarios following the same catchment principles as the calibrated phenomenological influent model. Even though the set of advantages derived from using these tools is extensive, the use of these tools also opens the door to several discussion points, which are analysed below.

5.1. Sampling method

In this study, grab samples were taken at different time intervals to analyse the diurnal variation of the pharmaceuticals. There has been discussion on the best way of sampling for micropollutants. Ort et al. (2010) developed guidelines on the appropriate way of sampling. Depending on the objective of the study, different sampling frequencies can be used and even though grab samples can be accurate in some cases, composite samples should be preferred. Grab samples can miss increases or decreases in concentrations, which composite samples would capture. However, one should be aware of the fact that degradation of micropollutants can also occur in composite samples (Baker and Kasprzyk-Hordern, 2011). In this study, it was decided to use grab samples, partly, to avoid degradation, and partly, due to its simplicity compared to the use of flow-proportional sampling techniques in sewer systems.

5.2. Description of compounds with irregular pattern

It is important to highlight that the load dynamics of almost all pharmaceuticals presented in this case study display a high correlation with the NH_4^+ dynamics, which clearly shows the impact of human urine. However, there are other types of pharmaceuticals with different medical uses, consumption rates, and excretion pathways and different catchment characteristics (low HRT) that would be difficult to characterize with the presented set of (phenomenological) models.

Likewise, micropollutants other than pharmaceuticals, could have a more random occurrence at the inlet of a WWTP and could therefore also not be described by the same phenomenological approach.

In order to cope with this type of compounds with random occurrence, we implemented a prototype module in the BSM2 influent generator based on Markov Chains (Snip et al., 2014). In the simplest form, the occurrence of a compound X is modelled by two states. The two states represent the presence or absence of the micropollutant and the transition probability matrix describes the probability of switching between these states. In the transition matrix information can be introduced about the frequency, intensity and duration of the events by defining: i) the set of probabilities; and, ii) the number of states. The profile obtained by the Markov Chain approach can also be combined with a more deterministic weekly and seasonal variation by multiplication. The resulting output is the pollutant flux. Further research in the practical use of the Markov chain based approach is on-going, but not presented in this study since the available data did not contain a pharmaceutical with random occurrence. A correlation with either NH_4^+ or *CODpart* was found for the pharmaceuticals considered in this study. In order to calibrate a Markov Chain, enough data has to be available to distinguish between the different states and to calculate the transition probabilities between these states (Madsen et al., 1985; Saagi et al., 2016).

5.3. Calibration procedure

The Bootstrap method is used for the automatic calibration of the traditional variables and is based on the generation of additional sets of parameters. As a result of these additional sets, no prior information on the parameter is needed and the result is an estimate of the parameter with confidence intervals (Efron, 1979; Joshi et al., 2006). A drawback of the Bootstrap method is that it needs many measured data points, which were not available for the pharmaceuticals. Also, the method is computationally heavy as the optimization is repeated for the number of additional parameter sets that are estimated (Bootstrap samples). In order to decrease the computational effort, parameters that could be estimated manually were excluded from the procedure. As has been shown by Flores-Alsina et al. (2014) the influent generator uses many non-identifiable parameters, which would increase the computational burden of an automatic calibration. Another possibility for the automatic calibration could be the Bayesian technique. Bayesian approaches are better choices for model predictions when there are poorly identifiable model parameters (Omlin and Reichert, 1999). However, the justification of the available knowledge that would be required to obtain the *a priori* distribution of the model parameters when using a Bayesian approach can be considered an entire study on its own (Lindblom et al., 2011; Rieckermann et al., 2011). In addition, the computational burden required in order to obtain "reasonable" results exponentially increases the required calibration time and effort.

The objective function used in the optimization is focused on the minimization of the error between the data and the simulation results. However, this optimization might overlook the magnitude or locations of the peaks. This was revealed when trying to use the automatic method for the *CODpart* calibration as the increases in *CODpart* after a rain event were not captured. In order to overcome this drawback, the objective function could be changed to focus on the timing or magnitude of the peaks.

5.4. Structural model deficiencies

The simulation results of the different variables (traditional and micropollutants) obtained by using the influent generator showed some deviations from the data, which are also demonstrated by the values of the evaluation criteria. An important factor which could explain some of these deviations is structural model uncertainty, or in other words, that the current model is not describing all of the fundamental phenomena. For example, there are existing models that are more accurate in accounting for pollution run-off (Bertrand-Krajewski et al., 1993; Ashley et al., 2002), combined sewer overflows (Ashley et al., 2004), storm tanks (Schütze et al., 2002; Langeveld et al., 2014) and back-flow effects (Borsányi et al., 2008) in the sewer system. Depending on the micropollutants of concern, e.g., pesticides, some of these phenomena could have a significant effect and should thus be considered as well when creating a model aiming at generating realistic influent concentration dynamics of such compounds (Loos et al., 2013).

Another simplification made in this work is in *scenario 2* (Section 4.2). For this reason, the analysis of those results must be done with care. For example, the sewer system model is a rather simplified representation, and some of the processes occurring (e.g. biofilm formation) are not accounted for. To consider the effect of the biofilm on pharmaceuticals without having a proper biofilm model, we increased the fraction of (heterotrophic) biomass (X_{OHO}) in the total COD. However, mass transfer limitations are not taken into account either. Additionally, the parameters estimated for an activated sludge unit are used for reactions in the sewer. For this reason, there might be errors in the estimation of the conversion rates taking place during the transport. Nevertheless, the increased calibration effort to adjust the additional parameter(s) would come with the drawback of making this tool less attractive for process engineers and water/wastewater designers (Flores-Alsina et al., 2014).

