DEVELOPMENT OF A COMPUTER MODEL SIMULATING SOME ASPECTS OF THE CARDIOVASCULAR–RESPIRATORY DYNAMICS OF THE SALMONID FISH

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INTRODUCTION

Oxygen demand in teleost fishes varies as an exponential function of motor activity (Brett, 1964), and is markedly influenced by a wide range of intrinsic and environmental factors (Brett, 1962; Beamish, 1964a–c; Beamish & Mookherjii, 1964). The nature of the adaptive systemic responses which permit respiratory adjustment in these animals is, however, poorly understood at present. Nevertheless, a series of recent theoretical and experimental studies, which define the operation of the several factors influencing gas exchange in the aquatic environment, provide a basis for speculation upon several aspects of respiratory adaptation (Hughes, 1964; Rahn, 1966; Randall, Holeton & Stevens, 1967). These focus attention upon five probable sites of adjustment: ventilatory flow, cardiac output, branchial exchange area, blood oxygen capacity and the mean environment-to-blood diffusion pathlength. Consideration of the consequences of singly modifying these loci of control demonstrates that the system as a whole embodies a number of restrictive elements.

It is apparent, for example, that attempts to meet heightened oxygen demand solely through increases in ventilation quickly become self-limiting; this being largely due to the much-increased metabolic cost of operating the branchial pump (Schuman & Piiper, 1966). The situation, in essence, represents a form of positive feedback (Hughes, 1964), which, operating without control, would tend to de-stabilize the system. Furthermore, increasing flow velocity reduces the exposure time of any given volume of water to the exchange surface, while elevation of ventilatory stroke volume increases the diffusional deadspace within the branchial chamber (Rahn, 1966). Shunting of substantial portions of the respiratory current between adjacent branchial arches, rather than over their lamellar surfaces, also follows increases in ventilation (Pasztor & Kleerekoper, 1962). In net, these factors lead to a sharp diminution of the efficiency of oxygen extraction as maximum flow rates are approached (Saunders, 1962). Thus, much of the potential benefit of heightened ventilation is lost as a consequence of the reduced efficiency of the exchanger system, and the increased energy requirement of pump operation.

Adjustment of branchial perfusion rate (essentially cardiac output in the teleost) provides a second possible mechanism for meeting increasing oxygen demand. The metabolic costs of cardiac function have apparently not been accurately evaluated as
yet, but are thought to be less than half of that associated with ventilation (Hughes, 1966; H. Rahn, personal communication). However, the effective operation of a countercurrent exchange system of the type represented by the teleost gill requires precise adjustment of the ventilation: perfusion ratio. In theory, at least, maximally effective oxygenation is attained as this ratio approaches zero (Hughes, 1964). Consistent with this, experimentally determined ratio values in a variety of aquatic organisms are generally less than 0.1 (Rahn, 1966). Accordingly, it would appear that the extent to which cardiac output can be effectively elevated will be limited by the extent to which it is metabolically practical to increase ventilation.

An increase in oxygen uptake, other factors being equal, might also be achieved by expansion of the effective exchange area. The existence of alternate respiratory and non-respiratory vascular pathways in the teleostean gill, and the ability of the animals to govern flow distribution between these has been demonstrated (Steen & Kruyyse, 1964). Thus, respiratory compensation by some form of branchiovascular adjustment represents a distinct possibility. It should be noted, however, that although this type of response would undoubtedly be efficacious from the respiratory viewpoint it is not without concomitant disadvantages. Increases in functional exchange area must, in the absence of selective permeability adjustments, promote endosmosis, salt efflux and a reduction in carbon dioxide tension. Accordingly, a need for adjustment in the activities of the several components of the water-electrolyte and acid-base regulating systems would necessarily follow.

Finally, enhancement of blood oxygen capacity might resolve the problem of meeting increases in oxygen demand. This could be achieved through an increase in circulating haemoglobin level, or by a shift or form-change in the dissociation relationship. Although increases in haemoglobin levels do occur during activity (Black et al. 1962) and following acclimation to hypoxic conditions (Prosser et al. 1957) their magnitude must be functionally limited by the effect of increasing haematocrit upon blood viscosity. Similarly, although the blood of fishes typically displays a marked Bohr effect, the carbon dioxide tensions in these animals are normally low (Rahn, 1966).

