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Review

Modeling of vascular networks

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Summary

Vascular networks refer here mainly to the microscale capillary networks of the vascular system of mammals, although they may also be considered to include the small arteries that feed the capillaries and the small veins that drain them. The modeling of these networks for resting mammals is reviewed within the context of describing related scaling laws for mammals of vastly different size. Basic processes are considered and alternative approaches mentioned. All lead to the same scaling laws for the radius, length and number of the vessels. The applicability of the relations is illustrated using existing measurements. Discussion is also included on the effect of strenuous exercise on the scaling law for number of capillary vessels and matters related to it.

Key words: capillary networks, scaling laws, mammal, oxygen consumption, drug therapy scaling, resting, exercise state.

Introduction

The general subject of this review is the modeling of the microscopic vascular (capillary) networks in animals, with attention directed specifically to mammals. The modeling to be dealt with is that associated with the derivation and discussion of 'scaling laws' for these networks for mammals of vastly different size. For reviews of the basic concepts see also Dawson (1991, 2001, 2003). Experimental measurements on the scaling of the vascular networks of mammals have been reported by Schmidt-Nielsen and Pennycuik (1961), Gehr et al. (1981), and Hoppeler et al. (1981).

Scaling laws of the kind to be considered here are important in the general understanding of the vascular and cardiovascular system. If found appropriate, such scaling laws can illustrate that these systems all follow the same general pattern. Hence, the study of these systems on the basis of measurements from, say, the mouse can then reveal important information for the human, as well as other mammals.

Broad features of the vascular system

The vascular system of mammals consists of two major parts: the systemic part associated with transport of blood to the body and the pulmonary part associated with transport of blood to the lungs. The architecture is basically the same for both parts. The systemic vascular system, for example, consists of the aorta, carrying oxygenated blood directly from the left side of the heart, and the smaller vessels branching from it. The latter lead ultimately to the capillary networks spread throughout the body. These vascular networks consist of very small arteries (the arterioles) that take blood to the capillaries, the capillaries themselves, through which exchange of products with the tissues occurs, and then the very small veins (the venules) that take blood away from the capillaries and ultimately return it to the right side of the heart for circulation in the pulmonary system for discharge of unwanted gaseous products and for recharge of oxygen in the blood. The flow system is illustrated in Fig. 1 (from Dawson, 1991). Attention here will be directed mainly towards the systemic system, although some reference will also be made to the pulmonary system, as appropriate.

Modeling and scaling of the vascular networks

The systemic vascular networks of mammals consist of some 10–100 capillaries in each network. In muscle tissue, there are also reserve capillaries that open with exercise and provide increased blood flow, as first shown by Krogh (1920). This matter will be dealt with later; but for now, resting conditions will be assumed.

Each network may be considered to have its capillaries in parallel arrangement. Within each, viscous resistance to blood flow dominates over inertial resistance, because of the very small dimensions involved. Considering all the many vascular networks on the systemic side of the circulation, the net blood-pressure loss, ΔP, across them is therefore described by the famous Hagen-Poiseuille equation for flow in small vessels (Hagen, 1839; Poiseuille, 1840), which may be written as:

$$\Delta P = \frac{8\mu}{\pi}\frac{L_C}{N_C}\frac{Q_B}{{R_C}^4}\ , \qquad (1)$$

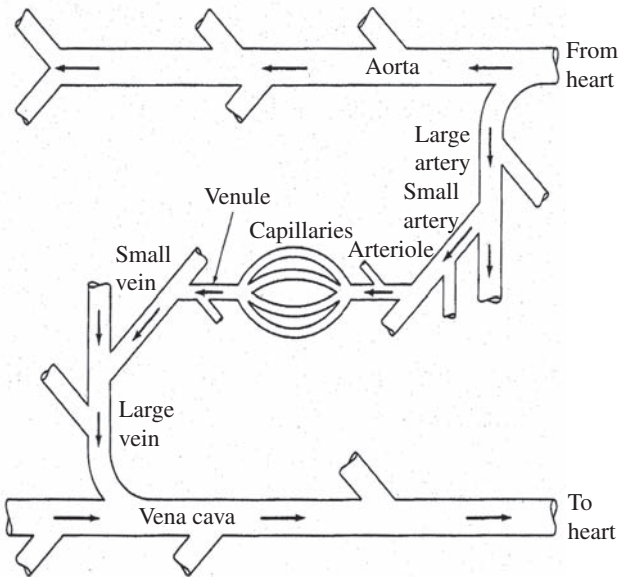

Fig. 1. Branching of systemic vessels in mammals illustrating vascular networks of capillaries and associated arterioles and venules.

where μ denotes the viscosity coefficient of the blood, R_C, L_C and N_C denote 'characteristic' (or typical) radius, length and number of capillaries, respectively, and Q_B denotes cardiac output, that is, the volume of blood ejected by the heart into the systemic vascular system over the time of a heart beat.

The blood pressures in the vascular system of resting mammals are all essentially the same, as demonstrated many years ago by measurements of Gregg et al. (1937), and Woodbury and Hamilton (1937). The pressure drop across the vascular networks may similarly be assumed to be independent of mammal size. The blood viscosity is likewise known to be independent of mammal size (Amin and Sirs, 1985), and the cardiac output is known to be proportional to the product of heart rate and mammal mass (Holt et al., 1968). The following proportional relation may therefore be written from Equation (1):

$$\frac{L_C \omega M_b}{N_C {R_C}^4} \propto {M_b}^0 \ , \qquad (2)$$

where ω denotes heart rate, M_b denotes mammal mass (with ${M_b}^0$ denoting no dependence on it), and where the symbol ∝ denotes proportionality.

