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A FUNCTION GENERATOR FOR THE MESENCHYMAL CELL ACTIVATION FUNCTION, FOR USE IN THE ELECTRIC ANALOG COMPUTER*

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INTRODUCTION

THE BEGINNING of a mathematical model of lamellar bone remodelling has been reported elsewhere by one of us.[1] The model, created for the purpose of analog computer-based explorations of remodelling system parameters, contains three basic elements or parameters. All bone resorption and formation may be explained in terms of these three parameters. Many diseases (i.e., osteoporosis; osteogenesis imperfecta; osteopetrosis; acromegaly; Cushing's syndrome) may be wholly or partly characterized statically and dynamically in terms of these parameters and of their variations and interactions throughout life and in disease.[1]

A computer-based exploration of the remodelling parameters is possible because the amount of bone present is known (and is the solution to the equation representing the integral of the balance between bone resorption and bone formation for the entire life span) or can be found, and some of the elements in the problem have been characterized by quantitative histological methods. Much of this quantitative histology has been based on the labelling of bone in vivo by the tetracycline antibiotics.[3,5]

The three major remodelling parameters vary in characteristic ways during life. In other words they are not constant. (See Figure 1.) If these parameters are to be modelled as a changing voltage on a computer, some means of reproducing them by the computer is needed. In analog computation a diode or potentiometric function generator is commonly used to reproduce known curves, but these devices have the major disadvantage that they produce curves by combining short segments of constant slope. In other words, the functions generated by these devices are not continuous,[4] although the biological functions being modelled are usually continuous.

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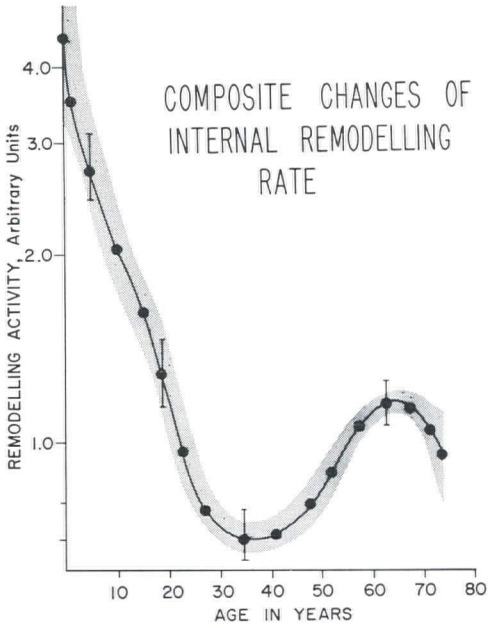

Figure 1

This curve is a composite of a number of separate indices of bone formation in internal remodelling of normal human ribs throughout life. The abcissa is linear, the ordinate logarithmic. The features mentioned in the text may be seen. In addition, the minimum in activity at age 35 and the subsequent increase in remodelling (and thus new bone forming) activity are important features. Many dynamic activities in normal bone physiology have been found in this laboratory to exhibit similar behavior. This suggests that some fundamental physiological change becomes manifest at age 35. The nature of the change is unknown, but the facts that it leads to an increase in remodelling and that this increase is normal were unsuspected before the first report on this matter in 1960.

We describe here a simple arrangement for generating the curve of the mesenchymal cell activation function. This function at present appears to be the most complex as well as the most intriguing of the characterizations of remodelling activity so far published from this laboratory. It is symbolized by (A_f).

In Figure 1, a curve is reproduced which shows the empirically determined values of the mesenchymal activation function throughout life in normal human ribs. This function, briefly, is the average number of places where new bone forming activity is going on in an arbitrary, constant amount of bone. The function probably is analogous to a similar property of tissue remodelling and cell turnover in soft tissues, so that knowledge of bone remodelling properties and the manner in which they have been modelled may be of interest to physiologists generally, as well as to the limited number of bone physiologists.

The major features of this curve may be summarized as follows: It is a damped cosine wave with a progressive negative skew along the ordinate. Both the damping and the skew appear to be nonlinear. The period appears to be about 65 years. It

