has a K much greater than 1, and the other much less than 1, a single extraction will cause nearly complete separation. This fortunate circumstance will arise only if two solutes are very different chemically, in which case the pair could no doubt be separated easily by some other method. If the two solutes have similar, but not identical, distribution coefficients, a single extraction will cause only a partial separation with an enrichment of one solute in one solvent and an enrichment of the other solute in the other solvent. If we are to make an adequate separation, we must repeat the process many times. After the first extraction, each phase may be further equilibrated with a fresh portion of the opposite solvent. By a systematic recycling of the various intermediate fractions, a satisfactory separation can eventually be achieved at a cost of considerable amounts of solvent and numerous manipulations. Lyman Craig has developed a machine to perform these operations semiautomatically. The mathematical relations describing the Craig process are helpful in understanding many column operations because the distribution profile of a substance as it passes through this apparatus approximates that obtained in a chromatographic separation to be discussed in the following chapters.

3–5 THE CRAIG METHOD OF MULTIPLE EXTRACTION

Craig Apparatus. The apparatus consists of a series of separatory vessels connected so that the outlet of one vessel flows into the inlet of the next. Each vessel consists of two chambers connected to each other as shown in Figure 3–5. The operation is begun by introducing through inlet A an amount of the heavier solvent which will fill chamber B somewhat less than half full. Each of the vessels in the train is filled in a like manner. The sample to be separated is introduced as a solution in the lighter solvent into chamber B of the first vessel. The assembly is rocked back and forth through an angle of about 35° around pivot P. After equilibration has been achieved and the solvents separated into two layers, the assembly is rotated 90° clockwise. The lighter solvent flows through connecting tube C into chamber D while the heavier solvent is trapped in the lower part of chamber B. When the assembly is rotated back to its original position, the lighter solvent now in D flows through outlet E into chamber B of the *next* stage. Hundreds of these assemblies can be mounted side by side or in banks, and all of them rocked and rotated simultaneously by a motor timed to operate as indicated.

The Craig Process. The Craig machine has been a very powerful and practical tool in biochemistry for extremely difficult separations of substances that are chemically very similar. In order to describe the operation mathematically, we will

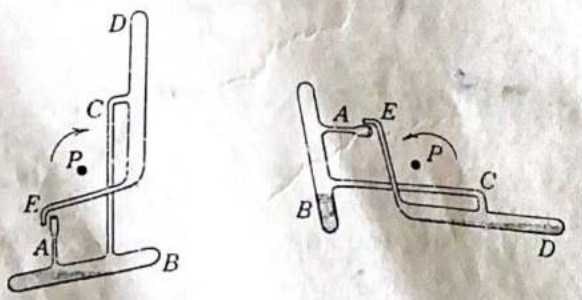

Figure 3–5 Extraction vessel of the Craig apparatus.

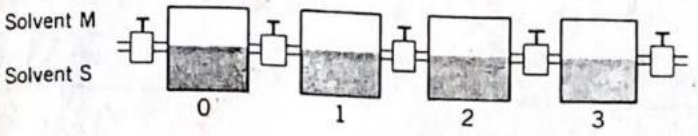

Figure 3–6 Apparatus for the ideal Craig process.

use a schematic representation of the machine shown in Figure 3–6. Consider a series of vessels numbered consecutively from 0. Each vessel is of the same size and is initially half filled with the heavier solvent to be used (solvent *S*). There is also a series of connecting tubes and valves so that the solvent to be contained in the upper half of the vessels can be transferred from one vessel to the next when desired. No mixing is allowed during the transfer. We will follow the course of a single solute, although whether or not it is present in a mixture is immaterial since each solute should behave independently of all others. The arithmetic will be greatly simplified if we assume that each phase occupies one-half the volume of the vessel and that the K_D of the solute is 1.