Thus, consideration of only four variables of the cardiovascular-respiratory complex clearly indicates the probable existence of a variety of restrictive elements. Under such circumstances, systemic adjustment to variations in oxygen demand can be achieved only through balanced responses of the several contributing components. This being the case, it is probable that attempts at a comprehensive analysis of respiratory adaptation in terms of conventional methods may prove either cumbersome or inadequate. On the other hand, there has, as yet, been apparently little effort directed toward the application of the simulation techniques which have proven useful in the analysis of human respiratory activity (Horgan & Lange, 1965; Milhorn & Guyton, 1965; Grodins, Buell & Bart, 1967). The present study was, accordingly, undertaken with the aim of developing a model consistent in operation with the limited experimental data presently in the literature. It was anticipated that such a simulation might well provide a more coherent picture of some aspects of respiratory response than is now available, as well as establishing a basis for further experimental investigations.
DEVELOPMENT OF THE MODEL

(1) General form and basic assumptions

The teleostean cardiovascular–respiratory complex has been visualized as consisting of two perfect mixing chambers, the 'branchial volume' and the 'body tissue volume' (Fig. 1). These areas represent effective volumes of dilution of dissolved oxygen, and do not necessarily correspond to anatomical volumes. The effective body volume, essentially a storage volume for oxygen, would presumably include the extrabranchial blood volume, and an undefined portion of the extravascular fluid system. The branchial volume is considered to be analogous to the volume of blood actually in contact with the effective exchange area. No attempt has been made to further compartmentalize the model, or to account for exchange phenomena between the blood, interstitial fluid and cellular phases.

Fig. 1. Diagrammatic representation of model system.

Flow through the system has been assumed to be continuous in character, and not subject to breath-by-breath or beat-by-beat variations.

Finally, for purposes of subsequent testing, the model has been taken as representing a salmonid fish of unit size (1–0 kg.) existing in a constant thermal environment (5°C.).

This conception of the respiratory–cardiovascular complex is basically similar to that proposed by Hughes (1964), differing from it only in the location of the neural control mechanism. Hughes has suggested that the error detector device is an oxygen receptor, probably located on the arterial side of the system. While the operation of the present model supports the hypothesis that cardiac and ventilatory activity is regulated by reference to oxygen tensions the necessary receptor has, for reasons to be brought out in subsequent paragraphs, been sited in the venous portion of the circulation.

Two series of equations have been used to describe the model. The first group (the
controlled system equations) summarize the principal physical exchange processes believed to operate in the system. The second series of equations (feedback, or system-controlling equations) are used to link the exchange processes into a coherent, responsive unit. In contrast to the controlled system equations, which are expressions of physical principles, the feedback equations are descriptions of physiological activities. Accordingly, they are to be regarded as essentially empirical, and approximate in character.

The symbols used in the model are defined in Table 1.

Table 1. Model symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>( V_b )</td>
<td>Effective volume of branchial compartment (ml.)</td>
</tr>
<tr>
<td>( V_s )</td>
<td>Effective volume of body compartment (ml.)</td>
</tr>
<tr>
<td>( V_a )</td>
<td>Effective extrabranchial volume (ml.)</td>
</tr>
<tr>
<td>( MR )</td>
<td>Metabolic rate, i.e. oxygen consumption (ml./min.)</td>
</tr>
<tr>
<td>( \dot{V}_{ao} )</td>
<td>Volume flow of oxygen across respiratory exchange surface (ml./min.)</td>
</tr>
<tr>
<td>( \dot{V}_{vo} )</td>
<td>Volume flow of oxygen in arterial system (ml./min.)</td>
</tr>
<tr>
<td>( \dot{V}_{vo} )</td>
<td>Volume flow of oxygen in venous system (ml./min.)</td>
</tr>
<tr>
<td>( \dot{V}_l )</td>
<td>Ventilatory flow (ml./min.)</td>
</tr>
<tr>
<td>( Q )</td>
<td>Cardiac output (ml./min.)</td>
</tr>
<tr>
<td>( C_{ao} )</td>
<td>Oxygen content of arterial blood (ml./100 ml.)</td>
</tr>
<tr>
<td>( C_{vo} )</td>
<td>Oxygen content of venous blood (ml./100 ml.)</td>
</tr>
<tr>
<td>( P_{ao} )</td>
<td>Oxygen tension of arterial blood (mm. Hg)</td>
</tr>
<tr>
<td>( P_{vo} )</td>
<td>Oxygen tension of venous blood (mm. Hg)</td>
</tr>
<tr>
<td>( P_{io} )</td>
<td>Oxygen tension of inspired water (mm. Hg)</td>
</tr>
<tr>
<td>( P_{io} )</td>
<td>Oxygen tension of expired water (mm. Hg)</td>
</tr>
<tr>
<td>( \alpha_{wo} )</td>
<td>Coefficient of oxygen solubility in water (ml./ml./mm. Hg)</td>
</tr>
<tr>
<td>( \alpha_{bo} )</td>
<td>Coefficient of oxygen solubility in blood (ml./ml./mm. Hg)</td>
</tr>
<tr>
<td>( A' )</td>
<td>Effective diffusion pathlength across respiratory lamellae (mm.)</td>
</tr>
<tr>
<td>( A )</td>
<td>Effective respiratory exchange area (cm.²)</td>
</tr>
<tr>
<td>( s )</td>
<td>Condition of resting or routine active, e.g. ( \dot{V}<em>l ), ( Q ), ( A' ), ( P</em>{io} ), etc.</td>
</tr>
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</table>