In addition to this relation, another may be written associated with the fact that the total blood volume in mammals varies directly with mammal mass, as shown by Brody (1945). The total blood volume in the capillary system, as part of the whole, can therefore similarly be assumed to vary in this manner. The following relation results:

$$N_C {R_C}^2 L_C \propto M_b \ . \qquad (3)$$

Direct evidence for the latter relation exists for the pulmonary capillaries (Gehr et al., 1981) and there is no reason to expect differently for the systemic capillaries. Relations (2) and (3) thus provide two relations, backed by measurement, between the four unknown quantities R_C, L_C, N_C and ω. Two additional relations are thus needed to complete the description. These may either be empirical or theoretical. The latter is first considered. The following discussion of these relations is based on earlier work by the author (Dawson, 1991).

Additional relations

The variables associated directly with the 'characteristic' capillary system of resting mammals can be expected to apply to the capillaries of any organ of the body. There is, in fact, some evidence for this in the case of the lungs, the kidneys and the muscles, as will be discussed later. Thus, the number of capillaries in the heart may be assumed to be proportional to the number of capillaries N_C associated with the relations (2) and (3). The number of cardiac cells in the heart can also be considered to be proportional to the number of capillaries supplying them. The volume of a single cardiac cell can therefore be expected to be proportional to the ratio of heart mass to capillary number; or, since heart mass and body mass are proportional (Brody, 1945), the volume of a single cardiac cell can be considered proportional to the ratio M_b/N_C. The characteristic length d of a cell is therefore expressible as

$$d \propto (M_b/N_C)^{1/3} \ , \qquad (4)$$

assuming all dimensions scale the same, like in fact the dimensions of the heart, which all scale as mammal mass to the power 1/3 (Dawson, 1991, 2001).

Now, cardiac tissue consists mainly of contraction fibers which, when excited, provide the pumping action of the heart. The fibers consist of series connections of small cardiac cells, separated by membranes. Contraction is initiated in the upper heart and spreads over the heart through progressive influx of ions into the cardiac cells, making the fibers contract. The required two relations follow from consideration of the resting heart rate as determined by the diameter of the cardiac fibers, with the latter assumed the same as the linear dimension d defined above; and from consideration of the influx of ions into the fibers.

The contraction (propagation) speed in cardiac fiber is assumed, like nerve fiber, to be expressible as a power-law relation with fiber diameter; that is, as d^b where 'b' denotes a constant. Based on experimental studies with isolated nerve fibers (generally considered analogous to heart fiber), a value of 'b' can be expected to be between 0.5 and 1.0 (Jack et al., 1975). A value of 'b' equal to 2/3 was determined appropriate previously (Dawson, 1991). Now, the period between heartbeats may reasonably be assumed to be proportional, under change of scale, to the ratio of heart length (proportional to mammal mass to the power 1/3) to contraction speed; and the heart rate must thus be equal to the reciprocal of this period. The following relation, therefore, results from these considerations (Dawson, 1991):

$$\omega \propto {M_b}^{-1/9} {N_C}^{-2/9} \ . \qquad (5)$$

A second relation follows from consideration of the

diffusion-like transfer of ions into the cardiac cells over a period of heartbeat. The mass, m, of ionic substance diffusing into (or out of) a cardiac cell can be expected to depend on the dimension, d, of the cell, the diffusion coefficient D (units of area per time), the concentration difference ΔC (units of mass per volume) between concentrations outside and inside the cell, and the heart rate ω (units of reciprocal time). The relation for m may be written in dimensionless form (so as to be independent of particular units), as

$$\frac{m}{\Delta C d^3} = f\left(\frac{\omega d^2}{D}\right) , \quad (6)$$

where $f(-)$ denotes a general function. The left-hand side of this equation, with concentration difference ΔC assumed scale invariant, is proportional to the diffusion mass per unit cell volume, and this may be expected to be independent of mammal size. With the diffusion constant D also scale invariant, as expected, it can be seen that the product of heart rate and square of cell dimension must likewise be constant under change of scale. Thus, heart rate is predicted to be inversely proportional to the square of the heart-cell dimensions. Using the definition of cardiac cell dimension of relation (4), the follow relation results (Dawson, 1991):

$$\omega \propto M_b^{-2/3} N_C^{2/3} \quad (7)$$

As may be confirmed with simple algebra of proportions, relations (2) and (3), together with the two expressions of relations (5) and (7), provide the solution for the scaling laws for the characteristic capillary vessels in the form:

$$R_C \propto M_b^{1/12} , \quad (8a)$$

$$L_C \propto M_b^{5/24} , \quad (8b)$$

$$N_C \propto M_b^{5/8} . \quad (8c)$$

The scaling relation for the resting heart rate is also determined from the relations and that for cardiac output from its previously noted connection with heart rate, that is,

$$\omega \propto M_b^{-1/4} , \quad (9a)$$

$$Q_B \propto M_b^{3/4} . \quad (9b)$$

Experimental evidence for the relation for heart rate has existed for many years (Rihl, 1926; Clark, 1927). More recent work by Holt et al. (1968) provides experimental support for both the heart-rate and cardiac-output relations.

