Handbook of Automated Electronic Clinical Analysis

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Preface

This book presents a technical overview of current automated clinical technologies and assay methods applicable for use by medicotechnical personnel associated with clinical and/or hospital laboratories. The techniques, equipment hardware descriptions, and operational directions should be of primary concern to biomedical technicians, paramedical assistants, nurses, maintenance personnel, students, and supervisory physicians responsible for the technical aspects of diagnostic interpretations delivered by clinically measured results.

To avoid creating a technical specialty book consisting only of equipment and operational procedures—bordering on a repetition of hardware manufacturers' instruction and operating manuals—this volume precedes each major physiological technology with a condensed section of tutorial background. This approach justifies an equipment's raison d'etre and serves to establish the groundwork for each of its major design and operating features.

Some of this material is intended to clarify and simplify for the user the final descriptive text; for instance, the basics of analytical chemistry makes the design and operation of automated titrimetry more textually palatable. Again, a hematological background upon differential WBC counting and the components of leucocyte structure aids in understanding the construction and operational details of the Hemalog D blood analyzer. The basics of hemeostasis, hemodialysis, and of centrifuge structure are valuable preliminaries to actual units included in automated equipment.

More than any other technology, titrimetry forms the central theme underlying most of the instrumental operations described in the text (chapters 2 and 6). In other words, since titration is a major phase of analytical chemistry, it centers the approach to equipment designs leading up to most types of automation. Thus, in each assembly of hardware covering the labor-saving phases of automation, most physio-chemical or mechano-pneumatic steps follow the techniques and chemical sequences used in manually titrating an unknown compound. This thread of approach is entwined in all of the equipment-descriptive chapters—Chapters 8, 11, 12, and 13.

Beyond the ultimate diagnostically oriented clinical automation there exists the gamut of semiautomatic support devices, many of which are contributory to final automation. These range from the elemental analysis

of materials—gravimetry, filtration, particle analysis—to more complex processes of viscosity, dissolution, etc. Along with these go the more preparatory systems of semi-automated centrifugation, fermentation, sterilization, and evaporation.

Also, not to be forgotten are the complex measurement technologies of chromatography and X-ray analysis which, although not within the step-by-step automation regime, embody automaticity within themselves and produce complex, compound analyses comparable and sometimes applicable to clinical uses.

This volume is a tutorially and operationally based guide book to clinical automation, describing and specifically surveying the predominantly automatic fields within clinical analysis; applicable data and specialties pointed toward a number of extracurricular laboratory techniques are covered in some dozen or more appendices.

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CHAPTER 1

Automation Preview—Gravimetry—Filtration

INTRODUCTION

Automated medicinal and clinical analysis stems from basic analytic chemistry, applied clinically to bodily substances and applied pharmaceutically to drugs and medicines. However, automated medical and clinical measurements derive much of their background from the processes and technology of industrial chemistry. Industrial influence is seen in discrete compound analyses and in preparative drug processes which might be considered halfway steps between pure identification analysis and the industrial regime of mass produced quantities.

Probably, outside of bulk processing the greatest difference between industrial and medicoclinical technologies is the nature of the mechanism for assay; bodily and drug analyses must usually employ extremely accurate and sometimes minute measurements while at the same time covering simultaneous identification of a wide range of substances and concentrations in a single sample. Industrial products on the other hand quite often employ "brute force" methods and more often than not encounter a disposal problem from the unwanted byproducts. Only in screening for purity do industrial products approach the specific and accurate measurements attained in clinical assays.

Automatic clinical procedures are a logical machine age development comparable to modern automatic machine tool advances. Their development parallels to some extent the growth in complexity of "wet" analytical chemistry procedures. The technology is dependent upon the highly specialized automatic mechanical structures needed to substitute mechanical performance for the manual tasks normally performed by the

laboratory chemical technician. Modern industrial engineering concurrently interjects a number of other technologies and consequently makes such automaticity possible; after all, with motor powered movement there comes the whole science of control engineering upon which has been pyramided sophisticated display devices, all of which has culminated in the availability of useful operator and/or diagnostic results. It should be noted that the final specific substance breakdowns have, however, been compounded and aided by the advances in optical engineering devices stemming from spectrometry, advanced colorimetry and photodetection. Thus, overall automated systems resulted from a composite network of electronic controls, detection devices, sophisticated display circuitry, and optical equipment—all completely integrated by computer-based data processing.

