

Chapter 1

Generalities of Gas Diffusion Applied to the Vertebrate Blood–Gas Barrier

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1.1 Introduction

This chapter intends to be an introductory overview of the physical aspects of gas diffusion as they apply to the vertebrates' blood–gas barrier (BGB). Specialised cases of diffusion, like the transfer of water molecules through biological membranes (osmosis) or the protein-mediated facilitated diffusion are not pertinent to the BGB and will not be considered. The reader interested in the thermodynamic basis and mathematical derivations of the laws of diffusion should consult specific reviews (e.g., Chang 1987; Macey and Moura 2011). The current ongoing series *Comprehensive Physiology* has republished several major analyses of the interaction between diffusion and gas convective mechanisms, formerly printed in various sections of the *Handbook of Physiology* (e.g., Piiper and Scheid 1987; Forster 1987; Loring and Butler 1987; Scheid and Piiper 2011).

The first two sections of this chapter recall the most fundamental principles of diffusion of gases in air and liquids. In the remaining portions, some specific cases are presented to illustrate and expand on the concepts touched in the preceding sections. Table 1.1 recapitulates the abbreviations and units most commonly adopted, on line with what originally proposed by Piiper et al. (1971) for gas exchange physiology. I limited the references to the essential minimum and almost entirely to review articles, which can be used as a starting point for further readings.

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Table 1.1 Abbreviations and common units

	Common symbols	MLT dimensions	Common units in respiratory gas exchange
Mass	M	M	g
Length (thickness)	θ	L	μm
Time	t	T	sec
Volume	V	L^3	ml (STPD) ^a
Flow	\dot{V}	$L^3 T^{-1}$	ml/sec
Force	N	$M L T^{-2}$	kg m sec^{-2}
Pressure	P	$M L^{-1} T^{-2}$	cm H ₂ O (or mmHg= 1.36 cm H ₂ O)
Diffusion rate	Q/t	$L^3 T^{-1}$	ml(gas) STPD/sec (or moles/sec)
Concentration gradient	$\Delta C/\theta$	L^{-1}	(moles cm^{-3})/cm
Diffusion coefficient	D	$L^2 T^{-1}$	$\text{cm}^2 \text{sec}^{-1}$
Solubility coefficient	α	$L T^2 M^{-1}$	ml(gas) STPD ml (liquid) ⁻¹ torr ⁻¹
Permeation coefficient	K	$L^3 T M^{-1}$	ml(gas) STPD $\text{cm}^{-1} \text{sec}^{-1} \text{torr}^{-1}$
Capacitance coefficient	β	$L T^2 M^{-1}$	ml(gas) STPD ml (liquid) ⁻¹ torr ⁻¹
Conductance	G	$L^4 T M^{-1}$	ml(gas) $\text{min}^{-1} \text{mm Hg}^{-1}$

STPD standard temperature, pressure and dry conditions

^a Volumes of gases can be expressed in moles or in volumes (ml) at STPD (1 ml \approx 0.0446 mMol)

1.2 Why Diffusion?

The answer to why diffusion is universally at the core of respiratory gas exchange (defined as the passage of respiratory gases through membranes) could be ‘because diffusion is an economical process’. The economy originates from the fact that diffusion is an almost unavoidable phenomenon built in the energy of the universe. Above the absolute zero, all particles have some thermal energy responsible for various forms of interactions. Atoms disperse spontaneously within a crystal of their own species. Particles suspended in a fluid continuously collide with the molecules of the fluid itself in seemingly random (Brownian) patterns. The thermodynamic activity is responsible for intermolecular reactions and the solubility of gas molecules into liquids. Most importantly, thermodynamic activity is the source of the pressure responsible for *diffusion*, that is, the passive displacement of particles from regions of high activity to regions of low activity; no additional energy is required other than the original thermodynamic activity.