It is worthwhile to note the differences that arise if different values of 'b' are used for the exponent in the above contraction-speed relation leading to relation (5). For the lower value of 0.5, the equations predict that heart rate should vary with mammal mass to a power of –4/15, that is, a power of about –0.27; and that the cardiac output should vary with mammal mass to a power of 11/15, that is, a power of about 0.73. For the higher value of 1, the equations predict an exponent value for heart rate of –2/9, that is, a power of –0.22; and that for cardiac output of 7/9, that is, a power of about 0.78. The differences are not especially significant, and for either choice of exponent 'b', the relations for heart rate and cardiac output, if determined experimentally, could reasonably be rounded to the exponent values of –1/4 and 3/4, respectively.

The value of 2/3 for the exponent 'b' in the contraction-speed relation, noted in connection with relation (5), was chosen earlier by the author (Dawson, 1991) because it led to the relations for cardiac output and heart rate, as generally accepted. Interestingly, if an extreme value for 'b' of zero is assumed, the resulting expressions are that heart rate varies as mammal mass to the power –1/3 and that cardiac output varies with mammal mass to the power 2/3. The latter is unlikely, based in part on the work of Holt et al. (1968).

In addition to showing that the scaling laws for the capillary networks, as well as the scaling laws for cardiac output and heart rate, can be determined from fundamental considerations, it has been illustrated here that heart rate varies inversely as the square of the diameter of the cardiac contraction fibers. The latter offers an explanation (and the only one that I am aware of) as to how and why the resting heart rate of, say, the mouse is many times that of the human; that is, about 600 beats min^{-1} for mouse and about 60 beats min^{-1} for human.

Additional means for obtaining the above scaling laws have been considered earlier and involved use of empirical relations for heart rate (reciprocal 1/4 power relation) and oxygen consumption rate (3/4 power relation), as described by Dawson (2001, 2003). This approach leads to the same scaling laws as relations (8a–c).

Some measurements

It may first be noted that direct experimental measurements are limited regarding the systemic side of the circulation, but the data available are consistent with the theory described here. In particular, there are the counting measurements of Kunkel (1930) for number of nephrons in the kidneys of mammals of various sizes. The nephron is the basic unit in the kidney and consists of a collection of capillary vessels. The number of capillaries per nephron can be expected to be the same for any mammal, and hence a count of nephrons in a kidney can be expected to be proportional to a count of capillaries in the kidney. The measurements of Kunkel (mouse to ox range) were analyzed by Adolph (1949) and shown to obey a power law relation, with mammal mass raised to the power 0.62, which may also be taken as 5/8, in agreement with relation (8c).

There are also measurements of Kunkel (1930) concerning the diameter of renal capsules of the nephrons that indicate variation with mammal mass to a power of essentially 1/12 (Adolph, 1949). This variation may be taken as evidence for the scaling relation for relation (8a), since the diameter of the renal capsules can be expected to be proportional to the radius of the contained capillaries within them.

In addition, there are measurements of rate of urine output of resting mammals (mouse to elephant range) that indicate variation with mammal mass to a power of essentially 5/6, as noted by Adolph (1949). Net fluid flow from the capillaries in the kidneys, insofar as scaling is concerned, can be expected

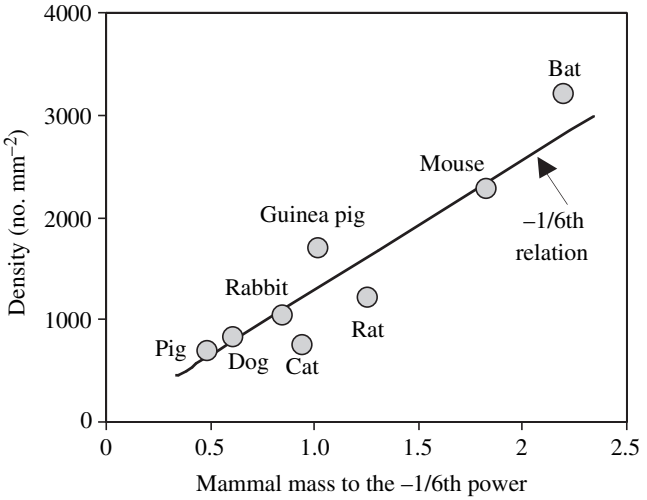

Fig. 2. Data for capillary density (no. capillaries per mm^2) in masseter muscle. (Data source: Schmidt-Neilsen and Pennycuik, 1961.)

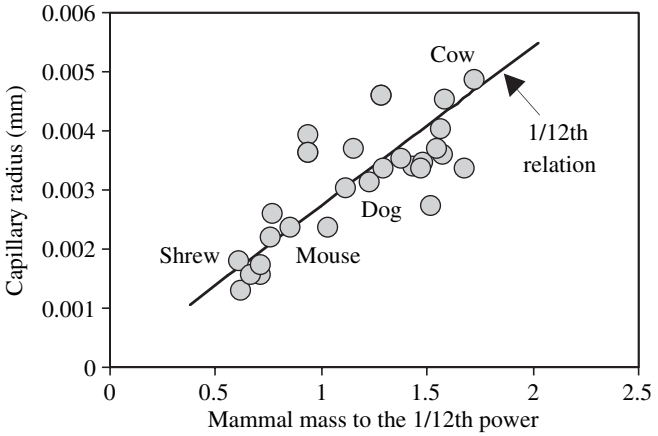

Fig. 3. Data for capillary radius in lungs, with only selected mammals indicated. (Data source: Gehr et al., 1981.)

to be proportional to the product of capillary number N_C and capillary length L_C as discussed earlier by the author (Dawson, 1991). Relations (8b,c) provide, in fact, the scaling exponent 5/6.