5.5. Development of control strategies in WWTP

The generation of multiple influent profiles can be used to develop (model-based) control strategies in the WWTPs. It is important to highlight that WWTPs are still one of the major disposal paths for micropollutants and they have not been designed to deal with those (Ternes et al., 2004). Nevertheless, there are different investigations that demonstrate that a change in operational conditions such as sludge retention time (Clara et al., 2005) can effectively improve the elimination of trace chemicals from the liquid phase by sorption, transformation or biodegradation. Co-metabolic/inhibitory behaviour with other substances present in the influent might have an overall effect on their fate within the WWTP. The results of the investigations carried out by Snip et al. (2014) demonstrate that different operating conditions can have opposite effects on the studied compounds, especially when they present co-metabolic or inhibitory behaviour with other substances present in the influent wastewater. The same has been shown for compounds with higher biodegradability at high sludge retention times compared to compounds with high sorption capacity. As the sludge turnover is lower, less compounds can sorb onto the sludge (Petrie et al., 2014).

5.6. Use in sewer epidemiology

The set of models presented here may be potentially used in sewer epidemiology. In the same way as demonstrated here for the model-based description of the influent dynamics of one anti-inflammatory compound, one antibiotic and one psychoactive drug, the modified version of the BSM2 influent generator could be used to model illicit drugs. In addition, the proposed approach could help to back-calculate consumption rates taking into account a list of possible uncertainties (sampling, analytical method, stability of biomarkers, estimation of the number of *PE* (Castiglioni et al., 2013)). As demonstrated in Section 4.2, also reactions in the sewer can be taken into account. As the ratio between the parent compound and the metabolite was closer to the theoretical excretion ratio when reactions were activated, it is probable quite likely that (some of) these reactions are indeed occurring. Considering the back-calculation of the consumption of illicit drugs and specifically cocaine as a well-known example which has shown to be unstable in wastewater, these in-sewer transformations should be taken into account (van Nuijs et al., 2011).

6. CONCLUSIONS

The key points of the presented study can be summarised as follows:

- The influent generator was capable of describing the time series for flow rate and NH_4^+ as well as *IBU* and *CMZ* (and metabolites). Nevertheless, it could not capture all the dynamics events for *CODpart*, temperature, *SMX* and *SMX-N4*. Possible causes might be data availability/quality issues as well as deficiencies in model structure.
- The potential use of the tool when: 1) interpolating incomplete data series; and, 2) extrapolating additional dynamics following the same catchment principles, were tested using the ibuprofen case as an example.
- The effects of in-sewer biotransformations and their potential impact when estimating consumption rates were pointed out using the sulfamethoxazole case. The ratios between the parent compound and the metabolite were closer to the theoretical excretion rates when biochemical reactions were activated within the sewer network
- The presented set of models has application for engineers, managers and regulators and can be used as a decision support tool in integrated (urban) water systems.

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REFERENCES

Ashley, R.M., Dudley, J., Vollertsen, J., Saul, A.J., Jack, A., Blanksby, J.R., 2002. The effect of extended in-sewer storage on wastewater treatment plant performance. Water Sci. Technol. 45, 239–246.

Ashley, R.M., Bertrand-Krajewski, J., Hvitved-Jacobsen, T., Verbanck, M., 2004. Solids in sewers. IWA Publishing, London, UK.

Ashley, R.M., Bertrand-Krajewski, J.L., Hvitved-Jacobsen, T., 2005. Sewer solids-20 years of investigation. Water Sci. Technol. 52, 73–84.

Aymerich, I., Acuña, V., Barceló, D., García, M.J., Petrovic, M., Poch, M., Sabater, S., Rodriguez-Mozaz, S., Rodríguez-Roda, I., von Schiller, D., Corominas, Ll. 2016 Attenuation of pharmaceuticals and their transformation products in a wastewater treatment plant and its receiving river ecosystem. Water Res. Accepted.

Baker, D.R., Kasprzyk-Hordern, B., 2011. Critical evaluation of methodology commonly used in sample collection, storage and preparation for the analysis of pharmaceuticals and illicit drugs in surface water and wastewater by solid phase extraction and liquid chromatography-mass spectrometry. J. Chromatogr. A 1218, 8036–8059.

Baquero, F., Martínez, J.L., Cantón, R., 2008. Antibiotics and antibiotic resistance in water environments. Curr. Opin. Biotechnol. 19, 260–265.

Belia, E., Amerlinck, Y., Benedetti, L., Johnson, B., Sin, G., Vanrolleghem, P.A., Gernaey, K.V., Gillot, S., Neumann, M.B., Rieger, L., Shaw, A., Villez, K., 2009. Wastewater treatment modelling: Dealing with uncertainties. Water Sci. Technol. 60, 1929–1941.

Bertrand-Krajewski, J.L., Briat, P., Scrivener, O., 1993. Sewer sediment production and transport modelling: A literature review. J. Hydraul. Res. 31, 435–460.

Borsányi, P., Benedetti, L., Dirckx, G., De Keyser, W., Muschalla, D., Solvi, A.-M., Vandenberghe, V., Weyand, M., Vanrolleghem, P.A., 2008. Modelling real-time control options on virtual sewer systems. J. Environ. Eng. Sci. 7, 395–410.

Buser, H.-R., Poiger, T., Müller, M.D., 1999. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environ. Sci. Technol. 33, 2529–2535.

Carballa, M., Fink, G., Omil, F., Lema, J.M., Ternes, T., 2008. Determination of the solid-water distribution coefficient (Kd) for pharmaceuticals, estrogens and musk fragrances in digested sludge. Water Res. 42, 287–295.

Castiglioni, S., Bijlsma, L., Covaci, A., Emke, E., Hernández, F., Reid, M., Ort, C., Thomas, K.V., van Nuijs, A.L.N., De Voogt, P., Zuccato, E., 2013. Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. Environ. Sci. Technol. 47, 1452–1460.

Clara, M., Strenn, B., Kreuzinger, N., 2004. Carbamazepine as a possible anthropogenic marker in the aquatic environment: Investigations on the behaviour of Carbamazepine in wastewater treatment and during groundwater infiltration. Water Res. 38, 947–954.

Clara, M., Kreuzinger, N., Strenn, B., Gans, O., Kroiss, H., 2005. The solids retention time - A suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants. Water Res. 39, 97–106.

Clouzot, L., Choubert, J.M., Cloutier, F., Goel, R., Love, N.G., Melcer, H., Ort, C., Patureau, D., Plosz, B.G., Pomiès, M., Vanrolleghem, P.A., 2013. Perspectives on modelling micropollutants in wastewater treatment plants. Water Sci. Technol. 68, 448–461.

