1 Our approach to modeling chromatographic processes

Let's start the journey . . .

The title of this book contains the words *processes*, *modeling*, *simulation* and *design*. Let us start by briefly commenting on their respective meanings.

According to the dictionary, the word *process* has a double meaning as it can refer to either:

- a series of actions that produce a change or development (e.g. the process of digestion)
- a method of doing or producing something (e.g. the Bessemer process for the mass production of steel).

In order to clarify the distinction, let us consider that the first definition refers to *elementary processes* while the second refers to *manufacturing processes*. When speaking of *chromatographic processes*, one can refer either to elementary processes (the physicochemical mechanisms at the origin of the separation) or to manufacturing processes (like the Parex© process for producing para-xylene).

The thesis of this book is that understanding elementary processes is of primary importance for properly designing manufacturing processes.

The difference between *modeling* and *simulation* may be less obvious for many chromatographers. By modeling, we mean the task of understanding and predicting processes (either elementary or manufacturing). By simulation, we mean the task of actually representing and quantitatively evaluating a process; this is typically associated with more or less complex numerical tools. A good simulator based on a poor model will give wrong predictions (e.g. simulating ion-exchange processes without taking into account electroneutrality constraints). A good model without a simulator can give useful information and trends (e.g. the equilibrium model neglecting all sources of hydrodynamic dispersion and mass transfer limitations, as presented in Chapter 3). With a good simulator in hand, one can then address the final step, consisting of designing the manufacturing process.

A good example of what modeling can do for the chromatographer is the determination of flow rates in simulated moving beds. I used to say that finding these parameters is like finding a small piece of blue in a dark sky: for the vast majority of flow rates, the SMB delivers "purified" fractions having the composition of the feed, and is thus totally inefficient. There are, however, some special combinations of flow rate for which

the system is very efficient and delivers pure products. When the "piece of blue" has been found, one can then use more sophisticated simulators for precisely predicting performance and finally designing the machine.

Many articles and books have been devoted to the tasks of modeling and simulating chromatographic processes; some outstanding contributions were made in the second part of the 20th century. My personal selection would include the book by (Helfferich, 1962) for a rational understanding of ion exchange, the books of (Rhee *et al*., 1989) and (Helfferich and Klein, 1970) for the development of multi-component non-linear chromatography, the books of (Ruthven, 1984), (Wankat, 1986a), (Wankat, 1986b) for bridging between theory and implementation and the book edited by (Rodrigues and Tondeur, 1981) containing a collection of articles from authors who contributed outstandingly to the development of chromatography understanding (Broughton, Klein, Rhee, Tondeur, Villermaux, Wankat). Many references to these contributions will be made in the subsequent chapters.

I don't believe, however, that a book containing a comprehensive presentation of a methodology based on chemical engineering tools and associated with a broad industrial experience is available. Delivering this comprehensive scheme and methodology is our task, and achieving this goal will require clear definitions, and choices that are sometimes not those generally accepted by chromatographers. This chapter, aimed at presenting our key definitions and choices, is thus fundamental for understanding the development presented in the following chapters.

Prior to starting our modeling presentation and system description, let us mention that the book neither describes nor presents chromatographic media and chromatographic equipment. For these matters the reader is referred to (Schmidt-Traub *et al*., 2012) and (Carta and Jungbauer, 2011) for pharmaceutical and biopharmaceutical applications, and to (Wankat, 1986a), (Wankat, 1986b) and (Ruthven, 1984) for large-scale adsorption processes.

It is certainly widely accepted that modeling chromatographic systems requires taking into account thermodynamic, hydrodynamic and kinetic processes, which are involved in mass- and possibly heat-balance equations. The way to address the above-mentioned processes is probably less widely accepted, and the literature proposes many different approaches. Prior to presenting the one that I believe is the most pertinent, let us take a bit of distance from the detailed modeling activity.

