MASTER

Final Report and Summary of Research Carried Out During the
Period of Grant EX-76-S-02-3253 (2/68-6/78).

This report summarizes the historical background for the research and its subsequent development. Various aspects of the research were supported by the U.S.A.E.C., ERDA, C.C.N.Y., C.U.N.Y., M.H.M.C. and personally by the Principal Investigator.

DISCLAIMER

This book was prepared as an account of work sponsored by or for the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or approval by the United States Government or any agency thereof. The views and opinions of authors contained herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

MASTER

Background for the Research and Subsequent Developments in the Research Program

Analysis of radioisotope tracer data has often involved assuming complete compartmentalization of the biological system being studied. If the experimenter has access to all compartments of a truly N compartment system, complete determination of all rates and volumes of steady state and non-steady state systems is possible by simultaneous measurements of $N-1$ different isotopes (1,2,3). Completely accessible steady state systems can also be solved by appropriate analysis of the tracer concentration time dependencies of a single isotope (4). When all compartments are not accessible, a solution or range of solutions may still be obtained by studying the various constraints imposed by the physical nature of the problem (5,6). Perturbation methods can also be combined with tracer determinations (24).

The point of view emphasized in the above treatment finds expression mathematically principally in terms of systems of coupled first order linear differential (or difference) equations in which the classical mathematical program is reversed. Instead of finding the solution (i.e., concentration curves) from the equations and boundary conditions, the objective is rather to determine that system of equations which gives rise to the experimentally observed specific activity curves. It was recognized, however, that the integrated values alone of the specific activity curves might, in

some cases, provide enough information to solve a multi-compartment system (7), (i.e. determine rates and volumes) an approach recently extended (8,9) to various, partly accessible, special multi-compartment topologies for which systems of differential equations did not necessarily apply since non-contiguities and therefore time lags could exist. This latter development suggested that general multi-compartment analysis might not have to be restricted to contiguous topologies at all and that integral equation approaches previously principally restricted either to two-compartment systems, vascular flow treatments, and individual parameter (i.e. volume) determinations (10,11,12,13,14,15), or focused essentially on the inverse problem of predicting the tracer time dependencies from known transfer characteristics (16) could in fact be adapted to solve steady-state, non-contiguous, multi-compartment systems (17,18) in the sense that all the actually determinable intercompartment transfer properties of generally injectable systems could be specified. While the resulting integral equation approach permitted analysis of many previously rather intractable systems, two difficulties remained. Since the method focused on transport from one compartment to another, flows of material leaving a measurement compartment and subsequently reentering the same compartment without having been in any measured site in the interim, could not be treated readily in the analysis. Secondly, the data obtained from compartments which were measurable but not injectable was not easily incorporated into the formalism. The integro-differential equation approach was developed in an effort to deal with these difficulties (19,20,21).

The integro-differential equation approach is probably applicable to all of the many situations in which a realistic representation of the tracer data curves can be made in terms of decaying exponentials. There are, however, situations in which sufficiently accurate measurements of the early points are not really feasible. Also any curve in which "bumps" appear is difficult to effectively represent exponentially.

Discrete analogs of the integral and integro-differential equation approaches have been developed to deal with these difficulties. The discrete method avoids all analytic curve fitting and simply makes use of the counts sequentially recorded in successive time intervals. The inherent simplicity of the formalism made possible, to our knowledge, a novel analysis of monocompartment randomized data (22). In collaboration with medical investigators a discrete integral equation approach has been used in studying calcium metabolism (36). The rate of absorption of calcium from the gut into the vascular system is determined by correlating the results of external probe measurements following i.v. and oral administration of Ca^{47} (25). The method may have direct clinical applicability in diagnosing hyperparathyroidism (26).

Our research in the field of diffusion-interaction was fundamentally motivated by the importance of this area to cell metabolism and to antibody-antigen systems. A diffusion-interaction equation for the reaction $A + B \rightleftharpoons C$ has been derived by the group (23), and the rate of thermal dissociation calculated for an antigen-antibody-antigen like system (27).

By applying many of the same physical principles used in the thermal dissociation calculation a theory was now developed which appears to predict in a reasonable quantitative way those antibody, antigen and particulate concentrations at which flocculation will occur. To our knowledge this is the first general theory of antigen-antibody-latex flocculation and perhaps flocculation in general in which the very significant role played by dissociation is quantitatively treated. A brief report of this work has appeared (33).

Complete determination of a multi-compartment contiguous system by means of tracer measurements was, of course, demonstrated over 20 years ago. The method initially proposed involved injection into one compartment and measurement in all compartments. Subsequently it has been demonstrated that a solution can also be obtained by a series of injections in all N compartments with the repeated measurements restricted to a single compartment. Characterization of the general sets of N injections and measurements necessary and sufficient for complete determination of an N compartment system has until recently not been possible. A solution to this rather classic type of problem has now been obtained principally by Ms. P. Spetsieris. A brief report of this work has appeared (34).