Coe, T.S., Hamilton, P.B., Hodgson, D., Paull, G.C., Stevens, J.R., Sumner, K., Tyler, C.R., 2008. An environmental estrogen alters reproductive hierarchies, disrupting sexual selection in group-spawning fish. Environ. Sci. Technol. 42, 5020–5025.

Collado, N., Buttiglieri, G., Ferrando-Climent, L., Rodriguez-Mozaz, S., Barceló, D., Comas, J., Rodriguez-Roda, I., 2012. Removal of ibuprofen and its transformation products: Experimental and simulation studies. Sci. Total Environ. 433, 296–301.

Copp, J.B., 2002. The COST simulation benchmark: description and simulator manual. Office for Official Publications of the European Community, Luxembourg.

Daughton, C.G., Ruhoy, I.S., 2009. Environmental footprint of pharmaceuticals: the significance of factors beyond direct excretion to sewers. Environ. Toxicol. Chem. 28, 2495–2521.

De Keyser, W., Gevaert, V., Verdonck, F., Nopens, I., De Baets, B., Vanrolleghem, P.A., Mikkelsen, P.S., Benedetti, L., 2010. Combining multimedia models with integrated urban water system models for micropollutants. Water Sci. Technol. 62, 1614–1622.

Delgadillo-Mirquez, L., Lardon, L., Steyer, J.-P., Patureau, D., 2011. A new dynamic model for bioavailability and cometabolism of micropollutants during anaerobic digestion. Water Res. 45, 4511–4521.

Efron, B., 1979. Bootstrap methods: another look at the jackknife. Ann. Stat. 7, 1–26.

Ferrando-Climent, L., Collado, N., Buttiglieri, G., Gros, M., Rodriguez-Roda, I., Rodriguez-Mozaz, S., Barceló, D., 2012. Comprehensive study of ibuprofen and its metabolites in activated sludge batch experiments and aquatic environment. Sci. Total Environ. 438, 404–413.

Flores, X., Rodríguez-Roda, I., Poch, M., Jiménez, L., Bañares-Alcántara, R., 2007. Systematic procedure to handle critical decisions during the conceptual design of activated sludge plants. Ind. Eng. Chem. Res. 46, 5600–5613.

Flores-Alsina, X., Rodríguez-Roda, I., Sin, G., Gernaey, K.V., 2008. Multi-criteria evaluation of wastewater treatment plant control strategies under uncertainty. Water Res. 42, 4485–4497.

Flores-Alsina, X., Saagi, R., Lindblom, E., Thirsing, C., Thornberg, D., Gernaey, K.V., Jeppsson, U., 2014. Calibration and validation of a phenomenological influent pollutant disturbance scenario generator using full-scale data. Water Res. 51, 172–185.

García-Galán, M.J., Rodriguez-Mozaz, S., Barceló, D., Petrović, M., Rodríguez-Mozaz, S., Petrovic, M., Barceló, D., 2016. Multiresidue trace analysis of 14 pharmaceuticals, their human metabolites and transformation products by fully automated on-line solid-phase extraction-liquid chromatography-tandem mass spectrometry. In prep.

Gernaey, K.V., Flores-Alsina, X., Rosen, C., Benedetti, L., Jeppsson, U., 2011. Dynamic influent pollutant disturbance scenario generation using a phenomenological modelling approach. Environ. Model. Softw. 26, 1255–1267.

Gernaey, K.V., Jeppsson, U., Vanrolleghem, P.A., Copp, J.B., 2014. Benchmarking of control strategies for wastewater treatment plants. IWA Scientific and Technical Report No. 23. IWA Publishing, London, UK.

Göbel, A., Thomsen, A., McArdell, C.S., Joss, A., Giger, W., 2005. Occurrence and sorption behavior of sulfonamides, macrolides, and trimethoprim in activated sludge treatment. Environ. Sci. Technol. 39, 3981–3989.

Henze, M., Grady, C.P.L., Gujer, W., Marais, G. v. R., Matsuo, T., 1987. A general model for single-sludge wastewater treatment systems. Water Res. 21, 505–515.

Henze, M., Gujer, W., Mino, T., van Loosdrecht, M.C.M., 2000. Activated Sludge Models ASM1, ASM2, ASM2d and ASM2. IWA Scientific and Technical Report No. 9. IWA Publishing, London, UK.

Hug, T., Benedetti, L., Hall, E.R., Johnson, B.R., Morgenroth, E., Nopens, I., Rieger, L., Shaw, A., Vanrolleghem, P.A., 2009. Wastewater treatment models in teaching and training: The mismatch between education and requirements for jobs. Water Sci. Technol. 59, 745–753.

Hvitved-Jacobsen, T., Vollertsen, J., Nielsen, P.H.H., 1998. A process and model concept for microbial wastewater transformations in gravity sewers. Water Sci. Technol. 37, 233–241.

Jelic, A., Rodriguez-Mozaz, S., Barceló, D., Gutierrez, O., 2015. Impact of in-sewer transformation on 43 pharmaceuticals in a pressurized sewer under anaerobic conditions. Water Res. 8, 98–108.

Jeppsson, U., Pons, M.-N., Nopens, I., Alex, J., Copp, J.B., Gernaey, K.V., Rosen, C., Steyer, J.-P., Vanrolleghem, P.A., 2007. Benchmark simulation model no 2: general protocol and exploratory case studies. Water Sci. Technol. 56, 67–78.

Johnson, A.C., Ternes, T.A., Williams, R.J., Sumpter, J.P., 2008. Assessing the concentrations of polar organic microcontaminants from point sources in the aquatic environment: Measure or model? Environ. Sci. Technol. 42, 5390–5399.

Joshi, M., Seidel-Morgenstern, A., Kremling, A., 2006. Exploiting the bootstrap method for quantifying parameter confidence intervals in dynamical systems. Metab. Eng. 8, 447–455.