(2) Controlled system equations

The sum of the rates of flow of oxygen into a given volume must equal the sum of rates of flow out of the volume, plus the rate of oxygen storage within the volume. Mass balance relationships were, therefore, developed to describe oxygen transport and storage in the extra-branchial, branchial and body phases.

For the body compartment such a relationship can be expressed in the form

\[
\dot{V}_{ao} - (\dot{V}_{vo} + MR) = \left( \frac{d}{dt} \right) V_{vo}.
\]

If

\[
\dot{V}_{ao} = \dot{Q}(C_{ao}/100)
\]

and

\[
\dot{V}_{vo} = \dot{Q}(C_{vo}/100)
\]

and

\[
\dot{V}_{vo} = V_s(C_{vo}/100),
\]

then, equation (1) can be recast in the form

\[
(\dot{Q}/100)(C_{ao} - C_{vo}) - MR = (V_s/100)(\left[ \frac{d}{dt} \right] C_{vo}).
\]

It will be apparent that equation (4) embodies the assumption that the body compartment, \( V_o \), is a perfect mixing chamber. This implies that oxygen concentrations within this compartment are at all points equal to the venous oxygen concentration.
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In actuality, distributive oxygen gradients are to be anticipated. A lumped-parameter model of the body compartment must, then, be accepted in order to express equation (1) in the form of equation (5).

An equation analogous to equation (5) can be developed for the branchial compartment,

\[ \frac{Q}{100}(C_{wO_2} - C_{aO_2}) + V_{O_2} = \frac{(V_g/100)(d/dt)C_{aO_2}). \]

(6)

A mass balance equation describing the fate of the dissolved oxygen brought in during inspiratory activity can be derived in much the same fashion as were equations (5) and (6). This has the form

\[ V_t \alpha W_O (P_{O_2} - P_{EO_2}) - V_{O_2} = V_o (d/dt) \alpha W_O P_{EO_2}. \]

(7)

If storage effects are accepted as negligible, an assumption supported by the recent findings of Stevens & Randall (1967a, b), equation (7) can be simplified to

\[ P_{EO_2} = P_{O_2} - V_{O_2}/\alpha W_O. \]

(8)

Oxygen transfer across the respiratory lamellae can be described in terms of the Fick diffusion equation

\[ P_{O_2} = -DA (d/dx)P_{O_2}. \]

(9)

Assuming the oxygen tension gradient across the lamellar wall to be spatially constant permits expression of the term \( d/dx P_{O_2} \) as \( \Delta P_{O_2}/\Delta x \). The mean oxygen tension, \( \Delta P_{O_2} \), is equivalent to \( (P_{aO_2} - P_{tO_2} + P_{wO_2} - P_{EO_2})/2 \). Accordingly, equation (9) can be expressed as

\[ V_{O_2} = DA/\Delta x (P_{O_2} - P_{wO_2} + P_{EO_2} - P_{tO_2}). \]

(10)

Finally, it is necessary to consider the oxygen uptake and release characteristics of haemoglobin in venous and arterial blood, and to relate oxygen tension to oxygen content. These functional relationships are symbolically represented by equations (11) and (12).

\[ P_{aO_2} = f(C_{aO_2}), \]

(11)

\[ P_{wO_2} = g(C_{wO_2}). \]

(12)

Quantitative expression of the foregoing equations has been based upon dissociation curves reported by Black, Kirkpatrick & Tucker (1966). These were approximated by a series of fifteen linear segments for purposes of incorporation into the model.

(3) Controlling system equations

Equations (5), (6), (8), and (10)–(12) are considered to depict the principal physical relationships prompting oxygen flow through the model system. To complete the simulation, a series of relationships describing the regulatory elements governing the expression of these processes is needed.