To start the operation, we introduce the sample dissolved in the first portion of the lighter solvent, *M*, into vessel 0. After equilibration (shaking and settling), one-half of the solute is in the upper phase and one-half in the lower phase, *S*. The upper layer, solvent *M*, is then transferred to vessel 1 and a fresh portion of solvent *M* is added to vessel 0. After equilibration, one-quarter of the solute is now found in each phase of each vessel, 0 and 1. Next solvent *M* in vessels 0 and 1 is transferred to vessels 1 and 2, respectively, along with a fresh batch of solvent *M* to vessel 0. The pattern of the operation has now been established and the distribution of the solute develops as in Figure 3–7 in which the vessels are labeled across the top and the number of transfers labeled down the side. To continue the process, it is easier to tabulate the fraction of the solute found in each vessel (including both layers) after *n* transfers and equilibrations as shown in Table 3–2.

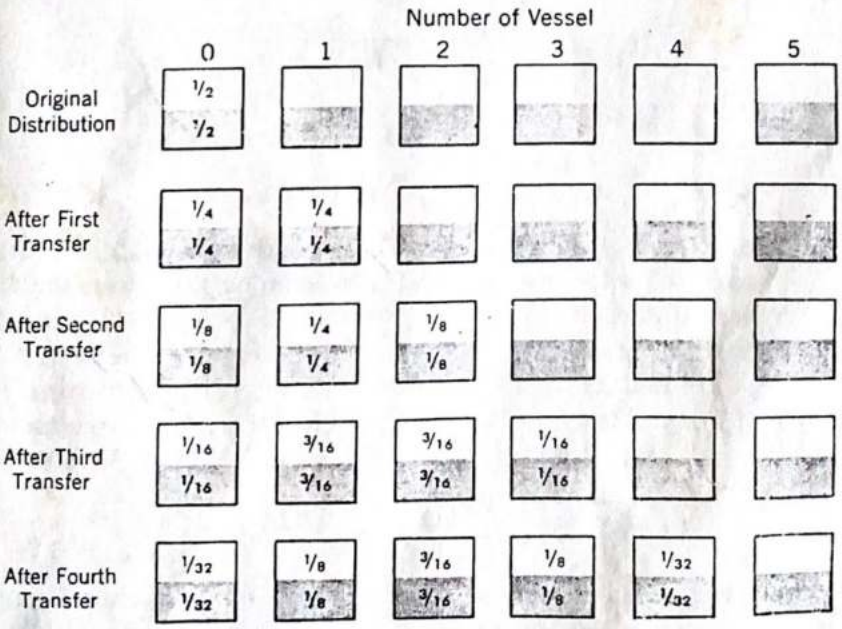

Figure 3–7 Successive distribution of solute in the Craig process. Fraction of total solute in each layer of each vessel for $K_D = 1$ and $V_M = V_S$.

Table 3–2 Distribution of Solute in the Craig Process: Fraction in Each Vessel

No. of Transfers	Vessel Number								
	0	1	2	3	4	5	6	7	
0	1								$\times 2^{0}$
1	1	1							$\times 2^{-1}$
2	1	2	1						$\times 2^{-2}$
3	1	3	3	1					$\times 2^{-3}$
4	1	4	6	4	1				$\times 2^{-4}$
5	1	5	10	10	5	1			$\times 2^{-5}$
6	1	6	15	20	15	6	1		$\times 2^{-6}$
7	1	7	21	35	35	21	7	1	$\times 2^{-7}$

The numbers on each line of the table are the successive terms in the expansion of the binomial $(p + q)^n$, that is,

$$(p+q)^n = p^n + np^{n-1}q + \frac{n(n-1)}{2!}p^{n-2}q^2 + \frac{n(n-1)(n-2)}{3!}p^{n-3}q^3 + \cdots + q^n \tag{3–12}$$

where p is the fraction of total solute which is in phase S of any vessel, q is the fraction of total solute in phase M of the same vessel, and n is the number of transfers. We define the distribution coefficient* as

$$K_D = \frac{C_S \text{ (the lower, or stationary phase)}}{C_M \text{ (the upper, or moving phase)}} \tag{3–13}$$