Research on F.C.C.S. was carried out for quite a few years beginning with the original experiments at Brookhaven National Laboratory (28,29,30). Detection of multi-millimeter sized cold lesions has recently been reported (35).

The 5 probe F.C.C.S. system described in last year's report has been further tested using a variety of phantoms. It has been shown that the F.C.C.S. approach is particularly well suited for detecting small cold lesions (considerably less than 1 cm^3) within a well defined limited volume. It is probably not likely to be as useful as a general purpose screening type instrument because the overall count rates are significantly lower than those obtainable with other approaches (36). For cold lesion detection within small organs or for re-scanning suspicious regions seen using other larger scale scanning techniques, however, F.C.C.S. is extremely promising. It may also be useful in obtaining some kinds of tomographic kinetic data.

The system has also been used successfully on animals, imaging ^{43}K in excised dog hearts extremely well. A three dimensional traverse for automating a complete scan has been constructed and plans are being completed to transfer the system to a Medical Institution (i.e. one of the Hospitals in the Albert Einstein College of Medicine Complex) for in vivo animal and possibly patient use.

We are grateful to the U.S.A.E.C. and its successor ERDA for past support.

Harold Hart
8/25/78

REFERENCES

1. Sheppard, C.W. and A.S. Householder, J. App. Physics 22, 510, 1951.
2. Landahl, H.D., Bull. Math. Biophysics 16, 151, 1954.
3. Hart, H.E., Bull. Math. Biophysics 19, 61, 1957.
4. Hart, H.E., *ibid* 17, 87, 1955.
5. Berman, M. and R. Schoenfeld, J. App. Physics 27, 1361, 1956.
6. Berman, M., Ann. N.Y. Acad. of Sci. 108, 182, 1963.
7. Hearon, J.A., *ibid* 108, 36, 1963.
8. Gurpide, B., J. Mann. and S. Liebermann, J. Clin. Endo. 23, 1155, 1963.
9. Gurpide, B.J. and J. Mann, Bull. Math. Biophysics 27, 389, 1965.
10. Stephenson, J.L. *ibid*, 10, 117, 1948.
11. Branson, H., Cold Springs Symp. Quant. Biol. 13, 35, 1948.
12. Zierler, K.L., Ann. N.Y. Acad. Sci., 108, 106, 1963.
13. Sheppard, C.W., Basic Principles of the Tracer Method, J. Wiley Sons 1962.
14. Berkowitz, J.M., J.L. Sherman and H.E. Hart, Ann. N.Y. Acad. Sci. 108, 250, 1963.
15. Bergner, P., 10th Annual Symp. O.R.I.N.S. 1966.
16. Stephenson, J.L., Bull. Math. Biophysics 22, 113, 1960.
17. Hart, H.E., *ibid*. 27, 329, 1965.
18. Hart, H.E., *ibid*. 28, 261, 1966.
19. Hart, H.E., Second International Biophysics Congress, Vienna, 1966.

20. Hart, H.E., Proc. Symp. on Compartments, Pools and Spaces in Medical Physiology, Oak Ridge Inst. Nuclear Studies 11, 145, 1966.
21. Hart, H.E., Bull. Math. Biophysics 29, 319, 1967.
22. Hart, H.E. and J. Sondheimer, Comput. Biol. Med. 1, 59-74, 1970.
23. Hart, H.E., D. Sugarman and D.I. Shelupsky, Bull. Math. Biophysics 32, 377, 1970.
24. Hart, H.E., U. Mallik and D. Sugarman, Bull. Math. Biophysics, 34, 87, 1972.
25. Hart, H.E. and H. Spencer, Proc. Exp. Biol. and Med. 126, 365, 1967.
26. Barzel, U.S. and H. Hart, Nephron 10: 174-87 (1973).
27. Sugarman, D. and H.E. Hart, Bull. Math. Biol. 35, 219-235, 1973.
28. Hart, H.E., B. Warshaw and H.I. Stoller, IEEE Trans. on Bio-Med. Eng. BME-14, 96, 1967.
29. Hart, H.E. Radiology 84, 126, 1965.
30. Hart, H.E. Trans. N.Y. Acad. Sci., 30, 580, 1968.
31. Rider, K.L., S. Rudin and H.E. Hart, Biomed. Trans. IEEE, 32, 377-390, 1972.
32. Rudin, S., K.L. Rider and H.E. Hart, Radiology 102, 371, 1972.
33. Chak, K. and H.E. Hart, Physics in Canada - Special Issue 32, 38:1, 1976.
34. Spetsieris, P. and H.E. Hart, Physics in Canada - Special Issue 32, 22.6, 1976.

35. Hart, H.E. and S. Rudin, IEEE Trans. on Bio-Med. BME-24,
169-177, 1977.

36. Zacuto, P., S. Rudin and H.E. Hart, Physics in Canada - Special
Issue, 32, 14.1, 1976.