As mentioned by Octave Levenspiel, citing a sentence attributed to German mathematician Friedrich Gauss, "Give me four parameters and I will draw an elephant for you, with five I will have him raise and lower his trunk and his tail."[1] The idea was that better representing reality by adding parameters is not proof of a better model. If the problem is to estimate the weight of the animal, probably a four-parameter model is adequate (we could even assume the elephant to be spherical for a rough approximation!). If the problem is to propose a drawing that could have been produced by a gifted artist, things are different. Making this choice, adapting the complexity of the modeling to the needs,

[1] (Wei, 1975) then showed that a fairly decent elephant's silhouette can be obtained with 15 terms in a Fourier series.

is the art of the scientist. When the elephant is perfectly represented with a high number of parameters, we could even see him from his back moving away. Miracle, the elephant is symmetrical! One can divide the number of parameters by two: here starts modeling![2]

1.1 System description

We consider a system containing a *chromatographic medium*, made of particles at the origin of the retention of the different species, and a fluid in which solutes are dissolved. Our goal is to describe the different zones of the system in which the solute can be located. Only simple basics are presented here; more detailed descriptions are given in the subsequent chapters.

The chromatographic medium can be silica (modified or not), polymer resins, zeolites or generally any type of solid having adsorbing, ion-exchange or exclusion properties. The associated particles are described using the following simple assumptions:

- The particles are "well-formed" particles having a well-identified skeleton and well-defined pores.
- The particles are totally rigid so that no swelling or shrinking can occur.

These two assumptions are often legitimate and widely used, but one needs to have in mind that concepts such as pore, intraparticular pore fluid and wall surface become vague in a gel or with zeolites. We also know that resins can swell; taking into account this possibility would, however, introduce additional complexity that is not required at this introductory level.

Solutes contained in a chromatographic system can be located in at least three different zones:

1. The fluid outside the particles contained in the *external* (or *extragranular*) *porosity*, i.e. the solvent or carrier fluid. Later on, this fluid will systematically be called the *fluid mobile phase*.
2. The fluid contained in the *internal* (or *intragranular*) *porosity*. This does not move like the carrier fluid and will be called the *intragranular fluid*.
3. The *solid-phase skeleton*, which is at the origin of the separation process. It can be the adsorbing medium or it can be coated with a suitable adsorbent. We will speak of the solid-phase skeleton of the chromatographic medium, even if the term is not truly appropriate when considering a coated adsorbent like reversed-phase silica. This, however, allows us to make an unambiguous distinction from the intragranular fluid.

The model which differentiates the solid-phase skeleton and the intragranular fluid phase inside the particles will be called the *Porous Model*.

The different zones that are present in a chromatographic column are schematically represented in Figure 1.1. The column volume is the sum of two fluid volumes and one

[2] From a discussion with Daniel Schweich.

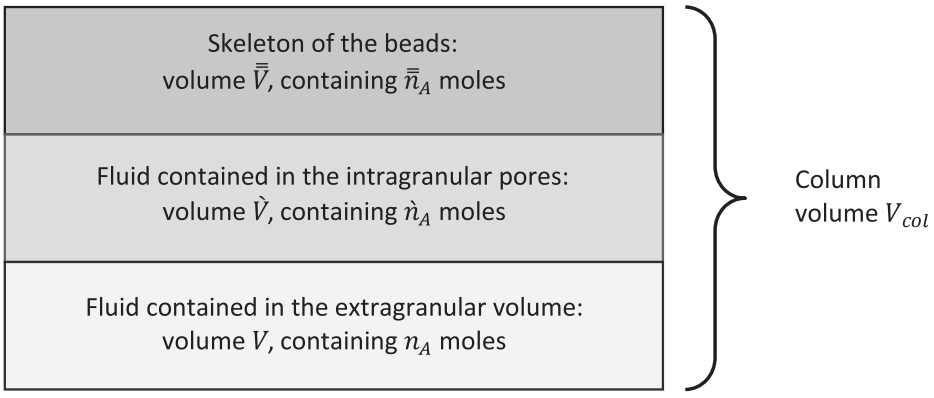

Figure 1.1 Schematic representation of the different solute locations in a chromatographic column according to the porous model.

solid volume:

$$V_{col} = V + \grave{V} + \bar{\bar{V}} \tag{1.1}$$

where V, $\grave{V}$ and $\bar{\bar{V}}$ represent respectively the volume of the fluid mobile phase, the volume of the intragranular fluid and the volume of the solid-phase skeleton.

Similarly, the total number of moles of solute in the system is also the sum of three contributions, two being in a fluid phase, one being in a solid phase:

$$n_A^{tot} = n_A + \grave{n}_A + \bar{\bar{n}}_A \tag{1.2}$$

where n_A, $\grave{n}_A$ and $\bar{\bar{n}}_A$ represent respectively the number of moles of solute A present in the fluid mobile phase, in the intragranular fluid and on the solid-phase skeleton.

