MATHEMATICAL THEORY OF BIOLOGICAL PERIODICITIES:
FORMULATION OF THE \( n \)-BODY CASE

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In a series of papers, L. Danziger and G. Elmergreen (Bull. Math. Biophysics, 16, 15–21, 1954; 18, 1–13, 1956; 19, 9–18, 1957) showed that a non-linear biochemical interaction between the anterior pituitary gland and the thyroid gland may result under certain conditions in sustained periodical oscillations of the rates of production and of the blood level of the thyrotropic and of the thyroid hormone. They treated the systems, however, as a homogeneous one. N. Rashevsky (Some Medical Aspects of Mathematical Biology, Springfield, Illinois: Charles C. Thomas, Publisher, 1965; Bull. Math. Biophysics, 29, 395–401, 1967) generalized the above results by taking into account the histological structures of the two glands as well as the diffusion coefficients and permeabilities of cells involved. The present paper is the first step toward the theory of interaction of any number \( n \) of glands or, more generally, \( n \) components. The differential equations which govern the behavior of such a system represent a system of \( 2n^2 + n \) non-linear first order ordinary equations and involve a total of \( 7n^2 + 3n \) parameters of partly histological, partly biochemical nature. The requirements of the existence of sustained oscillations demand \( 4n^2 + 2n + 2 \) inequalities between those \( 7n^2 + 3n \) parameters.

In previous publications (Rashevsky 1963, 1964, 1967), we have generalized the mathematical theory of thyroid-anterior pituitary gland interaction, developed by L. Danziger and G. Elmergreen (1954, 1956, 1957, 1958), who attempted to give a model of relapsing periodic catatonia in line with the earlier findings of R. Gjøssing (1932, 1935, 1938, 1939, 1953). Gjøssing found a periodicity in the basal metabolism which paralleled the periodicity of catatonia. This suggested a possible periodicity in the functioning of the thyroid gland. Danziger and Elmergreen showed that such periodicities may occur under certain conditions
due to a non-linear interaction between the anterior pituitary gland, which produces the thyrotropic hormone, and the thyroid gland, which produces the thyroid hormone that inhibits the production of the thyrotropic hormone. Their theory not only accounted for some of Gjessing's findings, notably for the beneficial effects of thyroid administration and for the necessity of proper timing of such an administration, but also suggested a possibility of improving Gjessing's technique, a possibility which was verified clinically on a few patients. (Danziger and Elmergreen, 1958; Danziger and Kindwall, 1954).

A serious drawback of the theory of Danziger and Elmergreen is that their equations correspond to biochemical reactions in a homogeneous system, whereas actually we deal with a very heterogeneous system. In his generalizations of the Danziger-Elmergreen theory, Rashevsky (1964, Chapter 23 and Appendix 14) considers the parts played by the size and shape of the cells of the two glands, which through their influence on the diffusion of the corresponding substances affect the reaction rates. He thus considered essentially three-compartment two-component systems: cells of the anterior pituitary, cells of the thyroid gland, and blood. Later on (Rashevsky, 1967), he also introduced the intercellular fluid. Rashevsky's results show that the presence or absence of periodicities is affected by the size and shape of the cells of both glands, the diffusion and permeability coefficients of the cells to each of the two substances, and the degree of vascularization of the two glands. He draws a number of conclusions which suggest new experimental and clinical investigations.

Inasmuch as actually every endocrine gland interacts, directly or indirectly, with practically every other one, both Danziger and Elmergreen's, as well as Rashevsky's approaches, which limit themselves to a two-component system, may be considered as rather unrealistic, though not necessarily so (Rashevsky, 1964, pp. 149–150). Danziger and Elmergreen (1957) did consider the general case of an \( n \)-component system. However, they still restricted themselves to a homogeneous system. Moreover, while discussing an \( n \)-component system, they practically limited themselves to a treatment of a three component system only.

The purpose of this paper is to lay the foundation for a theory of \( n \)-component systems of a heterogeneous structure. Such a problem cannot be tackled in all its generality. At first we must introduce certain limitations which later studies may remove. Familiarity of the reader with our previous work (Rashevsky 1954, 1967) is essential for the understanding of the present paper.

First of all, let us limit our problem precisely. The solution of the problem may have a bearing not only on pathological periodicities studied by Danziger