Joss, A., Zabczynski, S., Göbel, A., Hoffmann, B., Löffler, D., McArdell, C.S., Ternes, T.A., Thomsen, A., Siegrist, H., 2006. Biological degradation of pharmaceuticals in municipal wastewater treatment: Proposing a classification scheme. Water Res. 40, 1686–1696.

Kazadi-Mbamba, C., Flores-Alsina, X., Batstone, D.J., Tait, S., 2016. Validation of a plant-wide phosphorus modelling approach with minerals precipitation in a full-scale WWTP. Water Res. Submitted.

Lange, A., Paull, G.C., Coe, T.S., Katsu, Y., Urushitani, H., Iguchi, T., Tyler, C.R., 2009. Sexual reprogramming and estrogenic sensitization in wild fish exposed to ethinylestradiol. Environ. Sci. Technol. 43, 1219–1225.

Langeveld, J., Schilperoort, R., van Daal, P., Benedetti, L., Amerlinck, Y., de Jonge, J., Flameling, T., Nopens, I., Weijers, S., 2014. A new empirical sewer water quality model for the prediction of WWTP influent quality. 13th International Conference on Urban Drainage (ICUD), Sarawak, Malaysian Borneo, 7-12 September 2014.

Leclercq, M., Mathieu, O., Gomez, E., Casellas, C., Fenet, H., Hillaire-Buys, D., 2009. Presence and fate of carbamazepine, oxcarbazepine, and seven of their metabolites at wastewater treatment plants. Arch. Environ. Contam. Toxicol. 56, 408–415.

Lee, K.-C., Rittmann, B.E., Shi, J., McAvoy, D., Lee, A.K., 1998. Advanced steady-state model for the fate of hydrophobic and volatile compounds in activated sludge. Water Environ. Res. 70, 1118–1131.

Lindblom, E., Gernaey, K.V., Henze, M., Mikkelsen, P.S., 2006. Integrated modelling of two xenobiotic organic compounds. Water Sci. Technol. 54, 213–221.

Lindblom, E., Press-Kristensen, K., Vanrolleghem, P.A., Mikkelsen, P.S., Henze, M., 2009. Dynamic experiments with high bisphenol-A concentrations modelled with an ASM model extended to include a separate XOC degrading microorganism. Water Res. 43, 3169–3176.

Lindblom, E., Ahlman, S., Mikkelsen, P.S., 2011. Uncertainty-based calibration and prediction with a stormwater surface accumulation-washoff model based on coverage of sampled Zn, Cu, Pb and Cd field data. Water Res. 45, 3823–3835.

Loos, R., Carvalho, R., António, D.C., Comero, S., Locoro, G., Tavazzi, S., Paracchini, B., Ghiani, M., Lettieri, T., Blaha, L., Jarosova, B., Voorspoels, S., Servaes, K., Haglund, P., Fick, J., Lindberg, R.H., Schwesig, D., Gawlik, B.M., 2013. EU-wide monitoring survey on emerging polar organic contaminants in wastewater treatment plant effluents. Water Res. 47, 6475–6487.

Madsen, H., Spliid, H., Thyregod, P., 1985. Markov models in discrete and continuous time for hourly observations of cloud cover. J. Clim. Appl. Meteorol. 24, 629–639.

Martin, C., Vanrolleghem, P.A., 2014. Analysing, completing, and generating influent data for WWTP modelling: A critical review. Environ. Model. Softw. 60, 188–201.

Olsson, G., 2012. ICA and me - A subjective review. Water Res. 46, 1585–1624.

Omlin, M., Reichert, P., 1999. A comparison of techniques for the estimation of model prediction uncertainty. Ecol. Modell. 115, 45–59.

Ort, C., Schaffner, C., Giger, W., Gujer, W., 2005. Modelling stochastic load variations in sewer systems. Water Sci. Technol. 52, 113–122.

Ort, C., Gujer, W., 2006. Sampling for representative micropollutant loads in sewer systems. Water Sci. Technol. 54, 169–176.

Ort, C., Lawrence, M.G., Rieckermann, J., Joss, A., 2010. Sampling for pharmaceuticals and personal care products (PPCPs) and illicit drugs in wastewater systems: Are your conclusions valid? A critical review. Environ. Sci. Technol. 44, 6024–6035.

Petrie, B., McAdam, E.J., Hassard, F., Stephenson, T., Lester, J.N., Cartmell, E., 2014. Diagnostic investigation of steroid estrogen removal by activated sludge at varying solids retention time. Chemosphere 113, 101–108.

Plósz, B.G., Leknes, H., Thomas, K.V., 2010. Impacts of competitive inhibition, parent compound formation and partitioning behavior on the removal of antibiotics in municipal wastewater treatment. Environ. Sci. Technol. 44, 734–742.

Plósz, B.G., Langford, K.H., Thomas, K.V., 2012. An activated sludge modeling framework for xenobiotic trace chemicals (ASM-X): Assessment of diclofenac and carbamazepine. Biotechnol. Bioeng. 109, 2757–2769.

Plósz, B.G., Reid, M.J., Borup, M., Langford, K.H., Thomas, K.V., 2013a. Biotransformation kinetics and sorption of cocaine and its metabolites and the factors influencing their estimation in wastewater. Water Res. 47, 2129–2140.

Plósz, B.G., Benedetti, L., Daigger, G.T., Langford, K.H., Larsen, H.F., Monteith, H., Ort, C., Seth, R., Steyer, J.-P., Vanrolleghem, P.A., 2013b. Modelling micro-pollutant fate in wastewater collection and treatment systems: Status and challenges. Water Sci. Technol. 67, 1–15.

Ráduly, B., Gernaey, K.V., Capodaglio, A.G., Mikkelsen, P.S., Henze, M., 2007. Artificial neural networks for rapid WWTP performance evaluation: Methodology and case study. Environ. Model. Softw. 22, 1208–1216.

Richardson, S.D., 2012. Environmental mass spectrometry: Emerging contaminants and current issues. Anal. Chem. 84, 747–778.

Rieckermann, J., Anta, J., Scheidegger, A., Ort, C., 2011. Assessing wastewater micropollutant loads with approximate bayesian computations. Environ. Sci. Technol. 45, 4399–4406.