In the context of respiratory gas exchange, diffusion indicates the passive movement of oxygen (O₂) from the environment directly into the cells or, more commonly, into the blood and from the blood into the cells; the opposite path applies to carbon dioxide (CO₂). The word ‘passive’ is worth stressing because until the beginning of the twentieth century, a great controversy raged with eminent physiologists of the calibre of Bohr and Haldane believing that O₂ was actively secreted into the blood (Milledge 1985). This view, partially correct for some special cases like the fish swim-bladder (Berenbrink 2007), was given support by erroneous

measurements of arterial O_2 pressure, which appeared higher than the corresponding alveolar value.

For any molecule, the time required for diffusion increases with the square of the diffusion distance, as it is indicated below. Therefore, diffusion is an effective form of gas transport over very short distances; by itself, it can fulfil the metabolic needs only of protozoa and small multicellular aggregates, where the body surface area: volume ratio can be of the order of 10^5 (Fig. 1.1a). For almost the totality of multicellular organisms, the time required by diffusion would be incompatible with the survival of organs and tissues other than the cells most superficially located. Hence, various means, cumulatively known as *mechanisms of gas convection*, have evolved to enhance the transport of O_2 and CO_2 between the environment and the metabolically active tissues and cells. They consist of a gas-carrying medium (water, blood or air) made to circulate through a network of pipes in an effort to optimise diffusion. Differently from diffusion, the molecular transport by convection requires some energy expenditure to maintain the circulation of the medium and to overcome the frictional losses within the pipes.

Blood is a particularly convenient convective medium from the view point of respiratory gas exchange chiefly because its pigments, haemoglobin or similar molecules, raise the O_2 -carrying capacity to extraordinary high levels. The evolutionary introduction of blood circulation as a mechanism of gas transport necessitated a new diffusion barrier between environment and blood. The arrangement of diffusion (into the blood)-convection (via the blood)-diffusion (to the cells) is very efficient and represents the most common method of gas transport during the embryonic and fetal life of vertebrates (Fig. 1.1b). In mammals, the embryonic blood exchanges gases with the maternal blood via the placenta; in egg-laying vertebrates the embryonic blood exchanges gases through the chorioallantoic membrane (see Chap. 10). Postnatally, the simple coupling of cardiovascular convection and diffusion as means of O_2 transport is infrequent in vertebrates and extraordinarily rare in birds and mammals¹. In almost all vertebrates, an additional convection mechanism, the respiratory system, has evolved to maximise gas exchange between environment and blood. Hence, postnatally the in-series organization of the physical mechanisms for gas transport consists of convection - diffusion - convection - diffusion (Fig. 1.1c). The medium of the first convection system is either water or air and the first diffusion barrier is the BGB that represents the focus of the present volume. There are two main differences between diffusion and convection as mechanisms of O_2 transport in vertebrates. First, as mentioned above, diffusion does not require active energy expenditure because it results from the gradient in thermodynamic activity across the diffusive barrier. On the contrary, transport by convection always necessitates some energy expenditure usually in the form of a pumping mechanism. Second, the thermodynamic activity of a gas is not lost through the convection path, as long as the gas composition of the medium remains unchanged. For example,

¹ The only exceptions that I am aware of for birds and mammals are some of the smallest newborn marsupials, which can satisfy their O_2 requirements by gas exchange through the skin for days after birth.

