

Optimal experimental design in the evaluation of food packaging compliance with safety regulations

Miguel Mauricio-Iglesias

Department of Chemical Engineering, Universidade de Santiago de Compostela, Campus Sur, E-15782 Santiago de Compostela, Spain

Abstract: The determination of diffusivity of compounds that can be transferred from packaging into food products is a keystone to ensure consumer's safety. However, no clear guidelines exist as how the diffusion experiment should be designed in order to maximise the accuracy of the estimated parameter. With the perspective of optimal experimental design, a methodology to estimate the diffusivity of a migrating compound in a polymer is presented, both for global methods (that measure the overall concentration) and local methods (that measure the profile of concentration along the polymer thickness). To demonstrate the methodology, real experimental data (transfer of Uvitex OB from linear low-density polyethylene) are used, and the OED based methodology is benchmarked against other heuristics. It is seen that, although the OED methodology outperforms the rest of methodologies when good initial guesses are available, its performance becomes deteriorated when gross over- or underestimations of the true value are made.

Keywords: optimal experimental design; mass transfer; parameter estimation; uncertainty analysis; food technology

1. INTRODUCTION

Mass transfer from materials in contact with food, such as packaging, is a phenomenon commonly known as migration that can compromise the safety of food products. Therefore, most countries have strict regulations applying, not only to packaging, but to all materials that could be expected to be brought into contact with food (also known as food contact materials or FCM). Evaluating migration experimentally requires expensive and long experiments, consisting on testing the transfer of one or several compounds to model solutions (generally water, 10% ethanol, 3% acetic acid, olive oil). However, these experiments can be replaced or complemented by numerical simulations of mass transfer in a number of cases, thereby greatly reducing the cost and time burden. In effect, EU Directive 2002/72/EC allowed the use of *in-silico* experiments for plastic FCM, in cases where the predicted migration is well below the regulatory threshold, and provided that *generally recognised diffusion models* are available. In practice, only polymeric materials following Fick's law are considered suitable for the numerical experiments. The simulations are carried out by solving Fick's law at unsteady state (sometimes called Fick's 2nd law) which requires knowledge about the diffusivity of the migrant in the polymer (D), the mass transfer coefficient (k) and the partition coefficient between the polymer and the solution for a given migrant (KPL). In most situations, KPL and k are taken so that the estimation of migration is overestimated (e.g. $KPL \ll 1$ and $k \rightarrow \infty$), since the regulation requires carrying out a *worst-case prediction* of the level of migration (Simoneau 2010).

In contrast with other transport properties, only a handful of diffusivity values are available in databases. Furthermore, the extremely large variety of potential migrants (e.g. polymer additives) means that, in practice, the diffusivity of a migrant in a polymer must be first determined, and then that value can be used for all the applications of the migrant/polymer (i.e. different geometries, foodstuffs and/or shelf-life). Nevertheless, there is no guideline to date clarifying how the determination of the diffusivity must be carried out even though the design of the experiment can have a major impact on the result.

Predicting food safety depends critically on the prior estimation of parameters from experimental data (Versyck et al. 1999). Optimal experimental design (OED) has been used in food engineering as a means to improve the accuracy of the parameters estimated, to circumvent the existence of multiple suboptimal solutions and/or multiple equivalent solutions (Balsa-Canto et al. 2007). As a first step in the application of OED to the determination of mass transfer parameters in food packaging, in this paper we try to systematise and assess the different methods that can be used for diffusivity determination of a FCM. In particular, i) we present a methodology based on optimal experimental design (OED) aimed at defining the experimental conditions for the determination of diffusivity in FCM; ii) we propose other heuristics which lead to suboptimal but acceptable results and iii) we benchmark the methods using experimental data of a real migration experiment.

