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Dynamic Model of Oxygen Distribution in the Organism

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The paper deals with the theoretical analysis of the time behaviour of oxygen concentration in the various organs of the experimental animal on a mathematical model. The possibility of verification with the aid of methods used in automatic control employing analogue computers is discussed.

INTRODUCTION

In principle we may look upon the organism as an intricate control system which maintains the basic physiological parameters within a certain permissible range, if the environment changes. In the study of such systems we therefore cannot get along without the relatively complicated mathematical apparatus used in automatic regulation. One of the approaches is the modelling of vital processes with the aid of modern computing techniques. The aim of our work is to show on a dynamic model of oxygen distribution in the organism the basic problems we encounter in modelling the vital processes in biology, the methods that can be employed to verify the application of the model designed and, finally, how these methods can be used for solving practical problems. When designing the oxygen distribution model, we availed ourselves of the paper written by Jacques et al. [1], dealing with the mathematical model of the distribution of some substance through the blood circulation system, and of the communication by Horgan et al. [2, 3] treating the conditions of the origin of periodic respiration in man on a mathematical model, using analogue and digital computers. The model designed on the basis of both papers is intended to determine the time behaviour of the changes in the oxygen concentration in the different organs, if the oxygen concentration of the inhaled mixture changes in some manner.

The supply of oxygen to the different organs is a basic physiological function of all higher organisms. The schematic representation of oxygen distribution through the blood circulation system in mammals is illustrated in Fig. 1. The reception of oxygen from the surrounding air and the output of CO_2 are realized in the lungs. The oxygenized blood is then forced through the left heart into the large blood circulation system, where the different organs are mostly connected on parallel lines except for the portal system (intestines, stomach, spleen, liver), which is characterized by serio-parallel arrangement of the organs. The oxygen from the blood is consumed in the organs by metabolic activity, the resultant CO_2 being bound to the deoxydized blood. The former is then conveyed through the venous system into the lungs, where it is oxygenized again.

For the mathematical model of the circulation system under study, schematically illustrated in Fig. 2, we are introducing some simplifying provisions: the model is designed only for oxygen distribution and ignores CO_2 distribution which would be analogous. The organ is replaced in the model by one large capillary channel with a uniform medium blood flow conceived as a simple block into which flows blood of $U_{\text{input}}(t)$ oxygen concentration and out of which runs blood

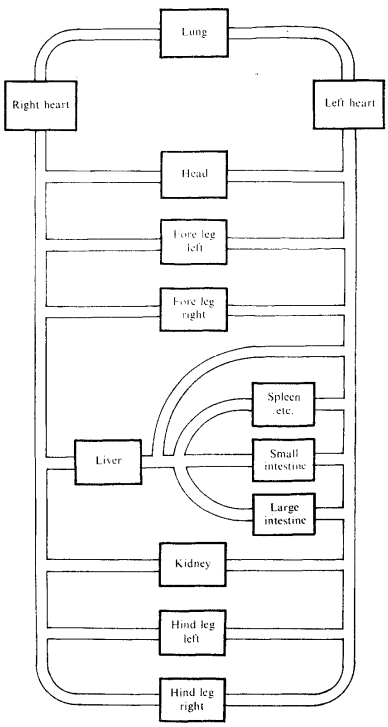

Fig. 1. Diagram of blood circulation.

of $U_{\text{output}}(t)$ O_2 concentration. The processes within a given tissue, i.e. oxygen diffusion from the blood into the extracellular and intracellular spaces, are not taken into account. All the organs are interconnected in the circulatory system, whereby the change of the oxygen concentration in one organ acts on the change of concentration in the other organs. How the organs influence one another is decided, above all, by their capacity and spatial arrangement in the circulatory system. An important factor which has to be taken into account if we want to determine the time behaviour of the concentration in the different organs, is the varying length of blood transportation through

the vessels into the organs that, as a result of the limited blood flow rate, causes a time lag (transportation delay) with which the organs respond to the change in the input concentration. Thus mixing of the concentrations takes place at various time intervals, making the model much more complicated. In a further analysis we shall deal in detail with the time behaviour of the oxygen concentration in the circulation system and formulate the relations for the calculation of the oxygen concentration or O_2 tension at any optional point of the circulation system at any optional time.