Hughes (1964) has reviewed information relating to the control of ventilation in fishes, and suggests that this is based upon the monitoring of arterial oxygen tensions. Until recently little experimental evidence bearing on this question has been available. Stevens & Randall (1967a, b) have, however, provided experimental values for \( \tilde{V}_t \), \( P_{wO_2}, P_{wCO_2}, P_{wCO_2} \), and \( P_{wCO_2} \), in moderately exercised rainbow trout. It is apparent from their data that \( \tilde{V}_t \) is correlated with \( P_{wO_2} \), but that no simple relationship obtains between ventilation and the remaining variables. This correlation has been approximated in the form of equation (13).

\[ \tilde{V}_t = \tilde{V}_t^0 + m_1 (P_{wO_2} - P_{wO_2}^0). \]

(13)
A similar relationship apparently exists between cardiac output and venous oxygen tension, and can also be described by means of a linear equation equivalent to (13). However, it would appear that $\dot{V}$ and $Q$ approach zero at the same value for $P_{vO_2}$, i.e., that the ratio $Q/\dot{V}$ is a system constant. This conclusion was subsequently verified using values scaled from the figures presented by Stevens & Randall (1967a, b). Accordingly, cardiac output has been expressed as a constant fraction of ventilation:

$$Q = K \dot{V}.$$

(14)

In a system of this type any increase in $MR$ should lead to a reduction in venous oxygen tension from the value represented by $P_{vO_2}$. Equations (13) and (14) specify that $Q$ and $\dot{V}$ will then increase. As a consequence $\dot{V}_{O_2}$ will rise, and $P_{vO_2}$ approach its original value, $P_{vO_2}$. It will be apparent, however, that the degree to which $\dot{V}_{O_2}$ can be increased depends to a large extent upon the magnitude of $\Delta P_{O_2}$. Preliminary trials with the model clearly indicated that increases in $\Delta P_{O_2}$ would not permit the model to adjust $\dot{V}_{O_2}$ so as to keep pace with $MR$. It became necessary, therefore, to make a decision upon the extent to which the model might be allowed to incur the biological equivalent of an oxygen debt, i.e. predict very low or zero oxygen tensions. The only data sufficiently detailed to permit testing of the model deal with the rainbow trout. This species, like most salmonids, has relatively little capacity for anaerobiosis. Accordingly, it was decided not to allow the model to accumulate any oxygen debt, and to establish the condition that $\dot{V}_{O_2}$ must approximate $MR$.

Accordingly, it became necessary to amplify $V_{O_2}$ beyond the limits permitted by variation in $\Delta P_{O_2}$. The work of Steen & Kruyyse (1964), alluded to earlier, suggests that controlled shunting of blood from non-respiratory to respiratory portions of the gill would achieve this through increasing the effective exchange surface area ($A$ in equation (9)). It has been assumed, therefore, that $A$ is a function of $Q$, and is, therefore, also related to $P_{vO_2}$. This relationship is indicated in equation (15).

$$A = A^e + m_2 (Q - Q^e).$$

(15)

**APPLICATION OF THE MODEL**

The relation of the various elements embodied in the controlled system and feedback equations are summarized in Fig. 2; a block diagram of the respiratory, circulatory and neuroregulatory components of the simulation. It will be apparent that the evaluation of this model requires information bearing upon several system constants, and the responses of the teleost to stress situations. As a consequence of several recent studies, data sufficient for preliminary testing of the model under conditions of (a) routine activity, (b) exercise-induced increases in oxygen demand, and (c) routine activity during progressive hypoxia is now available (Hughes, 1964, 1966; Rahn, 1966; Holeton & Randall, 1967; Stevens & Randall, 1967a, b).

The controlled situation (equations (5), (6), (8), (10)–(12)) and system-controlling equations (equations (13)–(15)) were simultaneously solved on an IBM 7040 digital computer. Numerical values for $MR$ or $P_{I0_2}$ were used as input-driving functions in the various experiments carried out. These, and the state of the system at any given time, were used to predict succeeding system states in terms of $\dot{V}_{O_2}$, $\dot{V}$, $Q$, $P_{vO_2}$, $P_{aO_2}$, $P_{E0_2}$, $C_{aO_2}$ and $C_{vO_2}$. The smallest time constant of the model proved to be the branchial
factor, $V_o/Q$, which varied in value from 0.70 (standard or routine activity) to 0.13 min. (maximum activity). Accordingly, solutions were generated at 0.01 min. intervals.

(1) Routine cardiovascular–respiratory activity

Testing the model under conditions of routine activity was largely associated with the development of approximations for several essential constants, and the adjustment of all relationships to yield reasonable values for the several parameters predicted.