2. METHODS

2.1 Modelling mass transfer in FCM

Mass transfer from a FCM to the foodstuff results of the combination of different mechanisms, namely diffusion within the FCM, desorption at the interface and mass transfer in the food product. We focus here in the case of polymeric FCM and a liquid foodstuff, given its importance in the food industry. In order to fully characterise the system, the following parameters are needed: the diffusivity of the migrant in the polymer (D), the mass transfer coefficient in the foodstuff (k) and the partition coefficient between the polymer and the solution for a given migrant (KPL). The partition coefficient is rarely known and current guidelines are to consider that most of the migrant is eventually transferred into the foodstuff, if the migrant is somewhat soluble. Likewise, the external mass transfer resistance can be considered as negligible if the Biot number, defined in (1) is very large (e.g. $>10^5$), which is generally acceptable for low-viscosity liquids. Otherwise, both the diffusivity and the mass transfer coefficient are to be determined jointly which is possible in certain experimental setups (Martinez-Lopez *et al.* 2015).

$$Bi = \frac{kL}{D} \quad (1)$$

where L is the film thickness. Hence, for large Bi and very low KPL , the mass transfer from the polymer to the foodstuff is governed by Fick equation at unsteady state:

$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2} \quad t > 0 \quad -L < x < L \quad (2)$$

where $c(x,t)$ is the concentration of migrant, t is the time variable and x is the space variable. Considering the previous hypothesis, the following boundary and initial conditions hold:

$$c(x,0) = c_0 \quad -L < x < L \quad (3a)$$

$$c(L,t) = 0 \quad t \geq 0 \quad (3b)$$

$$\left. \frac{\partial c(x,t)}{\partial x} \right|_{x=0} = 0 \quad t \geq 0 \quad (3c)$$

It is possible to write the previous equations in a dimensionless form by introducing the following variables:

$$C = \frac{c}{c_0} \quad 0 \leq C \leq 1 \quad (4)$$

$$X = \frac{x}{L} \quad -1 \leq X \leq 1 \quad (5)$$

$$Fo = \frac{Dt}{L^2} \quad Fo \geq 0 \quad (6)$$

where C is the dimensionless concentration, X is the dimensionless space and Fo (the Fourier number) stands for the dimensionless time.

Using the magnitudes defined in (4), (5) and (6) and replacing in (2), the resulting partial differential equation, boundary and initial conditions are written:

$$\frac{\partial C}{\partial Fo} = \frac{\partial^2 C}{\partial X^2} \quad Fo > 0 \quad -1 < X < 1 \quad (7)$$

$$C(X,0) = 1 \quad -1 < X < 1 \quad (8a)$$

$$C(1,Fo) = 0 \quad Fo \geq 0 \quad (8b)$$

$$\left. \frac{\partial C(X,Fo)}{\partial X} \right|_{X=0} = 0 \quad Fo \geq 0 \quad (8c)$$

This PDE can be solved analytically (Crank 1980), hence providing the evolution of the concentration in the polymer with time and space:

$$C(X,Fo) = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{2n+1} \exp\left[-\frac{(2n+1)^2 \pi^2}{4} Fo\right] \times \cos\left[\frac{(2n+1)\pi}{2} X\right] \quad (9)$$

This equation can be integrated in space to give the mass of migrant remaining in the polymer at a given time, such as:

$$\bar{C}(Fo) = \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left[-\frac{(2n+1)^2 \pi^2}{4} Fo\right] \quad (10)$$

As equations (9-10), only depend on the dimensionless variables space (X) and time (Fo), their solution is generic and applicable to every material where (2) and conditions (3a-c) hold (Fig. 1)

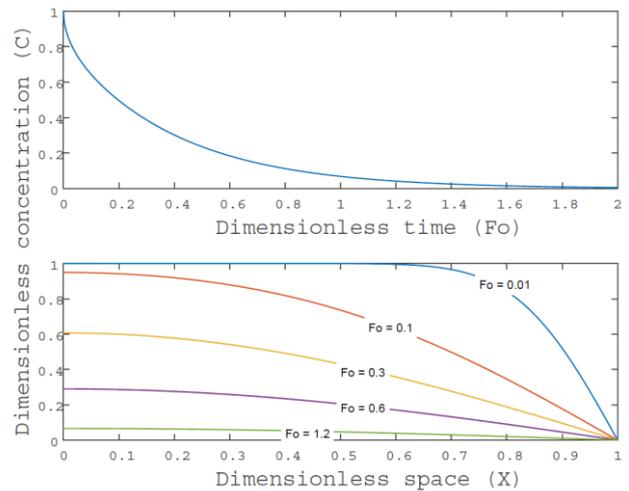


Fig. 1. Evolution of global concentration (top) and local concentration profiles (bottom) w.r.t. dimensionless time (Fo) and space (X).