THE FUNCTION OF THE LUNGS

In the lungs the venous blood is oxygenized with oxygen from the surrounding atmosphere through diffusion via the alveolar membrane, separating the blood from the alveolar air. The relationship between the amount of oxygen received from the surrounding atmosphere, and the increased amount of oxygen in the arterial blood with respect to the venous blood per time unit can be expressed by the following equilibrated differential equation:

$$C(U_P - U_{RP}) = \frac{\dot{V}_A(P_I - P_A)}{P_B - 47} - \frac{d}{dt}\left[\frac{V_P P_A}{P_B - 47}\right], \tag{1}$$

where C = minute volume of the heart (lit/min), i.e. the overall blood flow;
U_{RP} = O_2 concentration in the blood entering the lungs (venous);
U_P = O_2 concentration in the blood leaving the lungs (arterial);
$\dot{V}_A$ = alveolar pulmonary ventilation (lit/min);
P_I = O_2 tension (partial O_2 pressure) of the inhaled mixture (mm Hg);
P_A = O_2 tension of the alveolar air (mm Hg);
P_B = barometric pressure (mm Hg);
V_P = functional residual capacity of the lungs (litres), i.e. the volume of the lungs measured at the end of exhalation.

The first expression in equation (1) expresses the net incerase of the oxygen amount in the blood passing through the lungs per time unit. The second expression expresses the oxygen amount consumed from the inhaled air in the lungs per time unit. It is dependent on the pulmonary ventilation $\dot{V}_A$ and on the relative oxygen content in the alveolar air $(P_I - P_A)/(P_B - 47)$, the expression $(P_B - 47)$ expressing the fact that the alveolar air is saturated with water vapours. In the model, instantaneous O_2 tension is assumed on both sides of the alveolar membrane, where a constant pressure difference of 12 mm Hg is maintained. For the O_2 tension in the arterial blood P_P we can write:

$$P_P = P_A - 12 \quad [\text{mm Hg}]. \tag{2}$$

The third expression in equation (1) represents the delayed action of the lungs caused by their functional residual capacity. Owing to this, the O_2 concentration of the arterial blood in the lungs is compensated with a certain time constant. The time

constant of the actual diffusion through the alveolar membrane can be neglected in this respect.

By introducing equation (2) into equation (1) and expressing the time dependence, we obtain the equation for the oxygen concentration in the blood on leaving the lungs $U_P(t)$:

$$(3) \qquad U_P(t) = U_{RP}(t) + \frac{1}{C(P_B - 47)} \left\{ \dot{V}_A[P_I(t - \tau_{IP}) - P_P(t) - 12] - \right.$$
$$\left. - \frac{d}{dt} V_P[P_P(t) + 12] \right\},$$

where τ_{IP} is the time lag of the inhaled mixture in the respiratory ducts.

In equation (3) there is, in addition to the concentrations $U_P(t)$ and $U_{RP}(t)$, another time variable of O_2 tension in the arterial blood $P_P(t)$ which with the O_2 concentration $U_P(t)$ is bound by the so-called absorption curve. Generally, it is possible to write the absorption curve in the following form:

$$(4) \qquad U = 20(1 - e^{-bP})^c$$

where b, c are parameters that must be chosen so that the absorption curve passes through the normal arterial and venous points obtained through experimental measurements. With the aid of equation (4) we can convert the O_2 concentration in any optional point into the respective O_2 tension and vice versa.