Finally, on the systemic side, there are measurements of capillary density in muscles by Schmidt-Nielsen and Pennycuik (1961) that presumably apply to the resting state, as considered here. Capillary spacing in resting muscle can be expected to be proportional to capillary radius, and capillary density can therefore be expected to be inversely proportional to the square of capillary radius; that is, as mammal mass to the power –1/6, based on relation (8a). The relation just described was recently confirmed from theoretical considerations (Dawson, 2003). The measurements of Schmidt-Nielsen and Pennycuik (bat to pig range) support this variation as illustrated in Fig. 2 for capillary density in the masseter (jaw) muscle of mammals. Similar agreement exists for measurements of Schmidt-Nielsen and Pennycuik (1961) regarding resting capillary density in the gastrocnemius (leg) muscle of mammals (Dawson, 2003).

For the pulmonary side of the circulation, measurements exist for capillary volume and surface area (Gehr et al., 1981). These data (shrew to cow range) may be used to obtain data for capillary radius and net capillary length (Dawson, 1991). Typical values for the capillary radius are shown in Fig. 3 and support predictions from relation (8a). In average terms, the volume of the capillaries was found by Gehr et al. (1981) to be directly proportional to mammal mass, and their surface area was found proportional to mammal mass raised to about the power 0.93 (average of two sets of data). These results imply that capillary radius R_C and net capillary length $N_C L_C$ scale with mammal mass to powers 0.07 and 0.86, respectively, in good agreement with the theoretical value from relations (8a–c) of 0.08 and 0.83.

The basic scaling relations (8a–c) may also be derived by replacing the two theoretical relations (5) and (7) by the empirical relation for heart rate, and either of the above experimentally confirmed relations for capillary number and capillary radius.

Oxygen consumption rate

Among the many biological processes involved with the vascular networks, the most important is perhaps the transfer of oxygen from the blood to the surrounding tissues. The resting oxygen consumption rate of mammals (mouse to elephant range) is known to obey an average power-law relation with mammal mass raised to the power 3/4 (Kleiber, 1932; Brody and Procter, 1932; Brody, 1945). This relation applies over a wide range of mammal size, but, insofar as empirical relations are concerned, may be subject to modification for smaller mammals (Bartels, 1982; Heusner, 1991; Dodds et al., 2001). Interestingly, the careful work of Bishop (1999) on mammals and birds indicates no such deviations.

The oxygen consumption rate is considered in terms of the rate of oxygen transfer $\dot{V}_{O_2}$ across the capillaries. This is described by the diffusion equation:

$$\dot{V}_{O_2} \propto P_0(1–P_1/P_0)N_C L_C R_C/H_C \,, \qquad (10)$$

where P_0 denotes the oxygen pressure in the blood, P_1 denotes the oxygen pressure immediately outside the capillary, and H_C denotes the wall thickness of the capillaries. Now, as discussed in earlier work (Dawson, 2003), plausible assumptions can be made that the ratios P_1/P_0 and R_C/H_C are relatively independent of mammal size, at least when a wide range of mammal size is considered. In particular, the first ratio can be expected to be relatively independent of scale since a change in oxygen pressure in the blood is likely to be accompanied by a corresponding change in oxygen pressure in surrounding tissue. The second ratio can be expected to be constant, or nearly so, in order to maintain similar stress in the capillary walls from the scale-invariant blood pressure. Variations from either of these assumptions over a small range of size may, of

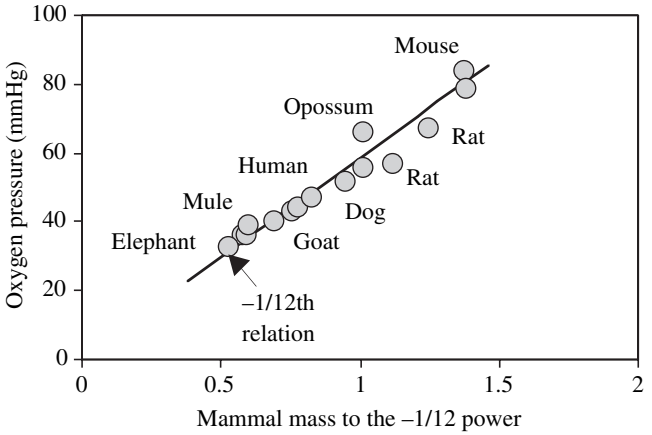

Fig. 4. Data for oxygen pressure in blood (75% saturation) of mammals, with only selected mammals identified. Data mainly from Schmidt-Neilsen and Larimer (1958). Value for the elephant is from Bartels et al. (1963). 1 mmHg ≡ 133.3 Pa.