Fig. 2. Block diagram of simulation indicating the interactions of the principal elements of the model.
The value for \( \alpha_{wO_2} \) (5.72 \( \times \) 10\(^{-8}\) ml./ml./mm. Hg) was interpolated from the data assembled by Rahn (1966), and corrected to coincide with the dimensions used in this study. The coefficient of diffusion, \( D \), was estimated according to the procedure used by Hughes (1966) as 3.29 \( \times \) 10\(^{-8}\). Values scaled from Holf & Randall (1967) and Stevens & Randall (1967a, b) were employed for \( MR^* \) (0.42 ml./min.), \( P_{IO_2} \) (134 mm. Hg), \( P_{co_2} \) (19 mm. Hg) and \( V_T \) (564 ml./min.). Hughes's investigations upon the functional dimensions of the teleost gill suggest that about 10\% of total blood volume is contained within the branchial apparatus at any given time. Using the mean of a number of recent estimates gives a value of 5.50 ml. for \( V_g \) (Schiffman & Fromm, 1959; Conte et al. 1963; Smith & Bell, 1964; Smith, 1966).

No similar values exist for the body-phase volume, \( V_s \). An empirical estimate was, therefore, made by solving the system for several trial values for this parameter. It may be assumed that the range of possible values for \( V_s \) is limited by a minimum corresponding to blood volume, and a maximum corresponding to the total volume of the body fluid system. Accordingly, the following values were used: (1) blood volume (taken as 5.5\% of body weight, 55.0 ml.), (2) extracellular phase volume (taken as 8.0\% of body weight, 80.0 ml.), and (3) total fluid volume (taken as 80.0\% of body weight, 800.0 ml.). Predictions of \( V_O_2 \) and gas tensions based upon these values were all similar in magnitude, suggesting that \( V_s \) is not a critical parameter in this model. Least squares analysis indicated, however, that \( V_s = 80.0 \) ml. provided the best correspondence between predicted and actual performance. This value was consequently employed.

Estimates of total gill area have been provided by Hughes (1966) for a variety of fishes, including the brown trout. It is unlikely, however, that all available respiratory exchange area is used in the state of routine activity (Steen & Kruuyse, 1964). An approximation of \( A_s \) was obtained by solution of equation (10) for the resting state, using the values for \( MR, D, P_{IO_2}, P_{co_2} \) and \( P_{ao_2} \) previously noted. This calculation also requires a value for \( \Delta x \), the mean diffusion pathlength. Hughes's analysis of respiratory function (Hughes, 1966) suggests that, under resting conditions, this is '...almost exactly that from halfway between two secondary lamellae to the centre of the blood space...'. Values for interlamellar distance range from 35 to 47 \( \mu \) in the brown trout (Hughes, 1966; Steen & Berg, 1966). Accepting 20 \( \mu \) as a reasonable estimate of diffusion pathlength suggests that \( A_s \) is 338 cm.\(^2\) in the resting state, or about one-tenth of the maximum area.

Table 2. Experimental and predicted variables under conditions of routine activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental*</th>
<th>Model-predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{IO_2} )</td>
<td>134</td>
<td>134.0</td>
</tr>
<tr>
<td>( P_{co_2} )</td>
<td>121</td>
<td>121.0</td>
</tr>
<tr>
<td>( P_{ao_2} )</td>
<td>85</td>
<td>84.5</td>
</tr>
<tr>
<td>( P_{co_2} )</td>
<td>19</td>
<td>19.0</td>
</tr>
<tr>
<td>( \dot{V}_T )</td>
<td>564</td>
<td>566</td>
</tr>
</tbody>
</table>

* Values scaled from figures presented by Randall & Shelton (1967).

Finally, at this stage in the testing of the model the parameter \( K \) was adjusted until realistic predictions of gas tensions were generated. The trial value accepted for \( K \) (1.42 \( \times \) 10\(^{-8}\)) lies in the same range of values as those calculated from experimental values for ventilation-perfusion ratios.
Cardiovascular–respiratory dynamics of the salmonid fish

The system was then solved for $\dot{V}_r$, $Q$, $P_{1O_2}$, $P_{EO_2}$, $P_{vO_2}$ and $P_{ao_2}$ under conditions of routine activity. As may be seen from the values summarized in Table II the model generated accurate predictions for this situation.

(2) Respiratory responses in exercised fish

In investigation of exercise-induced responses in rainbow trout Stevens & Randall (1967a, b) subjected specimens to a graded schedule of changes in water velocity, and followed immediate response and recovery processes. To simulate this situation $P_{1O_2}$ was set at 134 mm. Hg, which corresponds to that used experimentally. The input forcing function, $MR$, was developed for this simulation in accordance with the previously noted assumption that oxygen consumption faithfully reflects the actual metabolic rate. Temporal variations in metabolism were then expressed in a series of three equations ($16a, b, c$). In establishing this expression values scaled from figures presented by Randall & Stevens were histographically plotted (Fig. 3), and fitted with two exponential curves. The first ($16b$) describes oxygen uptake during exercise, the second ($16c$) indicating changes in metabolic rate during recovery. Both obey the restriction that the areas under equivalent portions of the curve and histogram have equal values. The resulting over-all curve differs somewhat from the visually fitted function described by the authors, but is felt to provide a more realistic description of the original data.