So, although the core of operations in clinical automation is chemically analytical, the supporting and operating structure is industrial-electronic-communication in nature. Thus, even though the compound breakdown in automated processes must depend upon the fundamentals of chemical analysis, the physio-electro-mechanical factors constitute almost an equal share of the development progress.

CLINICAL SCIENCES AND MEASUREMENT TECHNOLOGIES

Table 1-1 diagramatically illustrates a generalized relationship between the clinical sciences and modern instrumental technologies. Here we see that medically or industrially, analytic chemistry exerts its main thrust primarily toward separation of the subject substances into their useful or desired components. In industrial chemistry, separation processes aim at concentration and purifying and then applying specific analytical measurements in order to arrive at final product evaluation. In pure analytical chemistry, on the other hand, many precise separation and assay steps must first be initiated; these sometimes occur simultaneously in a single discrete reaction from which the results are obvious or can be calculated; in others the final derivative requires detailed processing.

Going beyond the main separation phases of indicated analytical chemistry in many clinical and pharmaceutical substances, detailed assay steps must sometimes be entered in order to establish complete quantitative analysis. More often than not, however, these subsidiary steps are congruent with the final separation, particularly in the case of in vivo bodily substances, where direct, immediate component isolation and measurement is necessary. Some assays, to be sure, require multi-step processing, but here again final assay is combined with the later steps in

Table 1-1. CLINICAL SCIENCES AND MEASUREMENT TECHNOLOGIES

DIVISION	*COMPONENTS AND PROCESSES*	*TECHNOLOGY*
Clinical chemistry	Blood	Gravimetry
	Serum	Acidimetry } pH Technics
	Plasma	Alkalimetry }
	Hemoglobin	Titrimetry–Viscosity
	Electrolytes	Gasometry–Rheology
	Fluids	Amperography–Coulometry
	Urine–bile	
	Chyle–spinal	
	Lipids–gastric	
	Tissues	
	Cells	
	Solids	
	Bone	
	Skin	
	Marrow	
	Ligaments	
	Hair	
	Gases	
	N_2,O_2, CO_2	
Hematology	Heme synthesis	Osmometry
	Iron and trace metals	Photometry–Flame–Spectral
	Vitamins	Chromatography
	Cell examination	Gas–liquid–thin layer
	Pathology	Electrophoresis
	Coagulation	Refractometry
Blood grouping	General techniques	Microscopy
	Rh–Hr system	Light–ultra–electron
	Plasma	Polarimetry
	Classifications	X-Ray Analysis
	Transfusions	Fluorometry
Histopathology	Biopsies	Chromatography
	Sectioning	Polarography
	Staining	Cytology
	Fixation	
	Embedding	
	Exfoliative cytology	
Microbiology	Bacteriology	Microscopy
	cultures	Spectrometry
	Serology	Mass–NMR–ESR–ISS–
	Viral–rickettsial	AAS–ESCA–Gamma Ray–
	Parasitology	Roman
	Mucology	Immunophoresis
Toxicology	Poison analysis	Isotope Analysis
	Alcohol	Chromotography
	Ethyl	
	Methyl	
	Salicylate	
	Barbiturates	
	Heavy metal salts	
	Irritants	
	Alkalies, acids	

processing. Table 1-1 shows that such steps may invoke the gamut of modern physical, electronic, spectral, thermal, optical, and atomic technologies, and indeed we shall see the usage of these technologies combined with many phases of conventional analytical chemistry assays.

More details of analytical and separation methods, particularly with respect to titration, are covered in chapter 6; the following exposition is

mainly aimed at relating the background of common analytic chemistry techniques to automatic processes described in later chapters.

ANALYTIC CHEMISTRY

Overview

From Table 1-1 we readily see the breadth of scientific technologies embraced by analytic chemistry; Table 1-2 categorizes the various sections and the means of separation and evaluation; it is intended to be an interpretative breakdown related directly to Table 1-1 and attempts to show how analytic chemistry is broadly based with respect to the physical sciences.