2.2 Experimental methods and Fisher Information Matrix

The methods to follow the kinetics of mass transfer can be divided into two groups:

i) Methods that follow the overall mass of migrant remaining in the polymer, either by measuring the concentration in the polymer (e.g. FTIR, chromatography after dissolution of the polymer) or by following the increase of migrant in the liquid (e.g. chromatography, fluorescence, UV spectroscopy). These methods are frequently called *global methods* and their observations follow Fig. 1 (top).

ii) Methods that can measure the evolution of the concentration profile in the thickness of the polymer, such as FRAP (Pinte *et al.* 2008), microtoming (Helmroth *et al.* 2003) and Raman microspectroscopy (Mauricio-Iglesias *et al.* 2009). Other promising methods, such as Raman depth-profiling, also provide the concentration profile but require a complex data treatment to correct optical deviations (Mauricio-Iglesias *et al.* 2011) and is therefore not treated here. These methods are frequently called *local methods* and their observations follow Fig. 1 (bottom)

As only one parameter is to be estimated, the Fisher Information Matrix (FIM) becomes a scalar both for global and local methods. For global methods it is defined as:

$$FIM = \frac{\partial \bar{C}(\mathbf{F}o_i)}{\partial D} \Big|_Q^T \frac{\partial \bar{C}(\mathbf{F}o_i)}{\partial D} \quad (11)$$

And for local methods:

$$FIM = \frac{\partial C(\mathbf{F}o_i, \mathbf{X}_j)}{\partial D} \Big|_Q^T \frac{\partial C(\mathbf{F}o_i, \mathbf{X}_j)}{\partial D} \quad (12)$$

where $\mathbf{F}o_i$ is the vector of time where the sample is measured and, for local methods, \mathbf{X}_j is the vector of space where the concentration is determined. Q is a column weighting vector related to the experimental error.

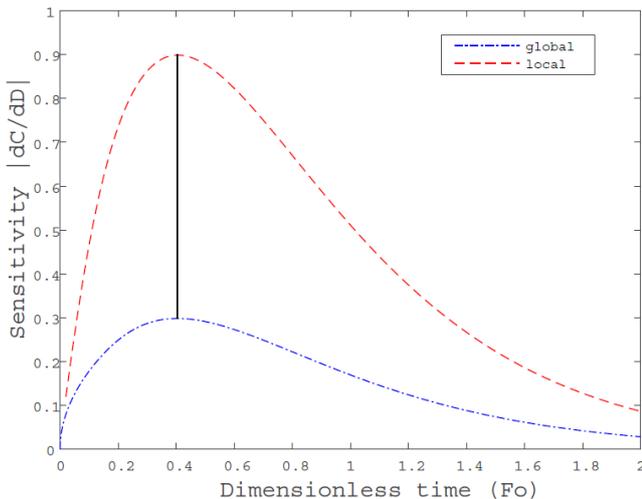


Fig. 2. Evolution of the concentration sensitivity w.r.t. the diffusivity for global methods and local methods (for local methods is the sum of 5 equally spaced samples in the sheet thickness)

The sensitivities of the concentration with respect to the diffusivity can be seen in Fig. 2. It can be seen that both

curves reach the maximum at the same point ($Fo = 0.40$), which is equivalent to a concentration of $C = 0.29$

3. METHODOLOGY FOR OPTIMAL DIFFUSIVITY DETERMINATION

The OED based methodology is summarised in Fig.3 and consist of the following steps.