THE FUNCTION OF THE HEART

The blood comes to the left heart with the time lag τ_{PL}, thus the input O_2 concentration in the left heart is expressed by the relation:

$$(5) \qquad U_{PL}(t) = U_P(t - \tau_{PL}) .$$

The right and the left heart can be imagined as two equal pumps featuring, during the cardiac cycle, two phases, namely, the ejection phase (systole), during which the blood volume V_E is forced into the aorta, and the filling phase (diastole), during which the heart is filled with an equal volume of blood. The total amount of blood pumped into the aorta per time unit – minute output of the heart C – depends on its ejection volume V_E and on the number of heart beats per minute R according to the relation:

$$(6) \qquad C = V_E R \quad [\text{lit/min}] .$$

This pump has also, of course, its own residual volume V_R which causes imperfect emptying of the heart volume and thus successive mixing of the concentration gradients, which in the case of an exact analysis has also to be taken into account. Due

to the pulsing activity of the heart, the course of concentration on the outlet of the left heart is of a step-like character. As a result of the elastic properties of the aorta and the longitudinal mixing of the blood in the vessels, the dependence takes the character of a continuous curve. On the outlet of the left heart, the following expression for the concentration can be obtained through an analysis of the activity of the heart:

$$U_L(t) = U_L(0)\, e^{-(C/V^*)t} + U_{PL}(t)\left[1 - e^{-(C/V^*)t}\right]. \tag{7}$$

The first part of the expression indicates the exponential decrease of the initial concentration down to zero, while the second part of the expression indicates the exponential increase of the new concentration to a stable level. Both exponentials have the same time constant $T = C/V^*$, where V^* is the reduced volume of the heart as of an ideal pump:

$$V^* = \frac{V_E}{\ln\left[1 + (V_E/V_R)\right]}. \tag{8}$$

THE CIRCULATION SYSTEM

The distribution of oxygenized blood through the arteries to the different organs and of the deoxygenized blood from the organs through the veins is schematically illustrated in Fig. 2, where all observed concentrations, blood flows, and time lags are plotted. The simplified model features parallel arrangement of the organs joined directly to the outlet section of the left heart and to the inlet section of the right heart. This can be imagined so that the main vessel is composed of an adequate number of thin vessels which are bound into a bundle and gradually ramified. The simplification holds good on the assumption that the pressure in the vessels is constant and that only the blood flow through the different organs is changed. The course of the concentration in the veins is a more complicated matter, for it represents the sum of the time behaviour of the concentrations at the outlets of the organs and can be defined only at the inlet to the right heart.

On the inlet to the n-th organ, the time behaviour of the concentration of the arterial blood is given by the equation:

$$U_{Ln}(t) = U_L(t - \tau_{Ln}), \tag{9}$$

where τ_{Ln} is the time lag of the left heart – organ. The oxygen consumption in the organ can be expressed by the equation:

$$C_n(U_{Ln} - U_n) = q_n + \frac{d}{dt}\left(\frac{V_{Sn}P_n}{P_B - 47}\right), \tag{10}$$

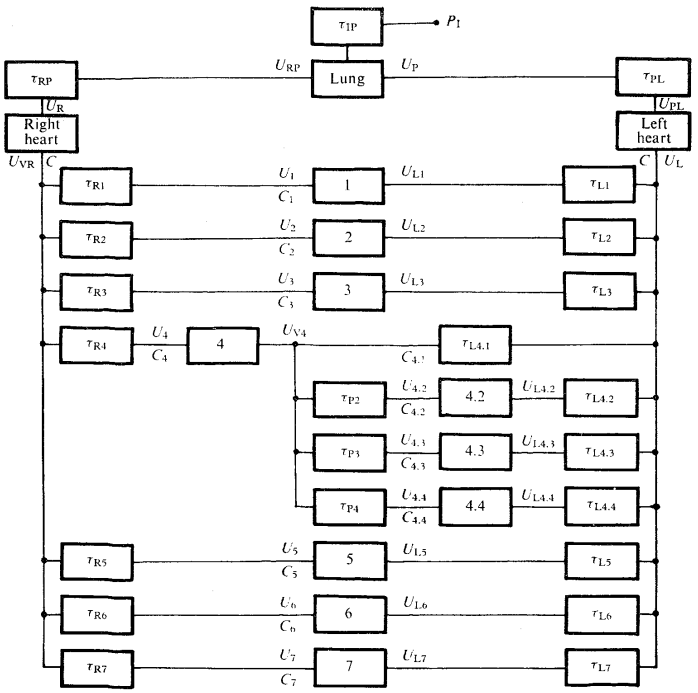

Fig. 2. Block diagram of oxygen distribution (1 — head, 2 — fore leg left, 3 — fore leg right, 4 — liver, 4.2 spleen etc., 4.3 — small intestine, 4.4 — large intestine, 5 — kidney, 6 — hind leg left, 7 — hind leg right).

