



A model free method for estimation of complicated adsorption isotherms in liquid chromatography



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ABSTRACT

Here we show that even extremely small variations in the adsorption isotherm can have a tremendous effect on the shape of the overloaded elution profiles and that the earlier in the adsorption isotherms the variation take place, the larger its impact on the shape of the elution profile. These variations are so small that they can be “hidden” by the discretization and in the general experimental noise when using traditional experimental methods, such as frontal analysis, to measure adsorption isotherms. But as the effects of these variations are more clearly visible in the elution profiles, the Inverse Method (IM) of adsorption isotherm estimation is an option. However, IM usually requires that one selects an adsorption isotherm model prior to the estimation process. Here we show that even complicated models might not be able to estimate the adsorption isotherms with multiple inflection points that small variations might give rise to. We therefore developed a modified IM that, instead of fixed adsorption isotherm models, uses monotone piecewise interpolation. We first validated the method with synthetic data and showed that it can be used to estimate an adsorption isotherm, which accurately predicts an extremely “strange” elution profile. For this case it was impossible to estimate the adsorption isotherm using IM with a fixed adsorption model. Finally, we will give an example of a real chromatographic system where adsorption isotherm with inflection points is estimated by the modified IM.

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1. Introduction

Today chromatography is increasingly important for analysis and purifications of pharmaceuticals, and other valuable chemicals such as antioxidants and intermediates, both in industry and in academia. However, improved technical and numerical methods for obtaining detailed knowledge about the thermodynamics and mass transfer kinetics of the processes are necessary. Estimation of adsorption isotherms are crucial for computer-assisted optimizations of preparative systems [1–3] and also give deeper understanding of the separation processes and its molecular interactions [4,5]. Chiral preparative chromatography stationary phases are much more expensive than achiral ones and also have more limited capacities. Therefore in this case it is especially important to accurately determine the, often very complex, adsorption isotherms in order to perform computer assisted optimization to determine the optimal operational conditions [1,6]. “Optimal conditions” often mean maximal production rate and/or minimum solvent consumption but it depends on the particular goal of the

separation; e.g. it desirable to have as robust, safe and environmentally friendly processes as possible [7].

Adsorption isotherms are often classified according to their shapes [8]. The most common ones is Type-I (Langmuir or similar) that are convex functions with a horizontal asymptote equal to the surface capacity. Type-III adsorption isotherms, sometimes called anti-Langmuir, on the other hand are concave with a vertical asymptote. Type-II, -IV, -V and -VI adsorption isotherms are more complex and contain at least one inflection point. Although there are many cases where the adsorption is best described by complex adsorption isotherms containing inflection points [9–12], for most liquid separation systems the adsorption is best described with Type-I adsorption isotherms that can have one (e.g. Langmuir) or several different adsorption sites (e.g. bi-Langmuir). The Langmuir model has a unimodal energy distribution and the bi-Langmuir has a heterogenic bimodal energy distribution. The bi-Langmuir model has successfully been used to describe the adsorption of enantiomers to protein and cellulose derivatized stationary phases [5], the adsorption of charged solutes [13] and the adsorption of uncharged solutes having both polar and nonpolar properties, e.g. phenol and caffeine [14]. The Tóth adsorption isotherm is an example of a one-site adsorption model that has a unimodal heterogeneous adsorption energy distribution and therefore

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accounts well for some energetically heterogeneous surfaces, e.g. polar hydrogen bindings between a polar surface and hydrogens at different positions in a peptide [15].

There are several chromatographic methods that can be used to measure adsorption isotherms, all with their advantages and drawbacks. Some methods are based on experiments where a constant stream of the solute molecules is introduced in the column, so called plateau methods. Other methods are based on processing of a few overloaded elution profiles. The Frontal Analysis (FA) plateau method is usually carried out in a series of programmed concentration steps, each step resulting in a so called breakthrough front giving one point on the adsorption isotherm curve. In the Perturbation Peak (PP) plateau method, a plateau is established and a small sample, with composition deviating from the plateau, is injected. The disturbance of the established equilibrium generates perturbation peaks with retention times related to the adsorption at that particular plateau level. The FA method is traditionally considered to be the most accurate one for determination of adsorption isotherms and it can be used for any type of adsorption [16]. However, it was recently showed that the PP method is as accurate as the FA method [17]. In both methods it is important to cover a large range of concentration plateau levels which is time-consuming, tedious and consumes large amounts of often expensive solutes.

The simplest method to obtain adsorption isotherms directly from overloaded elution profiles is Elution by Characteristic Points (ECP) where the diffuse tail of a large overloaded profile is integrated [1]. The ECP method is derived from the ideal model that assumes infinite column efficiency, but since the efficiency of a real column is finite this results in an error in the derived isotherms; the lower the column efficiency the larger the error [18]. Furthermore, the ECP theory assumes rectangular injection profiles which leads to large errors for the large injection volumes that are necessary to obtain sufficient overloading. Due to considerable post-loop dispersion for large injections the injection profiles will have extremely tailed rears. However, it was recently demonstrated, and validated, how easily this source of error can be eliminated by using the so called ECP-CUT method where a sharp slice is made on the rear of the injection sample zone before introduction into the column [19]. Interesting, and logically, is that the post-loop dispersion is not a problem when using ECP for Type-III adsorption isotherms [2].