- 1) *Problem definition.* The FCM to be tested is defined, including the material, the geometry (in the vast majority of cases, a thin plane sheet), thickness, etc. It is essential to define as well the migrant (at least the nominal concentration and the molecular weight), and the foodstuff (polar, nonpolar, fatty, viscous, acidic, temperature)
- 2) *Estimation of an initial guess for the diffusivity.* This step can be based on literature data. However they are very scarce. A reasonable alternative is to use Piringer's equation:

$$D = D_0 \exp \left(A'_p - 0.1351 M_w^{\frac{2}{3}} + 0.003 M_w - \frac{10454R}{RT} \right) \quad (13)$$

where A'_p is a parameter that depends on the polymer, M_w is the molecular weight of the migrant, R is the ideal gas constant and T is the temperature (Piringer 2007). This equation is supposed to overestimate the diffusivity so that, if a migration test is carried out with the obtained diffusivity value, the estimation of migration is a *worst-case prediction*.

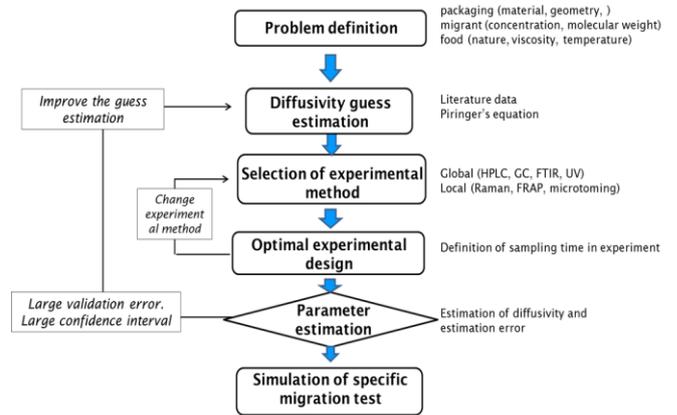


Fig 3. Task flowchart describing the methodology for diffusivity estimation based on OED

- 3) *Selection of the experimental method.* The experimental method, which can be in general local or global, must be selected based on the migrant concentration, threshold of quantification, specificity and sensitivity. In general local methods provide more information but also require more cumbersome sample preparation.
- 4) *Optimal design of the experiment to minimise the error of the diffusivity determination.* Based on the previously defined information, maximise eq. (11) for global methods or eq. (12) for local methods

using the sampling times as decision variables. A noteworthy fact is that, since (11-12) only depend explicitly on dimensionless variables, the OED sampling times determined can be used for any polymer and migrant. E.g. setting the number of samples as 5, maximising (11) would provide 5 values of Fo . These values can be translated into sampling time (t) by multiplying Fo by the guess of the diffusivity value and the thickness of the polymer.

- 5) *Experiment and parameter estimation.* Carry out the experiment and estimate the value of diffusivity together with the estimation error of the parameter (or the confidence interval) and the validation error of the estimation. If the results are not satisfactory, use the estimation to improve the experimental design; otherwise, the estimation can be used to carry out the *in-silico* specific migration test.

3.1 Suboptimal heuristic methodologies

A research on the literature dealing with food/packaging interactions showed that no specific methodology is used, at least explicitly. In order to test the proposed OED based methodology, two heuristic simple methodologies are proposed here:

- 1) Taking samples at equally spaced concentration (henceforth IsoC). This method consists on dividing the initial concentration by a given number of samples and estimating the time at which, equally spaced concentration takes place. Hence, a guess of the diffusivity value must be used to estimate the sampling times. Observing Fig. 1, this strategy is self-regulating since it will lead to taking more samples at the beginning of the experiment and fewer as the migrant is transferred.
- 2) Taking samples at equally spaced sampling time (henceforth IsoT). This method only uses the guess of the diffusivity value to determine a last point of the experiment, where the polymer would be practically depleted in migrant ($Fo = 2 \rightarrow t_{Max}$). Then, the rest of sampling times are determined by dividing the experiment duration into equally spaced time intervals.