Then

$$p = \frac{C_S V_S}{C_S V_S + C_M V_M} = \frac{K_D V_S}{K_D V_S + V_M} \tag{3–14}$$

and

$$q = \frac{C_M V_M}{C_S V_S + C_M V_M} = \frac{V_M}{K_D V_S + V_M} \tag{3–15}$$

In the example we have been discussing, $K_D = 1$ and $V_S = V_M$; therefore, from Equations 3–14 and 3–15, both p and q are 1/2. We can now generate the numbers in Table 3–2 by substituting $p = 1/2$ and $q = 1/2$ into Equation 3–12, carrying out the binomial expansion for any given number of transfers. For example, after 7 transfers, vessel 0 contains $(1/2)^7$ or 1/128 of the solute, vessel 1 contains $7(1/2)^7$ or 7/128 of it, vessel 2 contains $((7 \times 6)/2)(1/2)^7$ or 21/128 of it, etc. In the general case, $V_S \neq V_M$ and $K_D \neq 1$, and a combination of Equations 3–12 to 3–15 yields

$$(p+q)^n = \left(\frac{K_D V_S}{K_D V_S + V_M} + \frac{V_M}{K_D V_S + V_M}\right)^n \tag{3–16}$$

The calculations become tedious for many transfers, but the general approach is straightforward following Equation 3–16.

* Note that K_D defined here is the inverse of K_D defined for Equation 3–11.

***Example/Problem* 3–2.** Calculate the distribution of a substance after three transfers in a Craig apparatus for which $V_S = 2$ ml and $V_M = 4$ ml. The distribution coefficient as defined by Equation 3–13 is 3.0.

$$p = \frac{K_D V_S}{K_D V_S + V_M} = \frac{3 \times 2}{3 \times 2 + 4} = \frac{6}{10}$$

$$q = \frac{V_M}{K_D V_S + V_M} = \frac{4}{3 \times 2 + 4} = \frac{4}{10}$$

$$(p+q)^n = \left(\frac{6}{10}\right)^3 + 3\left(\frac{6}{10}\right)^2\left(\frac{4}{10}\right) + 3\left(\frac{6}{10}\right)\left(\frac{4}{10}\right)^2 + \left(\frac{4}{10}\right)^3$$

$$= \frac{216}{1000} + \frac{432}{1000} + \frac{288}{1000} + \frac{64}{1000}$$

Thus, the first four vessels contain 21.6%, 43.2%, 28.8%, and 6.4%, respectively.

So far we have considered only a single solute which is transferred a number of times, and we have shown that the distribution among the vessels is clearly a function of several variables: K_D, V_S/V_M and n. Let us now consider a sample which contains two components (solutes), each with a different distribution coefficient; for example, $K_A = 1/2$ and $K_B = 1$. If our sample is small so that none of the solutions become saturated, each of the solutes will behave independently. That is, we can calculate the distribution of each solute, as if it were the only one present. Curve A in Figure 3–8 shows the fraction of total solute A ($K_A = 0.5$) in each vessel (0 to 8) after eight transfers ($n = 8$). Curve B shows the distribution for solute B ($K_B = 1.0$). If the experiment is carried through 200 transfers, the distributions are as shown in Figure 3–8, curves A' and B'. Several important observations are worth noting:

1. With a separation factor of 2 ($\alpha = K_B/K_A$), 8 transfers give only a very partial separation of the solutes. All vessels, (except the first) contain significant amounts of both A and B.