Rieger, L., Gillot, S., Langergraber, G., Ohtsuki, T., Shaw, A., Takács, I., Winkler, S., 2012. Guidelines for using Activated Sludge Models. IWA Scientific and Technical Report No. 22. IWA Publishing, London, UK.

Rivas, A., Irizar, I., Ayesa, E., 2008. Model-based optimisation of wastewater treatment plants design. Environ. Model. Softw. 23, 435–450.

Rodriguez-Roda, I.R., Sànchez-Marrè, M., Comas, J., Baeza, J., Colprim, J., Lafuente, J., Cortes, U., Poch, M., 2002. A hybrid supervisory system to support WWTP operation: Implementation and validation. Water Sci. Technol. 45, 289–297.

Rosen, C., Rieger, L., Jeppsson, U., Vanrolleghem, P.A., 2008. Adding realism to simulated sensors and actuators. Water Sci. Technol. 57, 337–344.

Saagi R., Flores-Alsina X., Fu. G, Butler D., Gernaey K.V., Jeppsson U. 2016. Catchment & sewer network simulation model to benchmark control strategies within urban wastewater systems. Environ. Model. Softw. 78, 15-30

Schütze, M., Butler, D., Beck, B., 2002. Modelling, simulation and control of urban wastewater systems. Springer, London, UK.

Sharma, K.R., Yuan, Z., de Haas, D., Hamilton, G., Corrie, S., Keller, J., 2008. Dynamics and dynamic modelling of H2S production in sewer systems. Water Res. 42, 2527–2538.

Snip, L., Flores-Alsina, X., Plósz, B.G., Jeppsson, U., Gernaey, K.V., 2014. Modelling the occurrence, transport and fate of pharmaceuticals in wastewater systems. Environ. Model. Softw. 62, 112–127.

Suarez, S., Lema, J.M., Omil, F., 2010. Removal of Pharmaceutical and Personal Care Products (PPCPs) under nitrifying and denitrifying conditions. Water Res. 44, 3214–3224.

Talebizadeh, M., Belia, E., & Vanrolleghem, P. A. 2016. Influent generator for probabilistic modeling of nutrient removal wastewater treatment plants. Environ. Model. Softw. 77, 32–49.

Ternes, T.A., 1998. Occurrence of drugs in German sewage treatment plants and rivers. Water Res. 32, 3245–3260.

Ternes, T.A., Joss, A., Siegrist, H., 2004. Scrutinizing pharmaceuticals and personal care products in wastewater treatment. Environ. Sci. Technol. 38, 392A–399A.

Van Nuijs, A.L.N., Castiglioni, S., Tarcomnicu, I., Postigo, C., de Alda, M.L., Neels, H., Zuccato, E., Barceló, D., Covaci, A., 2011. Illicit drug consumption estimations derived from wastewater analysis: A critical review. Sci. Total Environ. 409, 3564–3577.

Van Nuijs, A.L.N., Abdellati, K., Bervoets, L., Blust, R., Jorens, P.G., Neels, H., Covaci, A., 2012. The stability of illicit drugs and metabolites in wastewater, an important issue for sewage epidemiology? J. Hazard. Mater. 239-240, 19–23.

Verlicchi, P., Al Aukidy, M., Zambello, E., 2012. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment-A review. Sci. Total Environ. 429, 123–155.

Vezzaro, L., Benedetti, L., Gevaert, V., De Keyser, W., Verdonck, F., De Baets, B., Nopens, I., Cloutier, F., Vanrolleghem, P.A., Mikkelsen, P.S., 2014. A model library for dynamic transport and fate of micropollutants in integrated urban wastewater and stormwater systems. Environ. Model. Softw. 53, 98–111.

Vieno, N., Tuhkanen, T., Kronberg, L., 2007. Elimination of pharmaceuticals in sewage treatment plants in Finland. Water Res. 41, 1001–1012.

Vree, T.B., van der Ven, A.J.A.M., Koopmans, P.P., van Ewijk-Beneken Kolmer, E.W.J., Verwey-van Wissen, C.P.W.G.M., 1995. Pharmacokinetics of sulfamethoxazole with its hydroxy metabolites and N4-acetyl-, N1-glucuronide conjugates in healthy human volunteers. Clin. Drug Investig. 9, 43–53.

Weigel, S., Berger, U., Jensen, E., Kallenborn, R., Thoresen, H., Hühnerfuss, H., 2004. Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. Chemosphere 56, 583–592.

Weijers, S.R., Vanrolleghem, P.A., 1997. A procedure for selecting best identifiable parameters in calibrating Activated Sludge Model No. 1 to full-scale plant data. Water Sci. Technol. 36, 69–79.

Wilén, B.M., Lumley, D., Mattsson, A., Mino, T., 2006. Rain events and their effect on effluent quality studied at a full scale activated sludge treatment plant. Water Sci. Technol. 10, 201–208.

Zhang, Y., Geißen, S.U., Gal, C., 2008. Carbamazepine and diclofenac: Removal in wastewater treatment plants and occurrence in water bodies. Chemosphere 73, 1151–1161.

Zuccato, E., Chiabrando, C., Castiglioni, S., Calamari, D., Bagnati, R., Schiarea, S., Fanelli, R., 2005. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ. Health 4.

Table 1. The inputs for the automatic calibration are given as an initial parameter estimate with lower and upper parameter value bounds, as well as the outputs of the Bootstrap method, i.e. the calibrated parameter and its standard deviation.

Parameter	First estimate	Lower bound	Upper bound	Calibrated parameter	Standard deviation
Flow rate					
QperPE [m^3/d.1000 PE]	150	50	500	*101.9085*	3.8876
Qpermm [m^3/mm]	1250	500	3000	*819.1962*	31.0751
Ammonium					
SNHgperdperPE [g N/d/PE]	6	1	25	*5.5295*	0.0198
COD particulates					
CODpartgperdperPE [g COD/d/PE]	80	0	200	*57.1122*	0.4720
Temperature					
T_{Bias} [$\circ$C]	18	10	30	*17.6735*	0.0049
T_{dAmp} [$\circ$C]	0.4	0	1	*0.3778*	0.0071
$G_{\mathrm{rain\_Temp}}$ [$\circ$C]	0.4	0	1	*0.1409*	0.0040

Table 2. The inputs for the automatic calibration are given as an initial estimate with lower and upper parameter bounds, as well as the resulting calibrated parameter value.

