Final Report

MATHEMATICAL THEORY OF MOLECULAR CONTROL SYSTEMS

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Major emphasis has been placed on the analysis of problems associated with the effects of surfaces on blood clotting and on the theory of blood clot regulation. This subject is now at the forefront of medical and surgical research because of recent advances in prosthetic materials and artificial organs.

A theory was developed (16) which may be of considerable importance in clarifying the effect of basic surface properties on clotting. There has been considerable discussion in the literature concerning the effects of surface energy and surface charge on the initiation of blood clotting. Much of this discussion deals with these factors in an unrelated way and it is one purpose of this paper to provide a unified theory of the interaction between proteins and surfaces which takes into account both surface energy and charge among other factors. Expressions are obtained showing among other things that the effect of surface energy (liquid-solid interface) depends on the relative partial molar surface area of the solvent and protein. It is also shown that the effects of surface charge density and interface energy are interrelated and ought not to be considered independently of one another. A second matter dealt with here is the development of a model describing the structural transformations undergone by adsorbed proteins. Experimental evidence is reviewed for the existence of several surface phases depending on surface pH and protein concentration. The relevancy of model to activation of Hagman factor is discussed.

A second study relates to the control theoretic aspects of blood clot regulation, extension of previously published work from this group, and is summarized in the attached.

Other Studies

Major emphasis has been given to some of the more basic problems arising from the application of mathematical techniques to physiological regulations. Thus two reports (1,2) have dealt with the very important regulatory mechanisms underlying protein synthesis, both linear and non-linear models have been investigated. It is satisfying to report that the publication (3) on the studies relating to the linear model seems to have aroused widespread interest as indicating by the receipt of over 55 reprint requests. Some of the predictions of this model agree with experimental data provided by Pardee and results appear to account for some of the features of adaptive enzyme formation.

In addition to the above work, the first phase of the study on renal electrolyte regulation has also been released (4,9). This work is directed towards establishing a mathematical model of the kidney and associated regulation of the body electrolyte system. In addition to the intrinsic interest of this problem, the results of the study should be applicable to the elucidation of environmental stresses associated with the life support systems employed in outer space explorations and elsewhere. Various aspects of this work were also presented at the International Biophysical Conference (10) and the 19th Engineering in Biology and Medicine Conference (11).

Greatest emphasis has been placed on the extension of the previously published work for the renal-electrolyte system. An effort is under way to include the regulation of calcium with the purpose of examining various models of decalcification disorders. The hemostatic control of calcium ions has been represented by a model which takes into account the action of parathyroid hormone on calcium adsorption from bone, renal tubules, and from the intestinal tract. The negative feed back effect of serum calcium on the production of parathyroid hormone is also considered as is the effect of the hormone on phosphate renal excretion. The influence of calcitonin and thyrocalcitonin has also been incorporated into the model.

Studies of this kind should play an important role in the elucidation of decalcification in the overall mechanism of renal electrolyte regulation. This work has elicited considerable interest as indicated by the receipt of several hundred reprint requests and invitations to speak at such universities as Texas and Cornell Medical Center. A number of commercial firms, (Sonotone, General Electric, etc.) have also expressed interest in this work as well as that on microcapsulation systems.

The work on the theory of the inverse piezoelectric effect of polymers which are encountered in living tissue was the subject of an invited paper (5) presented at the International Conference on Electrochemical Aspects of Molecular Biology sponsored by the Berlin Academy of Sciences. Some aspects of this work have also been published (6). This work may have some applications to non-mechanically driven pumps, for example.

Most recently the theory of enzyme amplifiers has been under study here and applied to the problem of blood coagulation. Brief communications have been released (7,8).

Work has also been carried out on the theory of stimulus electrodes which, for example, are used in pacemakers for the heart and elsewhere in bioengineering. Some results of these studies have been published (13) and extensions of this work were presented as an invited paper at the Gordon Research Conference June 17-21, 1968.

Finally, and perhaps most interesting of all, work has been started on the theory of the reactivity of microencapsulated systems (13). These systems may have a number of important practical applications including the artificial kidneys.

PUBLICATIONS AND REPORTS ISSUED UNDER PRESENT CONTRACT

(1) Gerst, I. and Levine, S. N. "Kinetics of Protein Synthesis of Polyribosomes" State University of New York at Stony Brook, College of Engineering Report No. 25, Sept. 1964.

(2) Gerst, I. and Levine, S. N. "A Nonlinear Model for Templet Regulated Protein Synthesis" State University of New York at Stony Brook, College of Engineering Report No. 27, Oct. 1964.

(3) Gerst, I. and Levine, S. N., "Kinetics of Protein Synthesis by Polyribosomes", J. Theoret. Bio. 9, 16-36 (1965)

(4) Levine, S. N., "A Model for Renal-Electrolyte Regulation," State University of New York at Stony Brook, College of Engineering, Report No. 56, Oct. 1965.

(5) Levine, S. N., "Behavior of Polyelectrolytes in Applied Electrical Fields," presented at Conference of Electrochemical Aspects of Molecular Biology, Jena, Germany, May 25, 1965.

(6) Levine, S. N., "Inverse Piezoelectric Effect in Polymers," J. Appl. Polymer Sci., Vol. 9, pp. 3351-3357 (1965).

(7) Levine, S. N., "Enzyme Amplifier Kinetics" State University of New York at Stony Brook, College of Engineering Report No. 59, Dec. 1965.

(8) Levine, S. N., "Enzyme Amplifier Kinetics," Science 152, 651 (1965).

(9) Levine, S. N., "A Model for Renal-Electrolyte Regulation," J. Theoretical Biology, 11, 242-256 (1966).

(10) Levine, S. N., "Control Systems Theory of Kidney-Electrolyte Response," Proc. Second International Conference on Biophysics, Vienna, Sept. 5-9, 1966.

(11) Levine, S. N., "Modelling of Renal Function and Regulation," Proc. 19th Annual Conference on Engineering in Medicine and Biology (1966).

(12) Levine, S. N., "Electrochemical Behavior of Metals as Stimulus Electrodes," J. Biomedical Materials Research, Vol. 1, pps. 27-31 (1967)

(13) Levine, S. N. and W. LaCourse, "Theory of Reactive Microencapsulated Systems with Application to Biomedical Engineering," J. Biomedical Materials Research, Vol. 1, pps. 275-284 (1967).

(14) Levine, S. N., "A Model for Calcium Regulation," State University of New York at Stony Brook, College of Engineering Report (in preparation)

(15) Levine, S. N., "Electrodes in Biology" invited paper Gordon Research Conferences in Biomaterials, June 17-21 1968.

(16) Levine, S. N., "Thermodynamic Theory of Protein Adsorption Onto Surfaces," J. Biomedical Materials Research Vol. 3, 83 (1969). invited paper presented at the Am. Chem. Soc. 156th National Meeting, Div. of Colloid and Surface Chemistry (Sept. 1968).

(17) Levine, S. N., "Negative Feedback Mechanisms in Blood Clotting," Proc. Conference on Engineering Medicine and Biology, 21st Annual Conference (1968).

(18) Levine, S. N., "Bioelectrodes," invited paper presented at the University of Denver Colorado School of Medicine Conference on Biomedical Materials (July 15-20, 1968).