The most recently developed method for adsorption isotherm determination is the so called Inverse Method (IM) [20–22]. Here adsorption isotherm parameters are determined from a few overloaded elution profiles in a fitting procedure that uses the whole profile, not only the rear as in ECP. The solute consumption and time requirements are very modest compared to plateau methods. However, as opposed to plateau methods, such as FA, adsorption data are not obtained directly from IM. Instead parameters in an adsorption isotherm model are estimated by solving an inverse partial differential equation problem by iteratively simulating elution profiles until the difference is small between the simulated and the experimental elution profiles.

To summarize, plateau methods such as FA and PP, are usually more accurate for adsorption isotherm determination compared to methods based on overloaded elution profiles, such as ECP and IM [1,17]. On the other hand the latter methods are much faster since the whole adsorption isotherm can be obtained from a few overloaded experiments. The ECP method has serious inherent problems and is limited to a few types of adsorption isotherms (mainly Type-I and III) and can only be used for single component adsorption isotherms. IM on the other hand can be used for multi-component problems and for separations with low column efficiency; IM is therefore the primary choice today for preparative and process chromatography. The great advantage with IM is the saving of laboratory time and solvents. One serious disadvantage with IM is that it cannot provide adsorption isotherm data directly;

it can only estimate adsorption isotherm parameters in an adsorption isotherm model. This requires that one selects an appropriate adsorption isotherm model prior to estimation.

It should be noted that small variations in the adsorption isotherm can be difficult to detect using plateau method as these small variations can be “hidden” between the measured data points and in the general experimental noise. However, extremely small variations, barely visible in the raw adsorption isotherm plot, can have a tremendous impact on the eluted overloaded profile. An interesting example of this is given in Ref. [3]. Here the elution profile, see Fig. 9 in Ref. [3], has a strange shape where the retention initially increases with increasing sample concentration, but further increases in the sample concentration decreases the retention. Such elution profiles can only be the result of having an inflection point in the corresponding adsorption isotherm. However, this inflection point is barely visible in the adsorption isotherm, see Fig. 4 in Ref. [3]. This illustrates how extremely sensitive the elution profiles are to a change in the adsorption isotherm. There are also several examples of complicated adsorption isotherms, with inflection points, that gives very “strange” elution profiles [9].

Because of the above, IM, that utilizes the whole elution profiles, could be a much better alternative than the plateau methods to handle very complicated adsorption behavior with, barely visible, (multiple) inflection points in the adsorption isotherm. However, IM is currently restricted by the need to choose an appropriate adsorption isotherm model prior to estimation. One should of course always strive to understand the adsorption behavior of the system and use this understanding to select a proper adsorption isotherm, or to derive a new adsorption isotherm; e.g. see Ref. [23] for an example of how a complex adsorption isotherm is derived. However, this might be very hard, or even impossible, for more complicated adsorption behavior. The purpose of this article is to solve the problem in these cases by approximating the adsorption isotherm with monotone piecewise interpolation, in a modified IM, instead of using a closed adsorption isotherm model.

The idea of using interpolation instead of a closed adsorption isotherm model has previously been investigated by Haghpanah et al. [24]. They used the Transport Dispersive model with a Linear Driving Force mass transfer model and estimated piecewise linear adsorption isotherms by the Inverse Method (IM) with a Sequential Quadratic Programming algorithm. They successfully applied the method to Type I and III adsorption (no inflection points) and to simple Type II adsorption (one inflection point). Here we will instead use Stineman interpolation [25] that offers significant advantages over the linear interpolation used in Ref. [24]. Significantly fewer segments are needed to estimate a nonlinear function with Stineman interpolation than with linear interpolation. In Fig. 1(a), it is shown that only 8 segments are needed to estimate a non-linear adsorption isotherm with Stineman interpolation whereas 24 is needed using linear interpolation to achieve the same accuracy. This means that the numbers of unknown parameters in the inverse problem will be considerably less when using Stineman interpolation compared to linear interpolation. More important is that Stineman interpolation has continuous derivatives whereas linear interpolation has discontinuous ones, see Fig. 1(b). This means that adsorption isotherms estimated using linear interpolation cannot be used by the reliable algorithms for chromatographic calculations that requires continuous adsorption isotherm derivative, such as Orthogonal Collocation On Finite Elements [26] or the Finite Volumes [27,28] algorithm for the Equilibrium-Dispersive model [1] that is used here.

When we are dealing with complicated adsorption behavior with multiple inflection points it is of utmost importance that the algorithm converge to an acceptable solution and not get stuck in local minima. For this purpose, we need to use a global optimization algorithm in IM, instead of a local one as used in Ref. [24]. Here we

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