where C_n = blood flow through the organ (lit/min);
U_{Ln} = O_2 concentration of the arterial blood;
U_n = O_2 concentration of the venous blood;
q_n = coefficient of the O_2 concentration rate in the organ (lit/min);
P_n = O_2 tension of the venous blood (mm Hg);
V_{Sn} = equivalent storage volume of the organ (litres), which is the amount of O_2 maintained in the organ as storage.

The first member of equation (10) represents the total amount of O_2 consumed per time unit. The coefficient q is dependent on the metabolic activity and on the function

of the organ in general. The third member of equation (10) is the delayed action with which the reaction proceeds as a whole. Here too, the time constant of diffusion through the membranes is also neglected. At the outlet of the n-th organ, by expressing the time in equation (10) we obtain the (following) expression for the O_2 concentration in the venous blood:

$$U_n(t) = U_{Ln}(t) - \frac{q_n}{C_n} - \frac{\mathrm{d}}{\mathrm{d}t}\left[\frac{V_{Sn}}{C_n}\,\frac{P_n(t)}{P_B - 47}\right]. \tag{11}$$

To determine the time behaviour of the concentrations in all organs under study, it is necessary to know the following figures for each:

the blood flow C_n, the oxygen consumption rate q_n,
the equivalent storage volume of the organ V_{Sn}, and
the corresponding time lags τ_{Ln} and τ_{Rn}.

The analysis of the time behaviour of the concentrations in the portal system is relatively intricate, for the blood comes to the inlet of the liver, on the one hand from the heart via the hepatic artery with the time lag $T_{L4.1}$ and the blood flow rate $C_{4.1}$, on the other hand from the outlets of the following three groups of organs:

a) spleen, stomach, and pancreas with the output concentration $U_{4.2}$, blood flow rate $C_{4.2}$, and time lag τ_{P2},
b) small intestine with the output concentration $U_{4.3}$, blood flow rate $C_{4.3}$, and time lag τ_{P3},
c) large intestine with the output concentration $U_{4.4}$, blood flow rate $C_{4.4}$, and time lag τ_{P4}.

For the concentration at the inlet to the liver $U_{V4}(t)$ we can thus write:

$$U_{V4}(t) = \frac{U_L(t - \tau_{L4.1})\, c_{4,1} + \sum_{k=2}^{4} U_{4.k}(t - \tau_{Pk})\, C_{4.k}}{\sum_{k=1}^{4} C_{4.k}}. \tag{12}$$

The time behaviour of the oxygen concentration in the venous blood at the inlet to the right half of the lungs $U_{VR}(t)$ can be expressed by the sum of the concentration contributions from the outlets of the particular organs according to the relation:

$$U_{VR}(t) = \frac{\sum_{n=1}^{7} C_n U_n(t - \tau_{Rn})}{\sum_{n=1}^{7} C_n}, \tag{13}$$

where $U_n(t)$ = time behaviour of O_2 concentration on the outlet of the n-th organ;
C_n = blood flow through the n-th organ;

τ_{Rn} = time lag between the outlet of the n-th organ and the inlet to the right heart.

In the right heart, further mixing of the concentrations takes place in accordance with equation (7). Finally, at the inlet to the lungs we obtain the expression for the O_2 concentration as follows:

$$U_{RP}(t) = U_R(t - \tau_{RP}), \tag{14}$$

where $U_R(t)$ = time behaviour of O_2 concentration on the outlet of the right heart;

τ_{RP} = time lag between the outlet of the right heart and the inlet to the lungs.