4. CASE STUDY: DETERMINATION OF THE DIFFUSIVITY OF UVITEX OB IN POLYETHYLENE

To demonstrate the proposed optimal methodology and compare it with the other simpler methods, a case-study is presented using the data reported by Mauricio-Iglesias *et al.* (2009). The experimental data are used to find the diffusivity of Uvitex OB, an anti-UV additive, in linear low-density polyethylene (LLDPE). The film thickness is $656 \pm 64 \mu\text{m}$ and the desorption experiments are carried out for 26 days at 40°C . According to the best fit of the experimental data, the true diffusivity is $D = 7.60 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$ which is henceforth taken as the true value.

To demonstrate the OED methodology, the following procedure was followed:

- a) The number of samples was set as 5 for global methods and 3 for local methods (each local profile consisted of 22 samples along the polymer thickness). This is the number of samples used in the mentioned article.
- b) The true value of the diffusivity was considered as unknown. Two estimations were carried out. A good guess set arbitrarily to $D = 7.20 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$ and a realistic estimation by using Piringer's equation. The temperature was set at 40°C and the molecular weight of Uvitex OB equal to 431 g/mol . The corresponding initial guess was $D = 51 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, almost one order of magnitude larger than the real value.
- c) As there are no experimental data available at the sampling times determined by the methodology, simulated experimental data were produced. To do so, the mass transfer kinetics was simulated with the real diffusivity value. Following a bootstrap procedure, experimental noise was randomly added to the simulated value of concentration. To estimate realistically the experimental noise, it was taken from the residuals between the experimental data and the predictions.
- d) The bootstrap parameter estimation procedure described in step c) was repeated 200 times, which was found to be enough for convergence. The results of the procedure both for local and global methods can be seen in tables 1-2.

The results show that all the methods converge close to the real diffusivity value (with a systematic bias that underestimates the true value). Focusing on the global methods, it can be seen that the narrowest confidence intervals for the case with a good initial guess is for the OED methodology, second best for the IsoC method and third for the IsoT method. However, when the initial guess is estimated by using Piringer's equation, which is supposed to provide an overestimation of diffusivity, it can be seen that the IsoT strategy shows the narrowest confidence interval, followed by the OED methodology and finally the IsoC. This trend is confirmed for the local method, although the confidence intervals are also smaller than for the global method, due to the larger amount of information provided by measuring the concentration profile along the sheet thickness.

Table 1. Estimated diffusivity using global methods w.r.t. using an initial guess close to the experimental value and an overestimation based on Piringer's equation.

	Good initial guess ($D = 7.2 \cdot 10^{-14}$)		Poor initial guess (Piringer) ($D = 51 \cdot 10^{-14}$)	
	$D \cdot 10^{14} (\text{m}^2 \text{ s}^{-1})$	CI	$D \cdot 10^{14} (\text{m}^2 \text{ s}^{-1})$	CI
OED	7.53	[6.27-8.81]	7.49	[5.33-9.58]
IsoC	7.59	[6.15-9.14]	7.59	[5.00-9.96]
IsoT	7.62	[5.77-9.40]	7.54	[6.22-8.91]

Table 2. Estimated diffusivity using local methods w.r.t. using an initial guess close to the experimental value and an overestimation based on Piringer's equation.

	Good initial guess ($D = 7.2 \cdot 10^{-14}$)		Poor initial guess (Piringer) ($D = 51.0 \cdot 10^{-14}$)	
	$D \cdot 10^{14} (\text{m}^2 \text{s}^{-1})$	CI	$D \cdot 10^{14} (\text{m}^2 \text{s}^{-1})$	CI
OED	7.52	[7.07-7.87]	7.45	[6.71-8.12]
IsoC	7.53	[7.10-7.93]	7.53	[6.58-8.25]
IsoT	7.50	[6.73-8.22]	7.52	[7.08-7.92]

In order to find out whether this trend of results was general or specific of the particular case-study, the following simulated experiment was carried out. The FIM (11-12) was calculated for an increasing number of samples at the sampling times that were determined considering perfect knowledge. Keeping the sampling times determined (i.e. the vector of F_{0i}), the true FIM was calculated for the case of i) an overestimation of the true diffusivity value and ii) an underestimation of the true diffusivity value. The results are plotted in Fig. 4 for global methods and Fig.5 for local methods. It can be seen that, as expected, the FIM corresponding to the OED optimisation is the highest if the estimation was good (top). However, the IsoT strategy outperforms the others in the case of an overestimation (as when using Piringer's equation as a guess). The IsoC strategy is the best for an underestimation but is matched by the OED strategy as the number of samples increase.