Parameter	First estimate	Lower bound	Upper bound	Calibrated parameter
Pharmaceuticals load [g/d.1000PE]				
IBUgperdperPE	1	0	5	*3.71*
IBU-2OHgperdperPE	1	0	5	*2.22*
SMXgperdperPE	0.01	0	1	*0.1227*
SMX-4NgperdperPE	0.01	0	1	*0.08*
CMZgperdperPE	0.01	0	1	*0.0886*
CMZ-2OHgperdperPE	0.01	0	1	*0.1538*

Table 3. Estimation results of *SMX* and *SMX-N4* loads with and without including reactions in the sewer system.

	Estimated load without reactions (g/d.1000PE)	Estimated loads with reactions (g/d.1000PE)	Difference in estimation (%)	Estimated consumption no reactions (g/d)	Estimated consumption with reactions (g/d)
SMX	*0.1227*	*0.1091*	*-11*	*14.02*	*12.47*
SMX-N4	*0.08*	*0.1281*	*+60*		

Figure 1. The catchment under study with the location of the WWTP and the different towns.

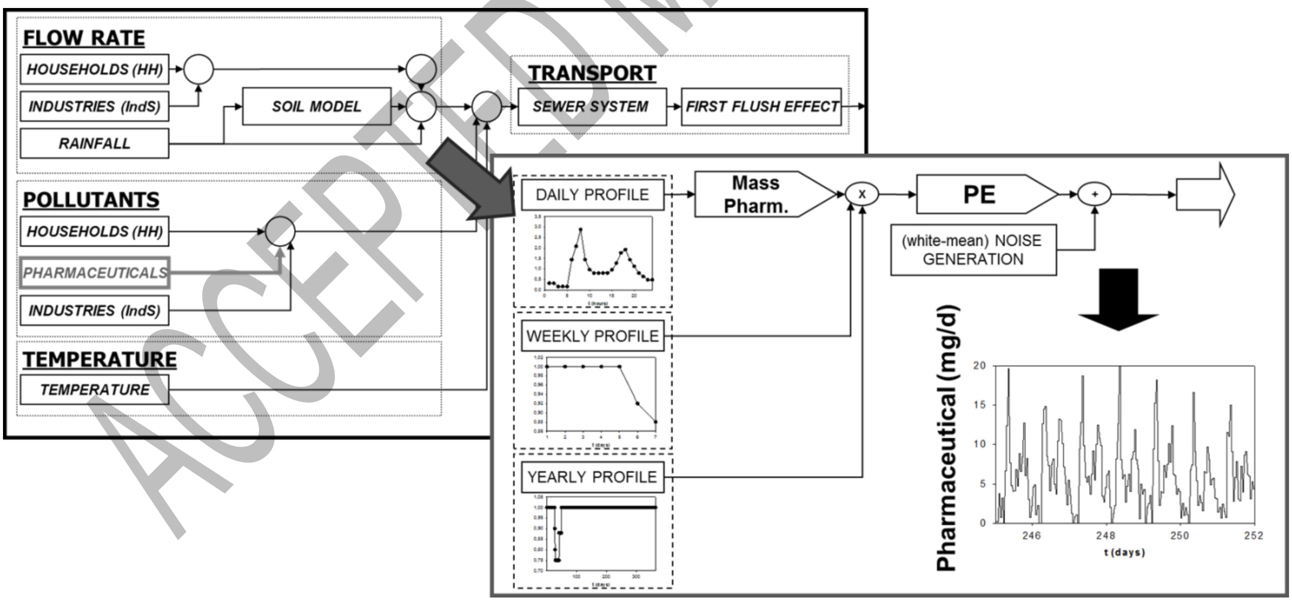

Figure 2. Model blocks used to create the different pharmaceutical loading profiles.

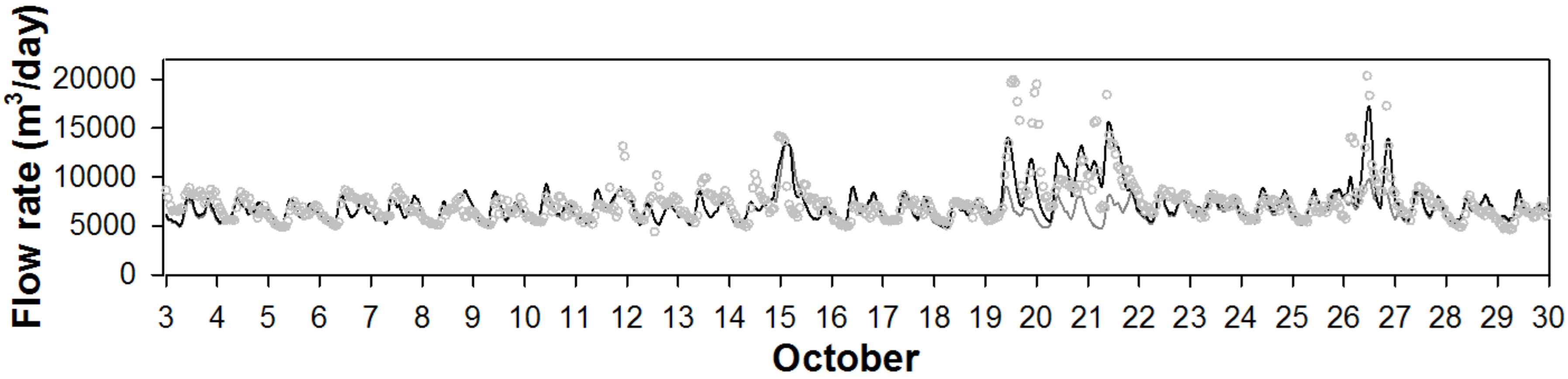

Figure 3. Calibration (grey line) of the influent flow rate data (grey dots, one hour interval) at the inlet of the WWTP. Synthetic rainfall data created to fill the missing rain events (black line) are shown as well.