The model as described here and its theoretical analysis, is a very involved matter and would require an analogue computer of medium size with a number of additional devices. The greatest obstacle to its realization is constituted by the large number of time lags (about 23) which are very difficult to model in an analogue computer and also by the numerous absorption curves occurring separately in each organ. Their modelling also presents great difficulties. On the computer we can carry out the theoretical solution of the model, if we introduce into the programme diagram all the parameters that appear in the equations. It goes without saying that this is very difficult, for the necessary physiological parameters are known only by the mean values and rather for the entire system than for the particular organs. The necessary parameters have, therefore, to be obtained by way of experiments, with of course a substantial simplification of the flow plan.

THE EXPERIMENTAL VERIFICATION OF THE MODEL

To verify the applicability of the model the electrochemical method of measuring the O_2 tension in the tissue [4] can be used to good advantage; an injection electrode with a low time constant reaction can be employed, the form of the reaction representing the response to the change of the input quantity being studied. In our experiments we use the simplest, i.e. the so-called step change in the concentration of the inhaled mixture, practically realizable by giving the animal pure oxygen to inhale for a period of 1 minute and recording the course of O_2 tension in the tissue. Examples of the response in the fore- and hind-legs of a rat are presented in Fig. 3. From the curves it is to be seen that the actual reaction sets in with a time lag of 4 seconds (in the fore-legs somewhat shorter) which expresses the blood transportation rate. The form of the reaction expresses processes at work, some of which counteracte each other e.g. the course of O_2 concentration in the arterial blood affected by the response of the lungs and the mixing in the heart, the rate of O_2 consumption due to metabolic activity, O_2 consumption due to the electrochemical process taking place on the electrodes, and, finally, the delayed action of the organ due to its O_2 storage volume.

The dynamic properties of each organ can be defined with the aid of the transition characteristic which is a reaction of the output quantity to the unit change of the input quantity and can be approximately obtained by the following techniques:

a) Simultaneous measurements of the course of O_2 concentration in several organs in the way in which they are engaged in series in the circulatory system, e.g. lungs, heart, organ, if we

effect a step change in the concentration of the inhaled mixture. We thus measure the successive prolongation of the time constant of the response, for the time constants of the particular organs are gradually multiplied. The transfer function of the organ under study, or of the entire part of the circulatory system, then gives us the proportion of the reaction at the outlet to the reaction at the inlet, which can easily be carried out on a computer, provided both courses are modelled to the generator of functions.

b) Another method of obtaining the transition characteristic of an organ consists in introducing step changes of the oxygen concentration in the blood immediately upon entering the organ. The experiment can be performed as follows:

By constricting the supply vessel (with a thread, tweezers, and the like) at the point where it branchess off from the main vessel, the blood flow through the organ is instantaneously stopped. The O_2 tension immediately drops to zero according to an approximately exponential curve on which the following factors come into play: oxygen consumption in the tissue, O_2 consumption as a result of the electrode process, and the delayed action of the organ due to its storage volume. After releasing the vessel, the oxygen concentration in the incoming blood registers a step change, for the blood continues to flow through the main vessel, while the vessel is closed. The recorded ascending curve then gives us directly the transition characteristic of the organ. Examples of dependences measured are shown in Fig. 4. The curves obtained can be further analyzed, in particular, on isolated organs where, by a suitable arrangement of the experiment, two separate processes taking part in the overall reaction can gradually be distinguished.

CONCLUSION

The importance of the dynamic modelling of oxygen distribution lies in the possibility of differentiating the reaction of blood transportation from the reaction of the organ actually studied, which cannot be carried out with the aid of conventional statistical investigations. In practice, it will always suffice for this purpose to measure simultaneously the O_2 tension in at least two sites, namely, in the organ under study and, if possible, at the outlet of the left heart, i.e. in the aorta, or in an organ which the results can be related to. In the study of individual radiosensitivity the dynamic characteristics obtained can serve to classify the experimental animals, as a criterion. Disturbance in the regulatory system due to damage by ionizing radiation also manifest itself by a deviation of the dynamic characteristics from normal values and that is why their analysis can indicate the causes of changes arising in the regulatory system.