Why this behaviour? First of all, taking a glance at Fig. 2 it can be seen that the evolution of the parameter sensitivity w.r.t time shows a considerably symmetric form. As a consequence, even if the sampling times taken are not the optimal, any strategy that distributes the sampling times along the experiment time is likely to capture most of the possible information. Secondly, as it is difficult in general to estimate the experimental error w.r.t. the concentration value (for a given migrant and a given polymer), homoscedastic error is most often assumed (characterised in the weighting matrix Q). However, when the diffusivity value used as a guess is overestimated, the IsoT strategy becomes interesting as it will estimate an experiment much shorter than expected, and therefore the sampling times will be closer to the beginning of the experiment where, the effect of the experimental error is less severe. If the overestimation is very large, the IsoT strategy will only explore a fraction of the range of concentrations (at the beginning of the experiment). This is not desired either, as the desorption experiments are usually carried out until total release in order to rule out non-Fickian effects due to solvent sorption (unless the experiment lasts more than a couple of months).

Finally, it must be borne in mind that the method test has been done here for a single iteration of the flowchart depicted in Fig. 3. In effect, if the iterative loop (from task 5 to task 2) is carried out, the OED will eventually outperform the rest of strategies as the value of the diffusivity will be known with accuracy. Albeit ideal, repeating the experiments to convergence can be a costly and time-consuming task and an

economic penalization may have to be taken into account in this case.

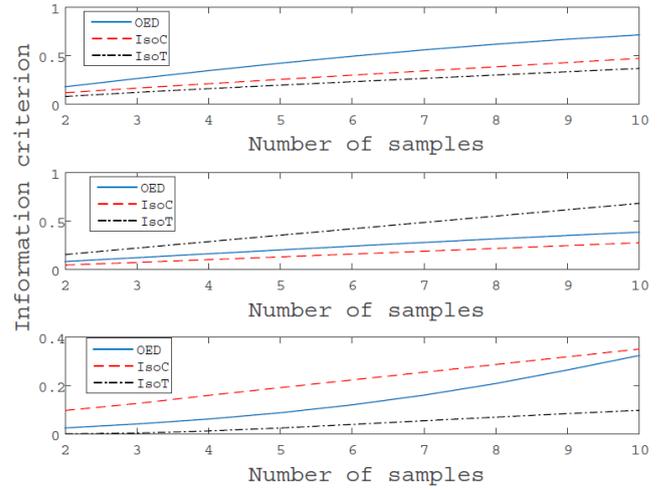


Fig 4. FIM element for the three featured strategies with global methods in case of perfect knowledge of the diffusivity ($D=1.0 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, top), overestimation ($D_{\text{guess}}=5.0 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, middle) or underestimation ($D_{\text{guess}}=0.5 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, bottom)

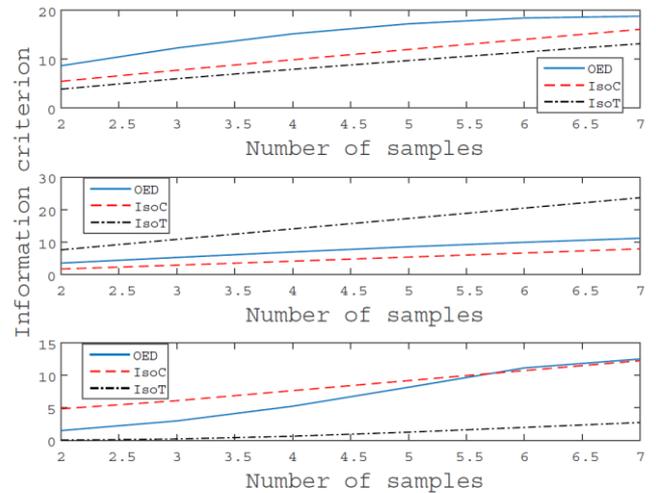


Fig 5 FIM element for the three featured strategies with local methods in case of perfect knowledge of the diffusivity ($D=1.0 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, top), overestimation ($D_{\text{guess}}=5.0 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, middle) or underestimation ($D_{\text{guess}}=0.5 \cdot 10^{-14} \text{ m}^2 \text{ s}^{-1}$, bottom)