Throughout this book, for a given variable X, we will call X its value in the fluid mobile phase, $\grave{X}$ its value in the intragranular fluid, $\bar{\bar{X}}$ its value on the solid-phase skeleton (thus excluding intragranular liquid). Additionally, we will denote by $\bar{X}$ the sum of $\grave{X}$ and $\bar{\bar{X}}$ for extensive variables (like volumes) or the volume average of $\grave{X}$ and $\bar{\bar{X}}$ for intensive variables (like concentrations).

It is important to understand this notation, as it will be used for many variables and parameters, including concentrations, adsorption isotherm expressions and coefficients, diffusion coefficients and temperature.

Using this notation convention, the two equations above can be further detailed:

- For volume (extensive quantity):

$$\begin{aligned} V_{col} &= V + \grave{V} + \bar{\bar{V}} \\ V_{col} &= V + \bar{V} \\ \bar{V} &= \grave{V} + \bar{\bar{V}} \end{aligned} \tag{1.3}$$

- For the number of moles (extensive quantity):

$$\begin{aligned} n_A^{tot} &= n_A + \grave{n}_A + \bar{\bar{n}}_A \\ n_A^{tot} &= n_A + \bar{n}_A \\ \bar{n}_A &= \grave{n}_A + \bar{\bar{n}}_A \end{aligned} \tag{1.4}$$

We can define concentration (intensive quantity) in the same way, so that one has:

$$\begin{aligned} C_A &= \frac{n_A}{V} \\ \grave{C}_A &= \frac{\grave{n}_A}{\grave{V}} \\ \bar{\bar{C}}_A &= \frac{\bar{\bar{n}}_A}{\bar{\bar{V}}} \end{aligned} \tag{1.5}$$

Three different concentrations are thus considered to fully describe the system: the concentration in the fluid mobile phase, C_A, the concentration in the intragranular fluid, $\grave{C}_A$, and the concentration on the solid-phase skeleton, $\bar{\bar{C}}_A$.

A fourth concentration, $\bar{C}_A$, in the fictitious pseudo-homogeneous solid of volume $\bar{V}$, is related to the others:

$$\bar{C}_A = \frac{\bar{n}_A}{\bar{V}} = \frac{\grave{n}_A \grave{V}}{\grave{V}\,\bar{V}} + \frac{\bar{\bar{n}}_A \bar{\bar{V}}}{\bar{\bar{V}}\,\bar{V}} = \grave{C}_A \frac{\grave{V}}{\bar{V}} + \bar{\bar{C}}_A \frac{\bar{\bar{V}}}{\bar{V}} \tag{1.6}$$

The concentration $\bar{C}_A$ will be named the *lumped solid-phase concentration* or *lumped concentration* for short, because the solute molecules located both in the intragranular fluid and on the solid skeleton are lumped together to define the average concentration that would prevail should the particle be a homogeneous phase. We will later speak of lumped solid phase, lumped diffusion coefficients, lumped adsorption isotherms, and so on.

The combined intragranular fluid phase and solid-phase skeleton are generally called the *stationary phase*. This is a misleading term since two phases of different concentration (solid and fluid) are involved and also because the stationary phase can be moving in a true moving bed. It is certainly a convenient concept provided it is not misused, but we prefer the term *lumped solid phase* in order to avoid ambiguities.

The concentrations defined above are volume-averaged concentrations. While non-uniform concentration profiles generally appear inside the particles during the saturation/desaturation process, we will see that the main chromatogram's characteristics depend primarily on volume-averaged concentrations.

Choices for concentration references and definitions call for the following remarks:

- A first practical remark: Instead of referring the concentrations to the volume of particles, one could choose the mass of the solid skeleton. The two approaches are strictly equivalent for rigid particles. Using the mass of the solid skeleton as a reference has some advantages in the case of possible swelling/shrinking since this mass is independent of experimental conditions, as opposed to the particle volume, which varies. The drawback of using the mass of the solid skeleton as

a reference is that modeling chromatographic columns involves mass balances written on volumes, so that the particle density must be determined. Instead of having to consider a volume of particles possibly varying with experimental conditions one has thus to consider a density of particles varying with experimental conditions. Consequently, the two approaches are equivalent, and I believe that using volume-averaged concentration is in general a bit easier to manipulate.