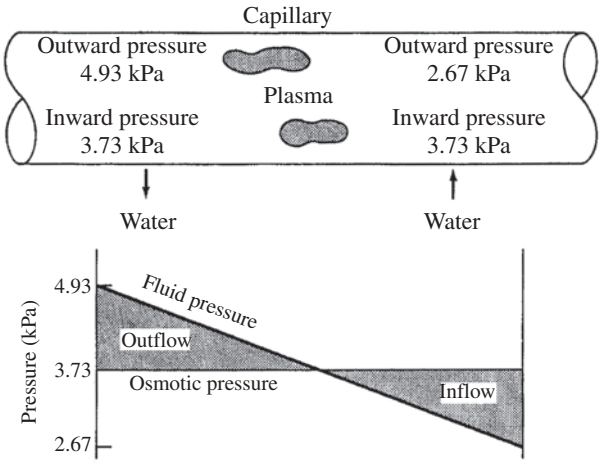

Fig. 5. Classical view of exchange of water and dissolved substances with surrounding systemic tissue. (Data source: Guyton, 1971.)

course, account for deviations from the average mentioned above. Adopting the assumptions, relation (10) reduces to the expression:

$$\dot{V}_{O_2} \propto P_0 N_C L_C \,. \tag{11}$$

Moreover, as already known (Dawson, 1991) on the basis of measurements by Schmidt-Nielsen and Larimer (1958), the oxygen pressure P_0 in the blood can be considered to be proportional to mammal mass to the power –1/12 (mouse to mule range). This correlation is illustrated in Fig. 4, together with an additional measurement for the elephant (Bartels et al., 1963). With the product $N_C L_C$ varying with mammal mass to the power 5/6, as required by relations (8a–c), the oxygen transfer rate is thus seen to vary with mammal mass to the power 3/4, in accordance with measurements over a broad range on mammal size.

It may be noted (at least within the writer's limited understanding) that 'constructal theory', based in part on the assumption that vascular formation is an optimized flow architecture, also provides the power 3/4 for resting oxygen consumption rate (Bejan, 1997, 2000).

Application of theory to drug therapy

A practical application of capillary scaling involves consideration of therapeutic drug concentrations in the blood of small mammals as they relate to humans. A specific example is provided by the chemotherapy drug methotrexate, which is a widely used (non-metabolized) drug in the treatment of cancer. Dedrick et al. (1970) showed that data from various mammals could be consolidated into a broad correlation by plotting the ratio of drug concentration in the blood to initial dose as a function of time since injection, when the latter was divided by mammal mass raised to the power 1/4. Since the blood-circulation time is proportional to mammal mass to the power 1/4 (Dawson, 1991), the resulting time scale is simply proportional to circulation time. It may be anticipated that some refinement could be gained by including the capillary geometry and scaling into the correlation.

The drug is assumed to be injected on the systemic venous side in a relatively short period of time. On passing through a general capillary, the classical view (Guyton, 1971) is that the blood initially expels some water and drug to surrounding tissue (Starling, 1896; Pappenheimer et al., 1951). Near the end of the capillary blood flow, some of the mixed drug is reabsorbed (see Fig. 5; from Dawson, 1991). Of course, in the event of fluctuating osmotic pressure, some capillary exchange, back and forth, could be expected along the entire length of the capillary.

In either case, a simplified process may be assumed for scaling purposes where the entire drug is removed by the capillaries during the initial cycle and some of the drug reabsorbed. In this case, the drug concentration at the injection site, after the initial cycle, will equal the amount reabsorbed. This process would perhaps lead to a reduced concentration at the site, compared with the actual process. However the same percentage difference may be expected (for a non-metabolized drug) for all mammals so that scaling is still possible in the present case.

The concentration of drug, C (in units of mass per volume of blood), in the blood after the first complete cycle of blood circulation in the above-simplified process will be proportional to the net volume of drug reabsorbed per unit volume of blood. Flow into and out of capillaries can be considered for scaling purposes (Dawson, 1991) to be proportional to a scale-independent constant and the net capillary length, that is, $BN_C L_C$, where B denotes the filtration-absorption constant (units of area per time). The concentration of drug reabsorbed over the time, T, for a complete circulation is thus proportional, for scale-independent initial concentration, to the ratio $N_C L_C T/V_B$, where V_B denotes total blood volume. For any arbitrary initial drug concentration D_0, the ratio is $D_0 N_C L_C/V_B)T$.

With additional cycles of blood circulation treated in the

same way, the effective initial dosage would (after the manner of Dedrick et al. 1970) be reduced by the factor $f(t/T)$, where $f(-)$ denotes an unspecified function. Thus, concentration of drug in the blood at any time, t, is described for scaling purposes by the relation:

$$\frac{C}{D_0} \propto \frac{N_C L_C T}{V_B} f\left(\frac{t}{T}\right) . \quad (12)$$

Now, if the ratio t/T is fixed, the ratio on the left-hand side of this relation will be proportional to the first ratio on the right. The product $N_C L_C$ varies with mammal mass to the power 5/6, as indicated by relations (8a–c), the total blood volume V_B varies directly with mammal mass (Brody, 1945), and the time for circulation T varies as mammal mass to the power 1/4, as indicated previously. The desired scaling relations may be written, for example, for the human relative to a smaller (or larger) mammal as

$$\left(\frac{C}{D_0}\right)_H = \left(\frac{M_H}{M_M}\right)^{1/12} \left(\frac{C}{D_0}\right)_M , \quad (13a)$$

$$t_H = \left(\frac{M_H}{M_M}\right)^{1/4} t_M , \quad (13b)$$

where subscripts 'H' and 'M' denotes values for the human and mammal, respectively.