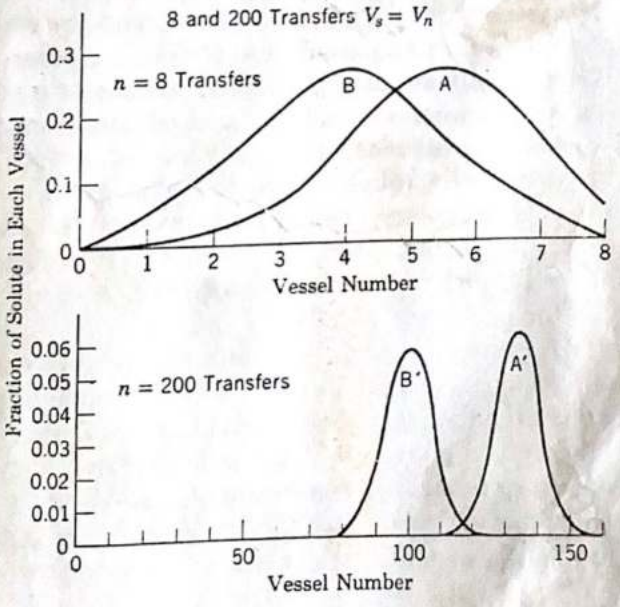

Figure 3–8 Distribution of solutes A ($K_A = 0.5$) and B ($K_B = 1.0$) in Craig separation after 8 and 200 transfers. $V_M = V_S$.

2. After 200 transfers, the separation is still not complete but probably adequate for most purposes. Vessels 80 to 117 contain nearly all of solute B and vessels 118 to 155 contain nearly all of solute A. Vessels 112 to 123 could be discarded to obtain a higher purity but with a lower yield.
3. Another 100 transfers would improve the separation but would increase the time and the amount of solvents required.
4. The concentration of the solutes decreases with an increase in number of transfers. With 8 transfers, the vessel at the center of the peak (maximum concentration) contains about 25% of the solute. With 200 transfers, the maximum amount of solute in one vessel is only about 6% of the total.
5. After 8 transfers, the solutes are spread over 8 vessels. After 200 transfers, each solute is spread over approximately 50 vessels. The "peaks" become broader with an increase in transfers; however, the solute occupies a smaller fraction of the vessels used.
6. The solute is never completely removed from even the first vessel, although after the first few transfers the amount remaining in the first vessel may be safely neglected. For example, if $K_D = 1$ and $V_S = V_M$, then $p = 1/2$ and the amount remaining in the first vessel is p^n, or 3% ($n = 5$), 0.1% ($n = 10$), 10^{-4}% ($n = 20$).
7. If the separation factor had been 1.1 instead of 2, 10,000 transfers would be required to achieve the same degree of separation—not very practical even with an automated Craig machine. Separations of this type are readily accomplished by chromatography, to be discussed in the next few chapters.

3–6 CONTINUOUS COUNTERCURRENT EXTRACTION

In the Craig apparatus, one solvent moves with respect to the other in a discontinuous fashion. Imagine now that the size of each equilibration vessel is reduced until the entire system becomes a single column, and that the extracting solvent is passed through the system continuously. If both solvents are restricted to thin layers, it is possible to approach an equilibrium state at all points in the apparatus even though it is not exactly attained anywhere. Instead of a series of discrete vessels, it is convenient to construct a column packed with some porous material which will hold one of the solvents stationary on its surface, while allowing the other solvent to percolate through it. The "stationary" solvent need not be fixed in position; it is only necessary that the two solvents "pass through each other," exposing a large interface. Thus the term "countercurrent" is appropriate. In this way an extremely large number of equilibrations can be achieved without expanding the apparatus unduly.

The relationship of continuous countercurrent extraction to the discontinuous Craig process is much the same as the relationship of continuous fractional distillation with a packed column to the ideal bubble-cap plate distillation. Hence, it is common to refer to "theoretical plates" in a continuous extraction column. Here this expression refers to the number of separate equilibrations and transfers which would have to be done in order to achieve the same degree of separation. Actually, countercurrent extraction is identical to one form of chromatography.