- A second practical remark: Chemical considerations favor the expression of concentrations in mol/m^3 (molar concentration), while chromatographers normally use kg/m^3 (massic concentration), perceived to be more practical. We plead guilty as we will often use massic concentration instead of molar concentration. The differences are in general purely academic (especially when one considers the separation of optical isomers having the same molecular mass) and we will warn the reader when this may not be the case. There is one situation for which massic concentration must be avoided: where ion exchange is concerned, molar or, even better, equivalent concentrations must systematically be used as this allows straightforward expression for the electroneutrality equation.

Nothing prohibits modeling of the chromatographic process using only lumped solid-phase concentrations, provided these concentrations are properly related to the fluid mobile phase concentrations and adequate mass balances are written. Under these conditions, the detailed structure of the particle is ignored and the chromatographic medium is approximated by a pseudo-homogeneous (lumped) phase of volume $\overline{V}$ containing $\bar{n}_A$ moles at concentration $\overline{C}_A$. A model considering only lumped solid-phase concentration will be referred to as a *Lumped Model*, in contrast to the porous model.

The choice between the lumped model and the porous model is largely a matter of convenience and objectives. When the objective is to model pressure drop, the lumped model is certainly adequate. When looking for a detailed description of the transport of solutes inside the particles in order to understand or improve these transport properties, the detailed porous model is necessary. The fact that the porous model is more detailed than the lumped model should not lead one to conclude that the former is more rigorous than the latter. Let us recall that the definitions of solid skeleton and pores are pretty fuzzy in some cases (gel ion-exchange resins, zeolites, etc.). Similarly or consequently, the definition of adsorbed phase versus fluid phase is not always as precise as it may appear: in ion-exchange resins, there is more of a continuum than two clearly different physical states, as shown in Section 4.5.4, and for adsorption, interpreting experimental results for diffusion coefficients can require assuming that adsorbed species can diffuse and are thus not as fixed as anticipated (Chapter 5). We are now approaching the profound meaning of the elephant joke ...

Finally, let us mention that, provided the *intragranular volume* is defined, the concentrations associated with the two models are related by Eq. (1.6), so that one can move from a more global description to a more detailed one or vice versa. This approach, consisting in lumping different sub-domains in a larger domain, allows for the construction of models of different complexity. This is a sort of Lego® approach, to be further presented in Chapters 2, 4 and 5.

By defining ratios between the different volumes, one can define different porosities (i.e. void fractions). The *external* or *extragranular porosity* is defined by:

$$\begin{aligned} \varepsilon_e &= \frac{V}{V_{col}} \\ 1-\varepsilon_e &= \frac{V_{col}-V}{V_{col}} = \frac{\bar{V}}{V_{col}} \end{aligned} \tag{1.7}$$

The *internal* or *intragranular porosity* is defined by:

$$\begin{aligned} \varepsilon_i &= \frac{\grave{V}}{\bar{\bar{V}}} \\ 1-\varepsilon_i &= \frac{\bar{V}-\grave{V}}{\bar{V}} = \frac{\bar{\bar{V}}}{\bar{\bar{V}}} \end{aligned} \tag{1.8}$$

The *total porosity* is a combination of the two:

$$\begin{aligned} \varepsilon_T &= \frac{V+\grave{V}}{V_{col}} = \frac{V_{col}-\bar{\bar{V}}}{V_{col}} = \varepsilon_e + (1-\varepsilon_e)\varepsilon_i \\ 1-\varepsilon_T &= \frac{\bar{\bar{V}}}{V_{col}} = \frac{\bar{\bar{V}}}{\bar{V}}\frac{\bar{V}}{V_{col}} = (1-\varepsilon_i)(1-\varepsilon_e) \end{aligned} \tag{1.9}$$

Introducing the intragranular porosity in the definition of the lumped solid-phase concentration $\bar{C}_A$ given in Eq. (1.6), one obtains:

$$\bar{C}_A = \varepsilon_i \grave{C}_A + (1-\varepsilon_i)\bar{\bar{C}}_A \tag{1.10}$$

Equation (1.10) allows a simple connection between the concentrations of the lumped model and those of the porous model. The only assumption is that intragranular pore volume, and thus porosities, can be defined.