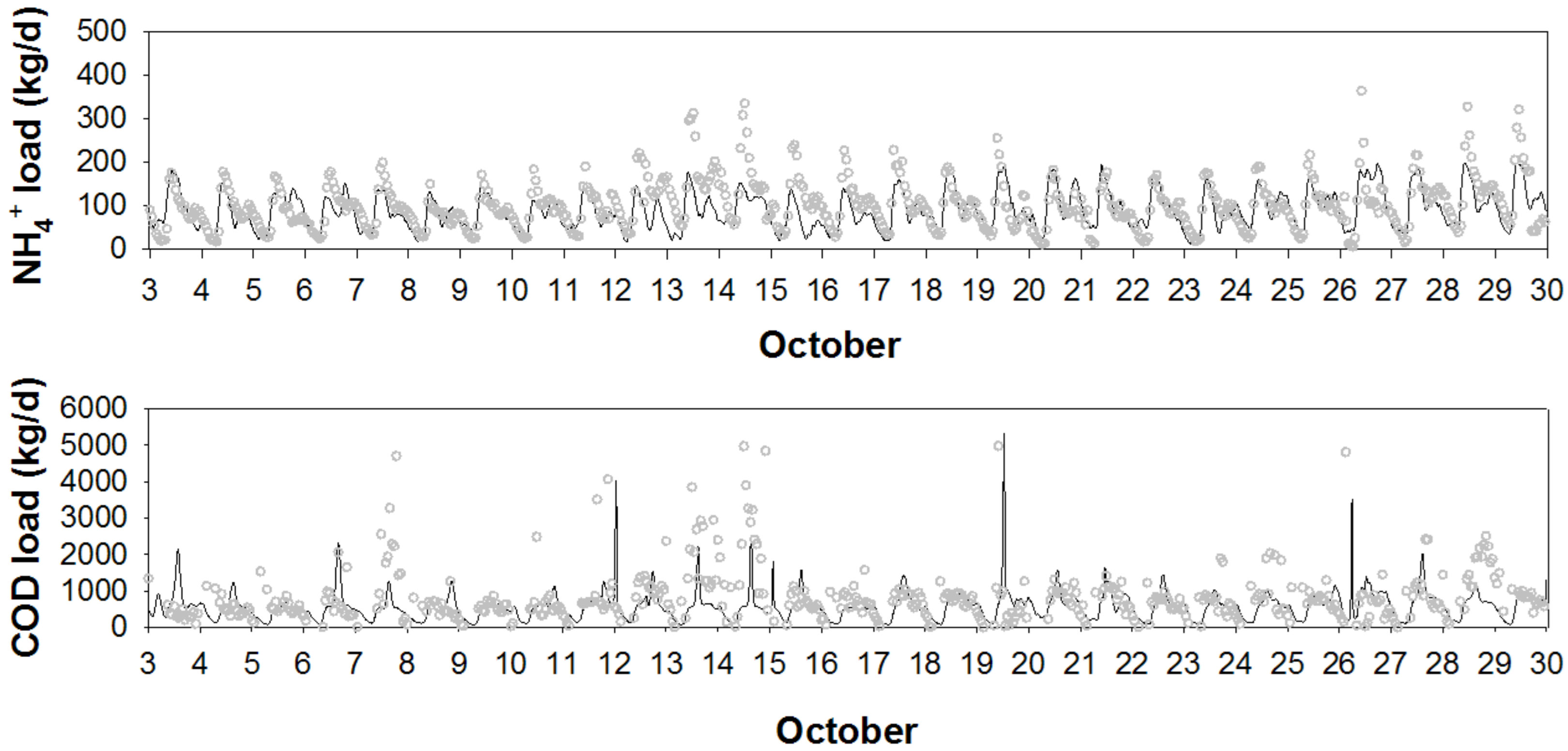

Figure 4. Calibration (black line) of the pollutant loads (top: NH_4^+, bottom: *CODpart*) data (grey dots, one hour interval) at the inlet of the WWTP.

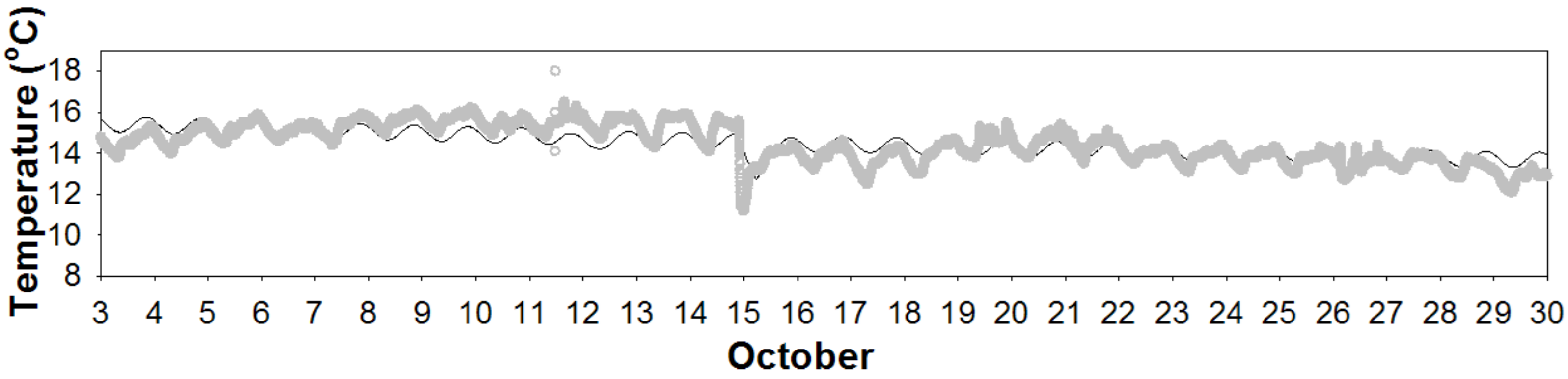

Figure 5. Simulation (black line) of the wastewater temperature data (grey dots) at the inlet of the WWTP.