Fig. 6 illustrates application of this scaling law in projecting measurements from the mouse (mass of 0.022 kg) to the human (mass of 70 kg) for the plasma concentration of methotrexate in the blood as a function of time. The basic measurements for the mouse, as used in developing the results of Fig. 6, are due to Dedrick et al. (1970) and the data for the human are due to Henderson et al. (1965). The solid curve shown in Fig. 6 is a simple 'best-fit' power-law expression for comparison purposes.

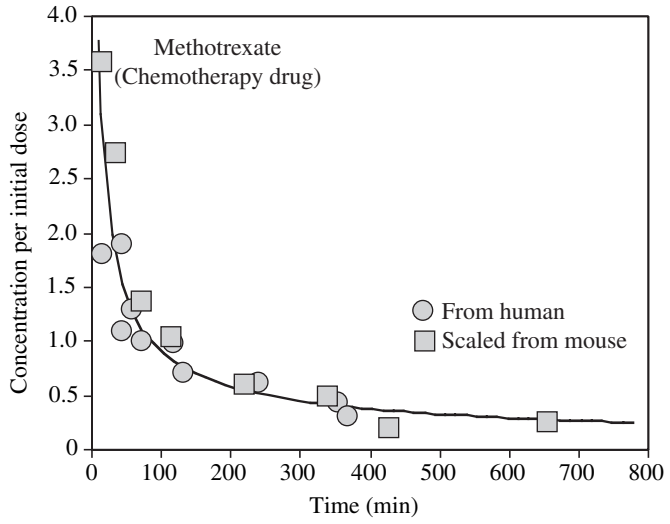

Fig. 6. Drug concentration (μg ml^{-1} of blood plasma) per unit of initial dose (mg kg^{-1} of body weight) as a function of time for the human. (Data sources: Dedrick et al., 1971; Henderson et al., 1965.)

The agreement of the scaled data from the mouse with that of the human, as shown in Fig. 6, is indeed very good. The factor $(M_H/M_M)^{1/12}$ in the scaling relation (13a) represents the effect of capillary process and is equal to 1.96. Without this factor, the predictions from the mouse would thus be reduced by a factor of about 2. Overall, the factor can be seen to improve the predictions over what they would be otherwise.

Effects of strenuous exercise of mammals

An interesting aspect of the work in the present discussion is that the scaling laws for the radius and length of the capillaries forming the vascular networks can be determined on the basis of the resting condition of mammals. This aspect has been noted earlier (Dawson, 2003). Since the size of the capillaries cannot change with exercise, there can only be one set of scaling laws for these, and resting conditions provide these laws. Of course, resting conditions also provide the scaling laws for resting heart rate, cardiac output and oxygen consumption rate, as illustrated here.

For a number of years, it was generally thought that all scaling relations associated with the physiological functions of mammals (for example, cardiac output, oxygen consumption rate and heart rate) were the same for both resting and exercise states. This could be the case if such physiological variables increased during exercise by the same factor for all mammals. This would change the proportional factor in the scaling relations, but leave the scaling exponents with body mass unchanged. This is now known not to be the case, as a result of work by Baudinette (1978), Taylor et al. (1981), Weibel et al. (1991) and Bishop (1997, 1999), among others.

In particular, the oxygen consumption rate of mammals (bat to steer range) in strenuous exercise has been shown by Bishop (1999), in careful analysis of existing data, to vary with mammal mass raised to the power 0.88, that is, a power of about 7/8. This result is consistent with earlier work of Weibel et al. (1991) and the more recent work of Weibel et al. (2004). The power 7/8 is also consistent with 'constructal theory' and the assumption that flow systems survive by forming easier access to the required flow (Bejan, 2000).

On the capillary scale, allowance appears to be made for exercise by increased activity of the capillary network through openings of reserve capillaries in the muscles (Krogh, 1920). This will change the scaling law for operative number of capillaries in the body, but will leave the scaling laws for dimensions of the capillaries unchanged. This view is, perhaps, consistent with the principle of 'symmorphosis' (Taylor and Weibel, 1981; Weibel et al., 1991; Hoppeler and Weibel, 1998) requiring (in simple terms) that nothing more be provided in the design of mammals than that required for their purposes.

In terms of the present work, the new condition for scaling of the average capillary number is a modified form of relation (11) such that

$$\dot{V}_{O_2}\,(\max) \propto P_0 N_C^* L_C , \quad (14)$$

where N_C^* denotes the modified capillary number for exercise.

With P_0 and L_C varying, as in the resting state, with mammal mass to the powers –1/12 and 5/24, respectively, and maximum oxygen consumption rate varying with mammal mass to the power 7/8, it can be seen that the scaling relation for the modified capillary number is

$$N_C^* \propto M_b^{3/4} . \quad (15)$$

This relation corresponds to a 'weighted' average for scaling of the number of capillaries in the body. The concept of a weighted average is consistent with recent discussion by Weibel (2002) and work of Darveau et al. (2002) on the rate of oxygen consumption during exercise. When compared with the resting state, with capillary number proportional to mammal mass to the power 5/8, the implication is that the ratio of average capillary number in strenuous exercise to resting number increases in proportion to mammal mass to the power 1/8. Perhaps gravity enters here in that larger mammals have to work harder than small mammals in overcoming their weight (as opposed to their mass) in exercise.