Briefly, it can be divided into:

1. Physiochemical separation operations, and
2. Analytical or identifying and trace-determining mechanisms.

As noted above, pure component separation deals heavily with quantitative factors (common to industrial production) where total amounts and concentrations are of prime importance; under category (2) operations are highly instrumented and cover identifying physical, electrical, optical, or atomic characteristics. It should be noted that these latter techniques employ highly complex and sophisticated instrumental apparatus chiefly due to the fact that analysis is conducted on complex substances and usually transcends the techniques employed in simple analysis by "wet" chemistry. In addition atomic generating and measuring equipment has relatively massive (electronically) construction accompanied by complex control and display accessories.

Elementally gravimetric and volumetric analyses come first among separation procedures as pictured in Table 1-2. Their execution is in many cases subject to automation. Basically these processes consist of component weight and volume determinations of solids following physical, chemical and electrical breakdown of a substance into its constituent components. These breakdowns and separation operations come under the familiar operations of precipitation, filtration, ignition, distillation, and volatilization (evaporation). Titration, a major nonsolid operation (see chapter 6) in its many forms is employed exclusively on solutions. As noted above and following, gravimetry and titrimetry analysis becomes more complex (and sometimes more specific) by entering phases of optical, electrical, spectral, chromotographic and atomic assays.

Table 1-2. SEPARATION AND EVALUATION IN ANALYTIC CHEMISTRY

METHODS		EQUIPMENT
Physio-Chemical		**Chemical Laboratory**
Gravimetric or weight determination	Precipitation Filtration—colation, decanting Distillation Oxidation-Reduction Evaporation	Scales, balances (conventional) Burets Pipettes Flasks Beakers Filters
Titrimetric (volumetric)	Acidimetry Alkalimetry Precipitimetry	Indicator reagents
Oxidation reduction	Valence changing Permanganimitry Iodimitry	pH meters Nitrometers Heaters—electric, gas
Gasometric	Absorbtion Evolution	Stills—Tolulene, conventional, fractional, molecular
Component breakdown and separation	Ignition—ash analysis Moisture content Distillation Centrifugation	
Special		
Extractive	Digestion—desiccation, maceration Expression Boiling, percolation Solubility	**Hardware** Centrifuges—disc, basket, bottle Crucibles Desiccators Digestors Furnaces
Processing of hydrocarbon specialties	Fats, oils—reduction Alkaloids—reduction	
Thermal	Melting Congealing Viscosity Rheology	
Physical		
Specific gravity Solubility Sedimentation Particle size	Weighing Dissolving Decanting Micrometrics Sieving	Viscometers—capillary, torque, time-flow, orifice, falling sphere, oscillation Pycnometers Hydrometers Balances—Westphal, electronic Sieves—hand-operated, automatic

Table 1-2 *(Continued)*

METHODS		EQUIPMENT
Optical		**Lensware**
Microscopy	Optical Polarizing Ultra Electron	Microscopes—optical, polarizing, ultra, electron Polarimeters Refractometers
Basic Optical	Polarimetry Refractometry Transparency—absorbancy Light scattering Spectral	Colorimeters Spectrophotometers Photometers
		Analytical Instruments
Chromotographic	Paper TLC LSC GLC Electrophoresis	Paper strips Columns Plates Flow systems Densitometers
Electromolecular		
Atomic	AAS ISS SIMS NMR	Spectrometers
Electrical	Deposition Conductivity Potentiometry Polarography Coulometry	Amperometers Wheatstone bridges Potentiometers Polarographs Coulometers
Surface	ESCA AES (Auger) RAMAN	Spectrometers Spectral analyzers Fluorometers
X-ray	Diffraction Fluorescence	

GRAVIMETRY

General

The fundamental breakdown of chemical substances is gravimetric—that is, the ultimate separation of weighable components involves a gravimetric process. This separation can be either chemical or mechanical in nature, requiring technologies listed in Table 1-2 and equipments outlined in Table 1-1. The end result is a definite quantity of a component