\[
MR_{\text{rest}}(t \leq 0) = 0.42 \text{ ml./min.,} \quad (16a)
\]
\[
MR_{\text{exercise}}(0 < t \leq 15) = 0.42 + 1.84 \frac{1 - e^{-t/3.8}}{3.8} \text{ ml./min.,} \quad (16b)
\]
\[
MR_{\text{recovery}}(t = 15) = 0.42 + 1.81 e^{-t(15)/4.4} \text{ ml./min.} \quad (16c)
\]

Using this group of equations values for $\dot{V}_r$ were recalculated by the Fick method employing the data for $P_{1O_2} - P_{EO_2}$ provided by Stevens & Randall (1967b), and the value for $\alpha_{WO_2}$ previously noted. The resulting curve is seen in Fig. 3.

The value for $m_1$, the slope of the relationship in equation (13) was estimated as $-1440$ from the data of Randall & Shelton (1967a, b). An empirical determination of $m_2$ was carried out, as before by solution of the model using a series of trial values. Of the various estimates used, $m_2 = 179$ provided the least deviation between prediction and actual performance. Lesser values lead to unacceptably large differences between actual and predicted gas tensions, while values of greater magnitude produced unrealistically large increases in ventilation.

In Fig. 4 the predictions of the model are compared to recalculated values for $\dot{V}_r$. Good correspondence is apparent. Predicted variations in $P_{vO_2}$ also parallel the changes observed in the trout. Less satisfactory agreement was obtained with respect to $P_{ao_2}$, although the over-all trends are similar. On the whole, nevertheless, the behaviour of the model can be taken as providing a reasonably good picture of the experimental situation.

This being the case, the role of branchiovascular adjustment (equation (15)) was further investigated by generating predictions of blood gas tensions with $A$ fixed at $A^*$, and $\Delta x$ held constant. The results of this simulation are also indicated in Fig. 4. As may be seen, arterial and venous oxygen tensions drop to zero within 3 and 4 min. respectively. Further trials using reduced values for $MR$ indicated that metabolic rate
could be approximately doubled without change in $A^e$, but that this represented the upper limit possible with this restriction. Reference to the recent work of Brett (1964) upon the relationship between temperature, oxidative metabolism and swimming speed in yearling sockeye salmon suggests that a doubling of $MR$ would permit less than one-third of the activity of which these animals are actually capable. The importance of a branchiovascular response of the type depicted by equation (15), or some functional equivalent, is clearly indicated.
Computer predictions of ventilation, and arterial and venous oxygen tension under conditions of rest, moderate exercise and recovery vs. experimental data (Stevens & Randall, 1967)

Fig. 4. Computer predictions of $V_i$, $P_{aO_2}$ and $P_{vO_2}$ during rest, exercise and recovery of rainbow trout; $P_{aO_2}$ and $P_{vO_2}$ during rest and exercise with $A = A^f$. Dotted lines: $V_i$ from Fig. 3; $P_{aO_2}$ and $P_{vO_2}$ from Stevens & Randall (1967b).
Prediction of cardiovascular-respiratory responses to environmental hypoxia

The response of rainbow trout to progressive environmental hypoxia has been investigated by Holeton & Randall (1967). The time scale of the study was such as to preclude acclimatory effects equivalent to those described by Prosser et al. (1957). Under such conditions it might be anticipated that an ever-increasing fraction of MR would be needed to satisfy the metabolic demands of the branchial pump (Hughes, 1964; Schuman & Piiper, 1966). This, in effect, represents a positive feedback loop which, in the absence of any braking action, would lead to system instability given sufficient stress. To test the consequences of an uncontrolled positive feedback loop of this type the model was adjusted to permit the expenditure of a portion of the total oxygen uptake in the form of ventilatory work. The value for MR was then expressed as the sum of respiratory (RMR) and non-respiratory (SMR) oxygen requirements.

\[ MR = RMR + SMR, \]  
\[ MR = m_0 (V_T - V_i) + m_0 (Q - Q_i) + SMR. \]  

Inasmuch as the perfusion-ventilation ratio has been taken as a system constant (equation (14)) the foregoing equation can be expressed in the form,

\[ MR = m_0 (V_T - V_i) + SMR. \]
Assuming that 25% of the oxygen consumed under conditions of routine activity is expended in ventilatory work the slope function of equation (19) can be estimated as

\[ m_s = \frac{SMR}{4\dot{V}_0}. \]  

(20)