5. CONCLUSIONS AND FUTURE PERSPECTIVES

The method proposed based on OED was seen as very accurate if a good initial guess can be provided but it becomes outperformed by the other proposed heuristics in case of severe over- or underestimation of the diffusivity value. The development of robust OED technique has been indeed developed in literature (for instance setting the OED problem as a minimax optimisation). However, for this particular application where the parameter guess is most probably an overestimation of the true value (use of Piringer's equation), it can be questioned whether a complex

procedure is suitable if only the diffusivity value is to be estimated. In contrast, other common migration estimation problems require the joint determination of KPL , k , or several diffusivities in the case of multilayer packaging. For these complex problems, the use of robust OED becomes essential as the parameters show a considerable collinearity (Martinez-Lopez et al. 2015)

This contribution is framed in a larger ongoing work to improve the design of experiments in food/packaging interactions. Future work will include the parameters that were not taken into account here (KPL and k) and a more accurate consideration of the experimental error in the optimal design of the experiments.

ACKNOWLEDGEMENTS

The author would like to acknowledge the reviewers for very constructive comments that have contributed to improve this work. This work is funded by the People Program (Marie Curie Actions) of the European Union's Seventh Framework Programme FP7/2007-2013 under REA agreement 627475 (GREENCOST). The author belongs to the Galician Competitive Research Group GRC 2013-032, programme co-funded by FEDER.

REFERENCES

- Balsa-Canto, E., Rodríguez-Fernández, M., Banga, J.R. 2007. Optimal design of dynamic experiments for improved estimation of kinetic parameters of thermal degradation. *Journal of Food Engineering*, 82, 178-188
- Commission Directive 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come into contact with foodstuffs
- Crank J. 1980. The mathematics of diffusion. New York (NY): Oxford University Press
- Helmroth, IE; M Dekker; T Hankemeier. 2003. Additive diffusion from LDPE slabs into contacting solvents as a function of solvent absorption. *J. Appl. Polym. Sci*, 90,
- Martinez-Lopez, B., Peyron, S., Gontard, N., Mauricio-Iglesias, M. 2015. Practical Identifiability Analysis for the Characterization of Mass Transport Properties in Migration Tests. *Industrial Engineering Chemistry Research* 54, 4725–4736
- Mauricio-Iglesias, M., Guillard, V., Gontard, N., Peyron, S. 2009. Application of FTIR and Raman microspectroscopy to the study of food/packaging interactions. *Food Additives and Contaminants*, 26, 11, 1515–1523
- Mauricio-Iglesias, M.; Guillard, V., Gontard, N., Peyron, S. 2011 Raman depth-profiling characterization of a migrant diffusion in a polymer. *J. Membr. Sci* 375, 165 - 171.
- Pinte J, Joly C, Plé K, Dole P, Feigenbaum A. 2008. Proposal of a set of model polymer additives designed for confocal FRAP diffusion experiments. *J Agric Food Chem*. 56(21):10003-11.
- Piringer, O. 2007 Mathematical modelling of chemical migration from food contact materials in *Chemical migration and food contact materials* by: Barnes, K. A.; Sinclair, R. and Watson, D. H. CRC.
- Simoneau, C. 2010. Applicability of generally recognised diffusion models for the estimation of specific migration in support of EU Directive 2002/72/ED. *Publications Office of the European Union*.
- Versyck, K. Bernaerts, K. Geeraerd, A.H., Van Impe, J. 1999. Introducing optimal experimental design in predictive modelling: A motivating example. *International Journal of Food Microbiology*, 51, 39-51