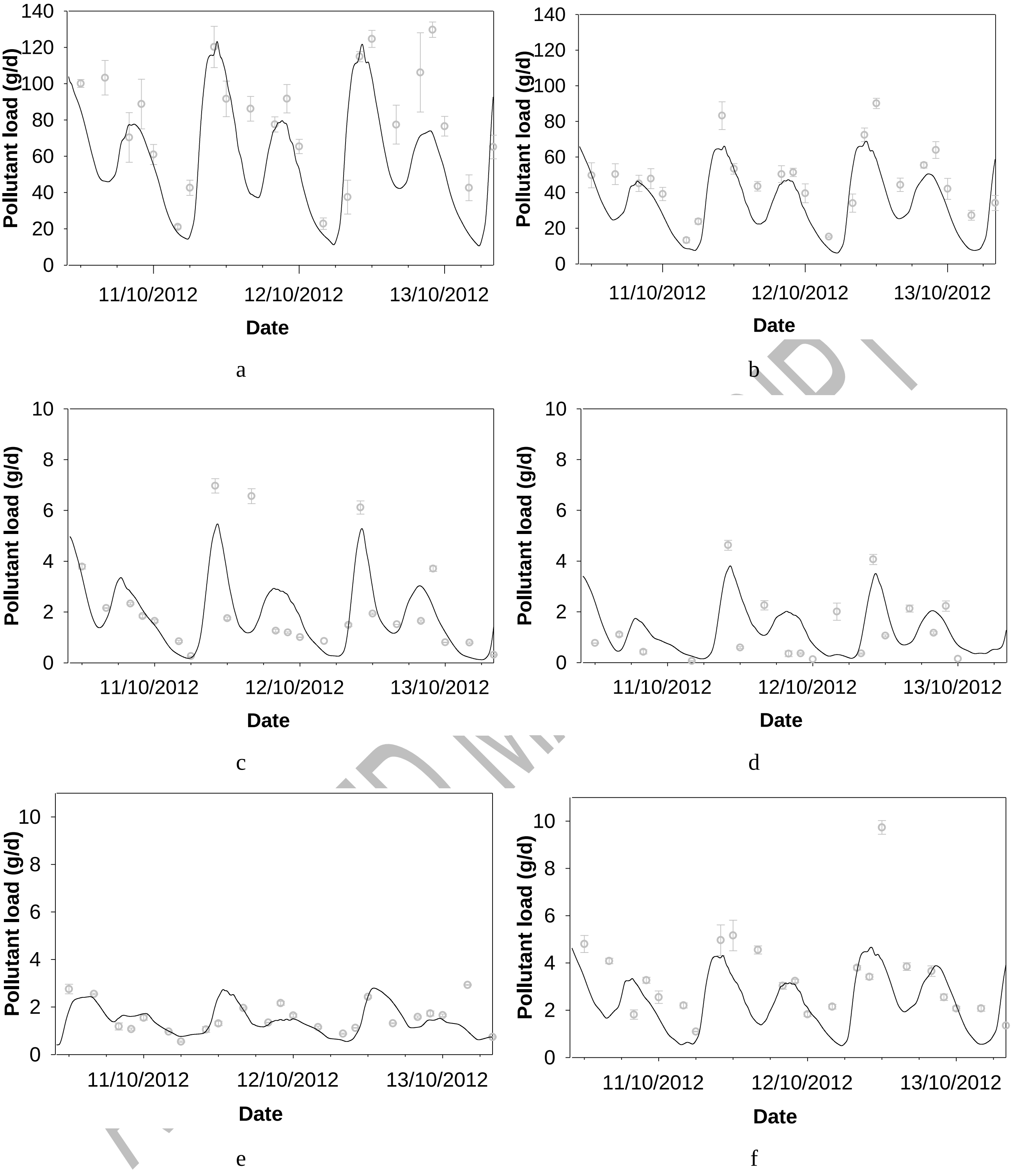

Figure 6. Simulations (black line) of the influent loads of *IBU* (a), *SMX* (c), *CMZ* (e) and the metabolites *IBU-2OH* (b), *SMX-N4* (d), *CMZ-2OH* (f) are compared to the measurements. Measurements are shown together with their standard deviations resulting from the chemical analysis (grey dots with error bars).

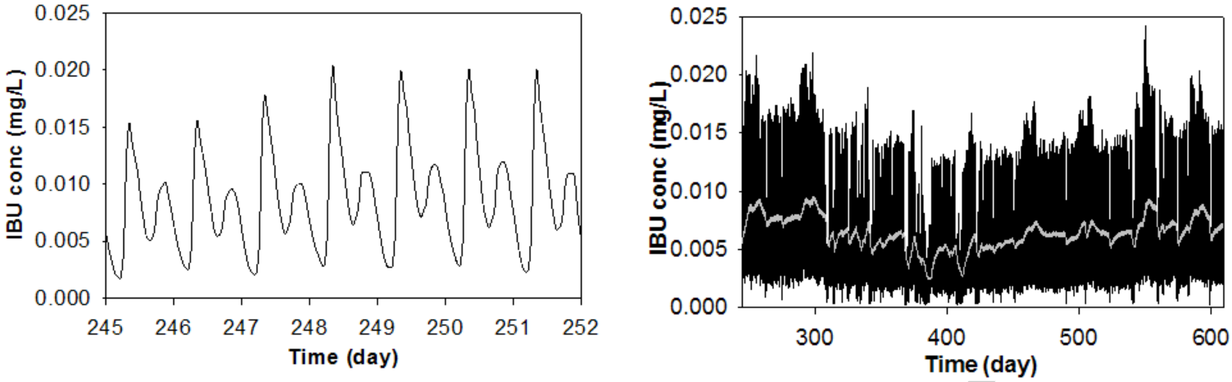

Figure 7. Simulations of influent *IBU* dynamics extended to a week (left) and a year (right, starting at 1st of January) with a smoothed yearly profile of the *IBU* (grey).