The model was then used to generate solutions for \( \dot{V}_T, P_{EO_2}, P_{ao_2}, \) and \( P_{so_2} \) at progressive 2 mm. Hg depressions in \( P_{IO_2} \) under conditions of routine activity. In this instance the available experimental data provide values for trout at 15°C, whereas the model was developed for trout respiring at 5°C. Furthermore, some uncertainty, of course, attends the assumption that \( RMR \) is actually fixed at the value selected under the conditions imposed. Therefore, qualitative agreement only was anticipated. Predicted variations in oxygen tensions are summarized in Fig. 5. Values for \( P_{EO_2} \) were lower than experimental values scaled from the figures presented by Holeton & Randall (1967) by some 2 to 10 mm. Hg. In general, \( P_{ao_2} \) in the trout corresponded closely to \( P_{EO_2} \), and was from 10 to 25 mm. Hg higher than the values predicted by the model. Better agreement between experimental and predicted venous oxygen tension was achieved. In all instances, however, qualitative correspondence existed.

Model predictions of \( \dot{V}_T \) under hypoxic conditions are indicated in Fig. 6. Again qualitative agreement is seen between experimental and model-generated values, at least down to a limiting value of \( P_{IO_2} = 50 \) mm. Hg. Further reduction in \( P_{IO_2} \) caused
the model to predict unbounded increase in $\dot{V}_T$. This can be regarded as verification of the de-stabilizing influence of a positive feedback element of the type alluded to earlier. In actuality, of course, this does not occur in the teleost. At low environmental oxygen tensions the rising phase of ventilatory flow is abruptly terminated, and ventilation stabilizes or actually diminishes (Hughes, 1964; Holton & Randall, 1967). Consequently it would seem reasonable to hypothesize the existence of at least one braking function which, coming into play under conditions of hypoxic crisis, overrides the influence of the positive loop.

**DISCUSSION**

The model developed in this study represents, in several respects, a gross oversimplification of the biological reality. Among other things it incorporates assumptions regarding flow continuity which are met only in the sense of mean flow and largely disregards intercompartmental transfer processes. The feedback elements of the system (equations (13)-(15)) have been depicted as linear relationships, whereas, by analogy with the mammalian system, it seems more probable that such functions would actually be non-linear in character. Nevertheless, despite these and other limitations the model does predict the performance of the fish quite closely, and provides insights relating to a number of aspects of teleostean cardiovascular-respiratory dynamics.

For example, the operation of the model strongly supports the view that respiratory responses, in the situations simulated, are based upon the monitoring of blood oxygen tension. No realistic simulations could be achieved in trials using either $P_{a\text{CO}_2}$ or $P_{a\text{CO}_3}$ as reference factors in the feedback equations modifying $\dot{V}_T$, $Q$ and $A$. Furthermore, the use of $P_{a\text{O}_2}$ did not provide correspondence of the responses of the model with those of the fish. The accuracy achieved with values for $P_{v\text{O}_2}$ as the reference point, therefore, suggests a venous rather than an arterial location of the receptor system.

This model study has also emphasized the probable importance of branchiovascular adjustments in the over-all pattern of response. This was not appreciated initially, and simulations of forced activity in the absence of this factor inevitably lead to quick depletion of stored oxygen, and the prediction of very low, or zero values for $P_{a\text{O}_2}$ and $P_{v\text{O}_2}$ (i.e. Fig. 4). On the other hand, the value for $m_2$ required for accurate predictions of $\dot{V}_O$ and blood gas tensions may be too high. This facet of the behaviour of the model undoubtedly stems from the restrictions incorporated in its development. For example, the model was not permitted to incur any oxygen debt whatsoever, i.e. $\dot{V}_O = MR$. As was previously noted the salmonid fishes do not, on the whole, have great capacity for anaerobic metabolism. They can, however, accumulate some degree of oxygen debt (Black et al. 1962; Brett, 1964), and this would reduce the necessity of keeping $\dot{V}_O$ abreast of metabolic demand. Accordingly, the value for $m_2$ would not have to have the magnitude necessary to satisfy the condition imposed, and $\Delta A$ could be reduced. The equation also carries the implication that area only is modified. In fact, however, it can be readily shown that this condition cannot be entirely satisfied. At the maximum value for $\dot{V}_O$ recorded (2.23 ml./min.) solution of equation (9) with $\Delta x$ at 20 $\mu$ requires that $A$ be approximately 1600 cm.$^2$. Hughes’s measurements of gill surface suggest a gill area of about 3400 cm.$^2$ for a 1.0 kg. trout (Hughes, 1966). Allowance must be
made for the probability that that portion of the lamellar surface which lies over the pillar cells cannot effectively contribute to gas exchange. Estimations of pillar surface area range from 30 to 40%, reducing the effective area to 2040–2380 cm²; values which are still in excess of that required. Brett (1964) has, however, shown that salmon exercised at low temperature can amplify resting \( V_{O2} \) by 12 to 13 times. Satisfaction of this level of oxygen flow demands full utilization of gill surface, plus a drop in \( \Delta x \) (mean diffusion pathlength) from 20 to 10.8–12.3 μ. Such a situation would appear to be biologically reasonable. Lloyd (1961) has discussed the relationship between \( P_{O2} \) and branchial ventilation, and suggests that the oxygen tension gradient extending outward from the lamellar surface varies as a function of the square root of flow velocity. Thus, although the efficiency of oxygen extraction is diminished by increasing ventilation, some degree of compensation is to be anticipated since shifting the diffusional dead-space boundary closer to the lamellar surface would, of course, effect a reduction in mean diffusion pathlength.