Of course, with strenuous exercise, resting-state similarity in the physiological response of mammals is lost. With fixed scaling of radius and length dimensions of the capillaries, it is impossible to satisfy all the earlier relations required for similar response among resting mammals. In this regard, capillary density in muscles that includes both resting and reserve capillaries (for strenuous exercise) cannot be expected to follow the simple scaling law noted earlier where resting capillary density varies with mammal mass to the power –1/6. This observation is consistent with sophisticated measurements of Hoppeler et al. (1981), which presumably detected both active and inactive capillaries as discussed recently (Dawson, 2003).

In spite of the loss of resting-state similarity in exercise, it is worthwhile to note that cardiac output in strenuous exercise appears to vary in the same way as oxygen consumption rate (Bishop, 1997), namely as mammal mass to the power 7/8. In this case, the pressure drop across capillary networks is still scale invariant like in the resting state, as can be seen from Equation (1). The rate at which energy is dissipated by viscous (frictional) resistance in the capillaries is proportional to the product of pressure drop and cardiac output. Considering all the capillary networks, this can then be seen to be proportional to the rate of oxygen supply to the body and, in particular, also to the heart since heart mass and body mass are proportional. A similar situation exists for the resting state. The ratio of rate of energy dissipation in capillary blood flow to rate of oxygen (fuel) supply to the heart is thus invariant with scale for both exercise and resting, consistent with good design practice.

This last matter may perhaps have implications regarding work by West et al. (1997), Banavar et al. (1999) and Dodds et al. (2001) on the efficiency of the design of the vascular networks of mammals. It may also have relevance in constructing a general basis for similarity in the strenuous-exercise state that provides, for example, the 7/8ths power law for oxygen-consumption rate, like that provided here for the 3/4-law for the resting state.

Concluding remarks

Modeling of the vascular networks of mammals has been reviewed here, with the expressed goal of discussing relevant scaling laws for resting mammals of vastly different size. Both geometry and process have been considered. Results have been shown to be in good agreement with measurements for a wide range of mammal sizes. A main conclusion to be drawn from this review is that similarity exists for the vascular networks of mammals, as well as for related physiological processes.

Overall, the design of the vascular networks of mammals appears to be the same, with predictable adjustments for scale for resting mammals and some additional adjustment for exercise. An interesting question that presents itself is why the design follows essentially the same pattern for all mammals. The answer would appear to be simply because it is the 'best' pattern, all things considered. In this regard, it has been noted that, for both resting and strenuous exercise, the rate of energy dissipation in blood flow in the vascular capillary networks appears to be proportional under change of scale to the oxygen rate supplied to the heart. The ratio of the two is thus invariant under change of scale for both resting and exercise.

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References

Adolph, E. F. (1949). Quantitative relations in the physiological constitution of mammals. *Science* **109**, 579-585.

Amin, T. M. and Sirs, J. A. (1985). The blood rheology of man and various animal species. *Q. J. Exp. Physiol*. **70**, 37-49.

Banavar, J. R., Maritan, A. and Rinaldo, A. (1999). Size and form in efficient transportation networks. *Nature* **399**, 130-132.

Bartels, H. (1982). Metabolic rate of mammals equals the 0.75 of their body weight. *Exp. Biol. Med*. **7**, 1-11.

Bartels, H., Hilpert, P., Barbey, K., Betke, K., Riegel, K., Lang, E. and Metcalfe, J. (1963). Respiratory function of blood of the yak, llama, camel, Dybowski deer and African elephant. *Am. J. Physiol*. **205**, 331-336.

Baudinette, R. V. (1978). Scaling of heart rate during locomotion in mammals. *J. Comp. Physiol.* **127**, 337-342.

Bejan, A. (1997). *Advanced Engineering Thermodynamics*, 2nd edn. New York: Wiley.

Bejan, A. (2000). *Shape and Structure, from Engineering to Nature*. Cambridge, UK: Cambridge University Press.

Bishop, C. M. (1997). Heart mass and the maximum cardiac output of birds and mammals: implications for estimating the maximum aerobic power input of flying mammals. *Philos. Trans. R. Soc. Lond. B* **352**, 447-456.

Bishop, C. M. (1999). The maximum oxygen consumption and aerobic scope of birds and mammals: getting to the heart of the matter. *Proc. R. Soc. Lond. B* **266**, 2275-2281.

Brody, S. (1945). *Bioenergetics and Growth.* New York: Reinhold Publishing.

Brody, S. and Procter, R. C. (1932). Relation between basal metabolism and mature body weight in different species of mammals and birds. *Univ. Missouri Agr. Exp. Station Res. Bull*. **166**, 88-102.

Clark, A. J. (1927). *Comparative Physiology of the Heart*. Cambridge, UK: Cambridge University Press.

Darveau, C. A., Suarez, P. K., Andrews, R. D. and Hochachka, P. W. (2002). Allometric cascade as a unifying principle of body mass effects on metabolism. *Nature* **417**, 166-170.

Dawson, T. H. (1991). *Engineering Design of the Cardiovascular System of Mammals*. Prentice Hall Biophysics and Bioengineering Series (ed. A. Noordergraaf). Englewood Cliffs, NJ: Prentice Hall.