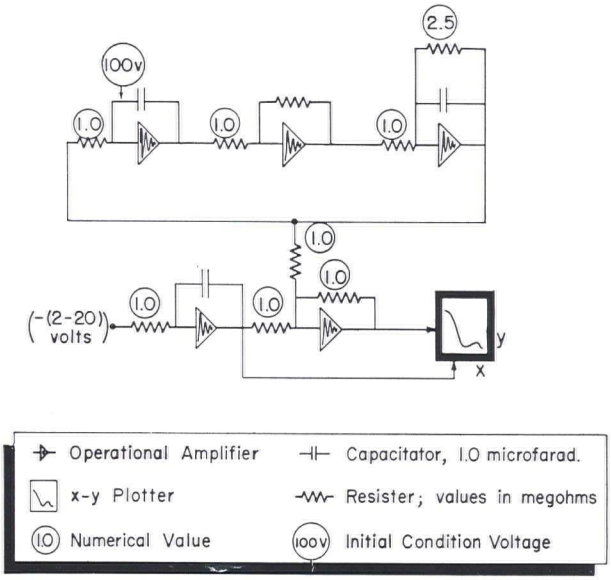

Figure 2

The operational amplifier setup and the impedances used are diagrammed for producing a voltage of the mesenchymal cell activation function whose curve is shown in figure 1. Most of the impedances shown may be varied if desired in order to produce improved fit to modifications of the fundamental curve of figure 1.

is possible that there is also a change in the period with time. (We have not modelled this feature.)

In Figure 2 the computer setup is diagrammed. The three operational amplifiers at the top generate the basic cosine wave. The 2.5 megohm resistor across the capacitance of the third amplifier generates the damping, and the degree of damping may be readily varied by changing this resistance. The period of oscillation may be varied to suit scaling problems by systematically chaging the input resistances to the amplifiers or their capacitors,[4] or both.

The integrator at the bottom left generates the negative skew and, with the arrangement that is illustrated, this skew is linear. An exponentially decaying skew could be generated by substituting for the input to this amplifier the input from a sine wave generator of period 2-4x the period of the basic oscillator setup at the top of the figure. Almost any monotonically changing function of time could be generated by changing some of the amplifier impedances of another cosine generator at this point.

The (Y) axis of this function represents a logarithmic plot of the (Y) axis of the empirically observed function. Little difficulty in fitting the computer output to scaled graph paper should be encountered, since by varying the initial condition voltage in

the computer setup, or by varying the attenuation of the plotting board amplifiers, a very wide range of (Y) output may be plotted against time.

Discussion

While the arrangement illustrated has the disadvantage of requiring five operational amplifiers, it has the advantage that a multiplier is not required. This frees a multiplier for use in another part of the problem and is an advantage because a number of mulitpliers are needed to observe all the remodelling system parameters in operation simultaneously.

This arrangement also has the advantage that it provides a continuous solution, permitting more efficient use of differentiation techniques in studying the effect of modification of some other remodelling system parameter during interaction with this one.

While the equations in which this computer setup is used will not be derived here, it may help to outline briefly the place of the present generated function in the schema. We may write the following equation:

$$V_f = k\ f(A_f)\ f(S_f)\ f(M_f) \qquad (1)$$

where the functions are equations—or computer function generators—whose solutions are functions of time and whose numerical values at any time accurately reproduce the empirically observed values of these functions at a comparable age in a standard normal bone. (V_f) is the amount of new bone formed, (k) the amount of bone originally present, (A) the number of foci of remodelling in an arbitary amount of bone, (S) the mean surface area of such foci, and (M) the linear rate of growth on this surface. The subscript ($_f$) indicates formation.

The value of (V_f) has been determined in many situations in this laboratory. Similarly the values of (A_f) and (S_f) have been determined. If suitable analogs of these functions are generated on the computer, then the necessary solution to the (M) function may be found by solving for it as the unknown. Since this is the most poorly defined of the remodelling parameters at present, this approach is useful in two respects. It can provide us with the necessary information about the values and linearity of the (M) function with respect to age, and by appropriate check against labelled bone it becomes possible to determine whether or not the mathematical model is adequate. Should (M) values be required for solution to equation (1) that are not found in real bones, a revision of the concepts on which equation (1) is based would be indicated.

Summary

A method of generating a continuous, damped, skewed sine wave on the electronic analog computer is outlined, making use of five operational amplifiers and associated impedances, but not requiring use of function multipliers.

This setup is arranged to produce an acceptably accurate voltage analog of the empirically measured changes in the mesenchymal cell activation function with respect to age.

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REFERENCES

1. Frost, H. M.: Bone Remodelling Dynamics, Springfield, Thomas, 1963.

2. Frost, H. M., Villanueva, A. R.: Human osteoblastic activity. I. A comparative method of measurement with some results, Henry Ford Hosp. Med. Bull. 9:76, 1961.

3. Frost, H. M., Roth, H., Villanueva, A. R., and Stanisavljevic, S.: Experimental multiband tetracycline measurement of lamellar osteoblastic activity, Henry Ford Hosp. Bull. 9:312, 1961.

4. Korn, G. A., and Korn, T. M.: Electronic Analog Computers, ed. 2, New York, McGraw-Hill, 1956.

5. Milch, R. A., Rall, D. P., and Tobie, J. E.: Fluorescence of tetracycline antibiotics in bone, J. Bone & Joint Surg. 40A:897, 1958.