1.2 Adsorption equilibria

Going further in the system description requires relating fluid to solid concentrations via so-called *adsorption isotherms*. The definition of the adsorption isotherm is affected by the choice of the structure model, be it the lumped model or the porous model. Again, both options are equally valid in theory and one can move from one definition to the other. The objective is to build the correct associated theoretical framework and to understand how these choices are connected with practical determination and modeling.

This section is aimed at defining equilibrium situations. This does not mean that the two phases are in general at equilibrium, but it will give us the state that the system is going to reach, given sufficient time.

- Lumped Model: The two phases considered are the fluid mobile phase and the lumped solid phase. At equilibrium, the concentrations of a single solute A in the two phases are related by:

$$\bar{C}_A = \bar{f}_A(C_A) \tag{1.11}$$

Strictly speaking, the equation $\bar{C}_A = \bar{f}_A(C_A)$ relating the lumped solid-phase concentration to the fluid mobile phase concentration of the single solute A is not the "phase equilibrium law" (or adsorption isotherm) as usually defined by thermodynamicists. We will name it the *lumped adsorption isotherm*.

Notice that when more than one solute is present, the adsorption of one solute is in general influenced by the presence of the others, as shown in Chapter 4.

- Porous Model: The three phases considered are the fluid mobile phase, the intragranular fluid and the solid skeleton. The fluid–solid equilibrium is assumed to be reached between the intragranular fluid phase and the solid skeleton phase, so the concentrations of a single solute A in these two phases must be related by:

$$\bar{\bar{C}}_A = \bar{\bar{f}}_A(\grave{C}_A) \tag{1.12}$$

Notice again that when more than one solute is present, the adsorption of one solute is in general influenced by the presence of the others, as shown in Chapter 4.

$\bar{\bar{f}}_A$ is the "phase equilibrium law" according to the thermodynamicists.[3] Equation (1.12) is awkward to use as it involves the concentration of solute in the intragranular fluid, which is unknown *a priori*.

At first glance, since the solvent is the "same" in the extragranular fluid and in the intragranular fluid, one may consider that $\grave{C}_A = C_A$. This is the case in many situations – with some meaningful exceptions such as Donnan ion exclusion and size exclusion, for which $\grave{C}_A \neq C_A$.

In general, one can assume that the intragranular fluid and the extragranular fluid concentrations are related by:

$$\grave{C}_A = \grave{f}_A(C_A) \tag{1.13}$$

Equation (1.13) is the partition law between intragranular fluid and the extragranular fluid. It will later be called the *partition law*.

The concentrations on the solid skeleton and in the fluid mobile phase are then related by:

$$\bar{\bar{C}}_A = \bar{\bar{f}}_A(\grave{C}_A) = \bar{\bar{f}}_A\left(\grave{f}_A(C_A)\right) \tag{1.14}$$

The lumped solid concentration being given by Eq. (1.10), the *lumped equilibrium law* $\bar{f}_A$ connecting the lumped solid-phase concentration to the fluid mobile phase concentration is related to the equilibrium law $\bar{\bar{f}}_A$ by:

$$\bar{C}_A = \bar{f}_A(C_A) = \varepsilon_i \grave{f}_A(C_A) + (1 - \varepsilon_i)\bar{\bar{f}}_A\left(\grave{f}_A(C_A)\right) \tag{1.15}$$

The two models are finally equivalent if one uses Eq. (1.15) to relate the different concentrations.

[3] This assumes that solute A is the only component present in the system, which is impossible in liquid chromatography. Defining a single-component adsorption isotherm is not that simple; more information will be given in Chapter 4.

The two approaches are thus theoretically connected. However, determining independently the partition law $\grave{C}_A = \grave{f}_A(C_A)$ and the adsorption law $\bar{\bar{C}}_A = \bar{\bar{f}}_A(\grave{C}_A)$ is not an easy task, even in the simplest situations.

We will further illustrate the models by successively assuming that:

- there are no exclusion-like processes, so that $\grave{C}_A = C_A$
- the equilibria are linear, or the solutes so dilute that the equilibrium law "reduces to its initial slope".