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REFERENCES

[1] J. A. Jacques, R. Bellman, R. Kalaba: Some Mathematical Aspects of Chemotherapy. II The Distribution of a Drug in the Body. Bull. Math. Biophys. *22* (1960), 309–322.

[2] J. D. Horgan, R. L. Lange: Analogue Computer Studies of Periodic Breathing. IRE Trans. *BME-9* (October 1962), No. 4, 221–228.

[3] J. D. Horgan, R. L. Lange: Digital Computer Simulation of the Human Respitatory System. 1963 IEEE Nat. Conv. Record, Part 9, 148–157.

[4] A. Vacek, F. Ševčík: Electrochemical Determination of the Tension of Oxygen in Tissue. Physiol. bohemoslov. *12* (1963), 269–274.

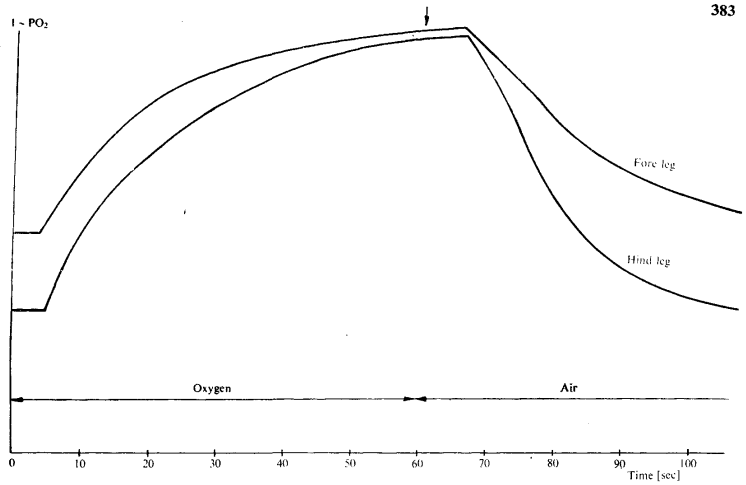

Fig. 3. Course of reaction of O_2 tension in the muscle to step change of oxygen concentration in the inhaled mixture.

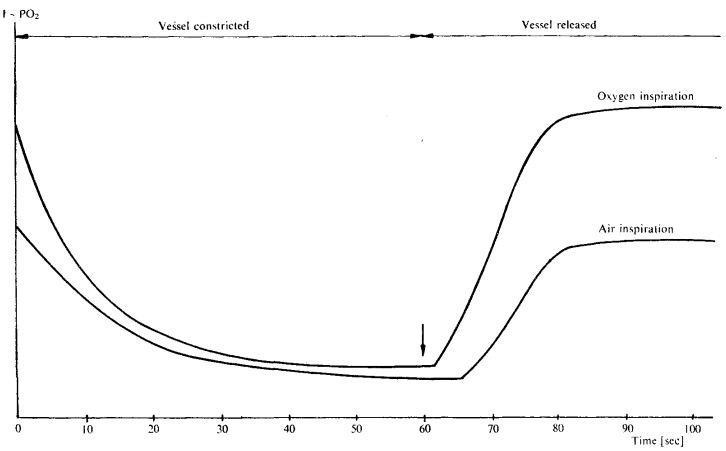

Fig. 4. Course of reaction of O_2 tension in the muscle to step change of oxygen concentration in the blood.

Dynamický model distribuce kyslíku v organismu

FRANTIŠEK ŠEVČÍK, TAČO TAČEV

V matematickém modelu je sledována časová změna koncentrace kyslíku v jednotlivých orgánech po skokové změně koncentrace kyslíku ve vdechované směsi. Navržený model bere v úvahu rovnovážný stav mezi koncentrací kyslíku v arteriální a venózní krvi ve všech důležitých orgánech, serioparalelní propojení orgánů prostřednictvím cirkulačního systému a jeho vliv na časové zpoždění reakce. Je diskutována možnost ověřování modelu metodami, používaných v automatické regulaci s využitím analogových počítačů.

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