Whether a decrease of the magnitude suggested is actually necessary is problematical. Although blood oxygen capacity has been assumed to be constant in the simulation it will be readily appreciated that an increase in this factor could resemble the consequences of either an increase in exchange area, or a decrease in diffusion pathlength. Although this parameter was not measured by Stevens & Randall, an increase in venous viscosity, which might be attributable to a rise in haematocrit, was observed (Stevens & Randall, 1967a). In context with this it is of interest that Black et al. (1962) report rapid and sustained elevation of haemoglobin levels in severely exercised trout. Consequently, it seems likely that the high value for \( m_2 \) needed to achieve reasonably accurate predictions probably represents the consequences of a lumping effect, to which individually smaller variations in \( \alpha_{BO2} \), \( \Delta x \) and \( A \) contribute.

Simulations of the response to progressive environmental hypoxia may also be considered. As has been noted, the ever-increasing oxygen demand of branchial pump operation under such conditions constitutes a type of positive feedback effect which, if of sufficient magnitude, might be expected to produce system instability. Under the conditions imposed this expectation finds verification in the predicted exponential increase in \( V_T \) at low values for \( P_{O2} \). In actuality, this does not, of course, occur in the teleost. Reduction in environmental oxygen availability is often accompanied by some elevation in ventilatory flow at intermediate tensions. However, stabilization or even reduction in \( V_T \) is typically encountered at critically low oxygen levels (Hughes, 1964; Holeton & Randall, 1967). It would seem reasonable to hypothesize, therefore, the existence of a ventilatory suppressor function, whose operation is invoked by exposure to acutely hypoxic conditions. Although the basis of this activity remains entirely speculative at present, the operation of a system of this type implies the existence of a mechanism capable of monitoring \( P_{O2} \). In connexion with this, it is of some interest that De Kock (1963) has identified large numbers of apparently chemoreceptor ‘end buds’ within the pharyngeal cavity of both the brown trout and Atlantic salmon. It is also of note from the viewpoint of functional analogy that a similar braking action upon the stimulatory effects of reduced blood oxygen-tension is also found as a component of the mammalian regulatory complex.

Finally, although the behaviour of the present model is reasonably consistent with available experimental evidence, it has not as yet been exploited in relation to many
critical features of the respiratory response. Forcing functions of the type so far considered operate too slowly to shed much light upon the fast dynamics of the system. Experimental studies are needed in which the test animals are exposed to stresses approximating step-input, rather than ramp functions as employed by Holeton & Randall (1967) and Stevens & Randall (1967a, b). Perturbations of the former type should yield much information concerning the operational characteristics of the system, including values for the time constants of the responding elements. Investigations of this type are now under way in this laboratory, and will be reported at a later date.

**SUMMARY**

1. A digital computer simulation depicting some features of cardiovascular-respiratory interaction in the salmonid fish has been developed. This embodies six controlled system relationships; three of which are mass balance equation describing oxygen transport and storage in the extra-branchial, branchial and general body phases. A Fick equation, and two relationships approximating the transport characteristics of venous and arterial blood are also included in the system equations. Three feedback equations provide for adjustments in cardiac output, ventilation and exchange surface area.

2. The model predicts, with reasonable accuracy, values for ventilation, cardiac output and blood gas tensions under conditions of routine and moderate activity in an oxygen-sufficient environment. Qualitative agreement between predicted and experimental values has been obtained in simulations of responses to progressive environmental hypoxia.

3. The study emphasizes the probable role of venous oxygen tension in the regulation of ventilatory and cardiac activity. A central role for branchiovascular responses in adaptation to elevated oxygen demand is also indicated. The existence of a depressor function, operating under conditions of acute hypoxia to dampen positive ventilatory feedback effects is suggested by simulation of responses to reduced environmental oxygen tensions.

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**REFERENCES**


Cardiovascular–respiratory dynamics of the salmonid fish