1.2.1 Equal concentrations in fluid mobile phase and intragranular fluid

Under the assumption $\grave{C}_A = C_A$, Eq. (1.15) connecting the adsorption law to the lumped adsorption law becomes:

$$\bar{f}_A(C_A) = \varepsilon_i C_A + (1 - \varepsilon_i)\bar{\bar{f}}_A(C_A) \tag{1.16}$$

This relationship shows that the lumped equilibrium law and the equilibrium law are simply related by a linear relation involving the concentration in the fluid mobile phase. The two models can thus be used in very similar ways, but, again, this assumes that the fluid mobile phase and intragranular fluid have the same concentration. In this case, besides purely academic considerations, the two models are indistinguishable at equilibrium.

1.2.2 Linear equilibria

We now relax the assumption of identity between concentrations in the fluid mobile phase and the intragranular fluid, but we assume that the concentrations in the different phases are linearly related. This may or may not be true, but non-linearity will not change our conclusions.

Under the linearity assumption, the concentration of solute A in the intragranular fluid is related to the concentration of solute A in the fluid mobile phase by:

$$\grave{C}_A = \grave{K}_A C_A \tag{1.17}$$

In the absence of exclusion, the coefficient $\grave{K}_A$ equals 1, so the concentrations in the intragranular fluid and fluid mobile phase are identical.

The concentration of the adsorbed phase is also assumed to be linearly related to the concentration in the intragranular fluid by a linear adsorption law:

$$\bar{\bar{C}}_A = \bar{\bar{K}}_A \grave{C}_A \tag{1.18}$$

The coefficient $\bar{\bar{K}}_A$ will be called *Henry's coefficient*. The reader may be more familiar with the expression "Henry's constant". However $\bar{K}_A$ is not constant: it varies with temperature, composition of the solvent and so on, so we prefer the term "coefficient".

The two above equilibrium relations together with Eq. (1.15) allow an estimate of the lumped solid-phase concentration:

$$\overline{C}_A = \varepsilon_i \grave{C}_A + (1-\varepsilon_i)\overline{\overline{C}}_A = \left[\varepsilon_i \grave{K}_A + (1-\varepsilon_i)\grave{K}_A \overline{\overline{K}}_A\right] C_A \tag{1.19}$$

which can also be written:

$$\overline{C}_A = \overline{K}_A C_A \tag{1.20}$$

with

$$\overline{K}_A = \varepsilon_i \grave{K}_A + (1-\varepsilon_i)\grave{K}_A \overline{\overline{K}}_A \tag{1.21}$$

The lumped solid-phase concentration is thus linearly related to the extragranular concentration via the *lumped Henry's coefficient* $\overline{K}_A$. The lumped Henry's coefficient is a linear combination of unrelated equilibrium constants. This means that the initial slope of an experimentally determined adsorption isotherm is a combination of intragranular porosity, partition law and adsorption. For readers familiar with the subject, this means that there is no way to investigate the adsorption law using retention time measurements unless intragranular porosity and partition law are known.

If the solutes are not excluded from the particles so that $\grave{K}_A = 1$, Eq. (1.21) expressing the lumped Henry's coefficient $\overline{K}_A$ becomes:

$$\overline{K}_A = \varepsilon_i + (1-\varepsilon_i)\overline{\overline{K}}_A \tag{1.22}$$

so that the lumped Henry's coefficient should at least equal the intragranular porosity even if the solute does not adsorb on the solid.

1.3 Mass balances: retention times

An important part of chromatography modeling consists in determining retention times. These retention times can be associated with a pulse injection of a given solute at trace level or with large frontal injections of a complex multi-component mixture. Their prediction systematically requires writing and solving mass balances. The way these mass balances are written is largely influenced by the choice of the lumped model or the porous model.

General methodologies for simulating chromatograms will be given in the following chapters. For the time being, we simply consider a column of infinite efficiency (equivalent to an infinite number of plates), initially solute-free, and fed by an *incompressible* carrier fluid at constant flow rate containing a solute A at concentration C_A^F. Additionally, we assume the establishment of a linear equilibrium. The concentration at the outlet of the column is thus expected to stay at zero until the so-called *retention time* t_R is attained, and then to abruptly increase to C_A^F. At the end of the saturation process, one assumes that, everywhere in the column, the extragranular fluid concentration equals C_A^F and that the concentrations $\overline{\overline{C}}_A$ and $\grave{C}_A$ are in equilibrium with C_A^F. The situation is schematically represented in Figure 1.2. At the very time t_R the outlet concentration reaches the inlet