Dawson, T. H. (2001). Similitude in the cardiovascular system of mammals. *J. Exp. Biog*. **204**, 395-407.

Dawson, T. H. (2003). Scaling laws for capillary vessels of mammals at rest and in exercise. *Proc. R. Soc. Lond. B* **270**, 755-763.
Dedrick, R. L., Bischoff, K. B. and Zaharko, D. S. (1970). Interspecies correlation of plasma concentration history of methotrexate. *Cancer Chemotherap. Rep.* **54**, 95-101.
Dodds, P. S., Rothman, D. H. and Weitz, J. S. (2001). Re-examination of the '3/4-law' of metabolism. *J. Theor. Biol.* **209**, 9-27.
Gehr, P., Mwangi, D. K., Ammann, A., Maloig, G. M. D., Taylor, C. R. and Weibel, E. R. (1981). Design of the mammalian respiratory system V. Scaling morphometric pulmonary diffusing capacity to body mass: wild and domestic mammals. *Resp. Physiol*. **44**, 61-86.
Gregg, D. E., Eckstein, R. W. and Fineberg, M. H. (1937). Pressure pulses and blood pressure values in unanesthetized dogs, *Am. J. Physiol.* **118**, 399-410.
Guyton, A. C. (1971). *Textbook of Medical Physiology*. Philadelphia, PA: W. B. Saunders.
Hagen, G. (1839). Uber die Bewegung des Wassers in engen zylindrischen Rohren. *Pogg. Ann. d. Physik. u. Chem.* **46**, 423-442.
Henderson, E. S., Adamson, R. H. and Oliverio, V. T. (1965). The metabolic fate of tritiated methotrexate: absorption and excretion in man. *Cancer Res*. **25**, 1018-1024.
Heusner, A. A. (1991). Size and power in mammals. *J. Exp. Biol.* **160**, 25-54.
Holt, J. P., Rhode, E. A. and Kines, H. (1968). Ventricular volumes and body weight in mammals. *Am. J. Physiol.* **215**, 704-715.
Hoppeler, H. and Weibel, E. R. (1998). Limits for oxygen and substrate transport in mammals. *J. Theor. Biol.* **201**, 1051-1064.
Hoppeler, H., Mathieu, O., Weibel, E. R., Krauer, R., Lindstedt, S. L. and Taylor, C. L. (1981). Design of the mammalian respiratory system. VIII. Capillaries in skeletal muscles. *Resp. Physiol*. **44**, 129-150.
Jack, J. J. B., Noble, D. and Tsien, R. W. (1975). *Electric Current Flow in Excitable Cells*. Oxford, UK: Clarendon Press.
Kleiber, M. (1932). Body size and metabolism. *Hilgardia* **6**, 315-353.
Krogh, A. (1920). A contribution to the physiology of capillaries. Nobel Lecture, Stockholm. Also in *Nobel Lectures, Physiology or Medicine* 1901–1921. Amsterdam, The Netherlands: Elsevier.
Kunkel, P. A., Jr (1930). The number and size of the glomeruli in the kidney of several mammals. *Bull. Johns Hopkins Hosp*. **47**, 285-291.
Pappenheimer, J. R., Renkin, E. M. and Borrero, L. M. (1951). Filtration, diffusion and molecular sieving through peripheral capillary membranes. *Am. J. Physiol*. **167**, 13-46.
Poiseuille, J. L. M. (1840). Recherches experimentales sur le mouvement des liquides dans les tubes de tres petits diametres. *Crit. Rev. Acad. Sci. Paris* **11**, 961-967.
Rihl, J. (1926). Die frequenz des Herzschlages. In *Handbuch der Normalen und Pathologischen Physiologie.* Vol.VII/1 (ed. A. T. Bethe). pp. 449-457. Berlin: Springer.
Schmidt-Nielsen, K. and Larimer, J. L. (1958). Oxygen dissociation curves of mammalian blood in relation to body size. *Am. J. Physiol*. **195**, 424-428.
Schmidt-Nielsen, K. and Pennycuik, P. (1961). Capillary density in mammals in relation to body size and oxygen consumption. *Am. J. Physiol.* **200**, 746-750.
Starling, E. H. (1896). On the absorption of fluids from the connective tissue spaces. *J. Physiol.* **19**, 312-326.
Taylor, C. R. and Wiebel, E. R. (1981). Design of the mammalian respiratory system. *Resp. Physiol.* **44**, 1-10.
Weibel, E. R. (2002). The pitfalls of power laws. *Nature* **417**, 131-132.
Weibel, E. R., Taylor, C. and Hoppeler, H. (1991). The concept of symmorphosis: a testable hypothesis of structure-function relationship. *Proc. Natl. Acad. Sci. USA* **88**, 10357-10361.
Weibel, E. R., Bacigalupe, L. D., Schmitt, B. and Hoppeler, H. (2004). Allometric scaling on maximal metabolic rate in mammals: muscle aerobic capacity as determinant factor. *Resp. Physiol. Neurobiol*. **140**, 115-132.
West, G. B., Brown, J. H., and Enquist, B. J. (1997). A general model for the origin of allometric scaling laws in biology. *Science* **276**, 122-126.
Woodbury, R. A. and Hamilton, W. F. (1937). Blood pressure studies in small animals. *Am. J. Physiol*. **119**, 663-674.