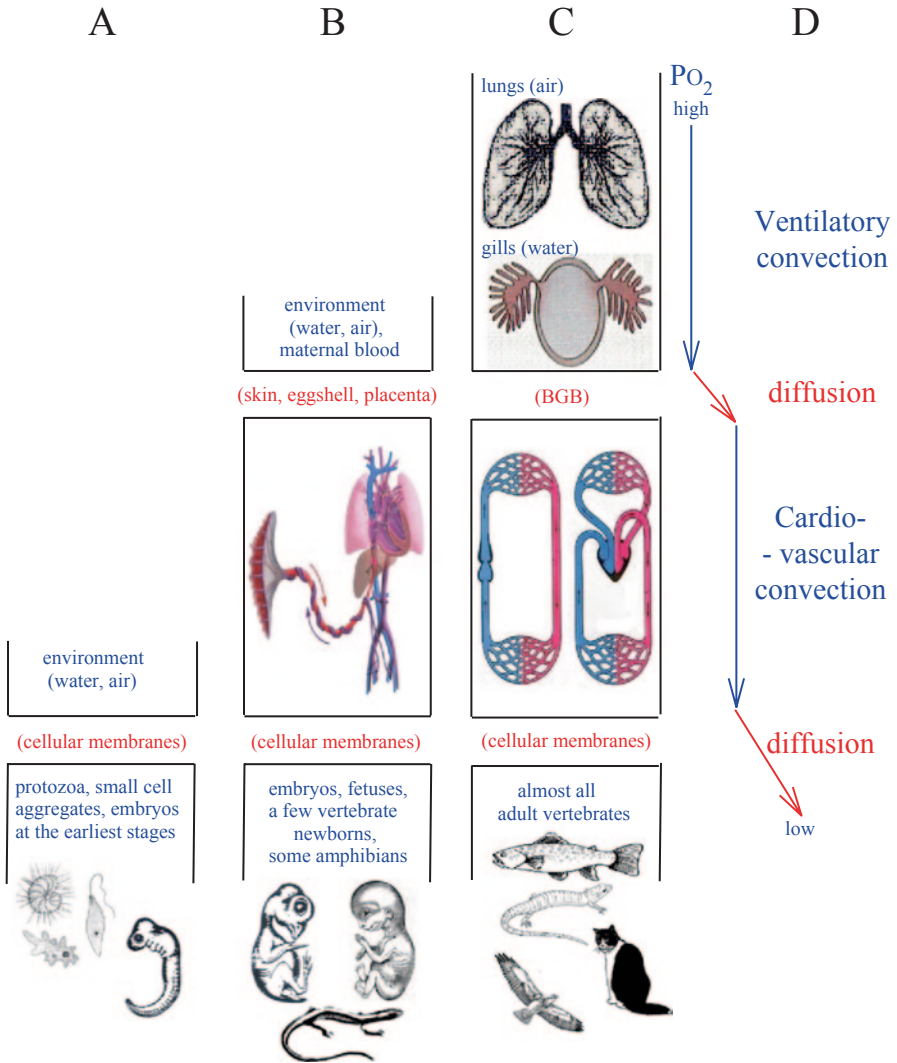


Fig. 1.1 Schematic arrangements of the physical mechanisms of gas transport. **a** Diffusion through cell membranes is sufficient to accommodate the metabolic requirements of unicellular organism or very early embryos. **b** Diffusion is coupled to cardiovascular convection, which implies an additional diffusive barrier between blood and environment. This barrier can be the organism's skin itself, as in the lungless salamander or some newborn marsupials. In embryos and fetuses, the blood exchanges with the environment through the placenta (in which case the environment is represented by the maternal blood) or the chorioallantoic membrane. **c** The addition of another convection system, ventilation, permits further enhancement of gas transport capabilities because of the enormous increase in the blood–gas-barrier (*BGB*). This is the arrangement for most adult vertebrates. **d** Gases transported by convection do not lose any activity (*blue vertical lines* in the cascade of the partial pressure of oxygen, PO_2) while diffusion always causes some loss in partial pressure (*red oblique lines*)

the partial pressure of O_2 (PO_2) remains unaltered throughout the whole arterial system irrespective of its distance from the lungs. Equally, PO_2 remains constant through the conductive airways of a unidirectional ventilatory system², like in fish or birds. Differently, diffusion always involves some loss of activity, does not matter how small the diffusive resistance may be. Hence, PO_2 drops whenever a diffusive step is encountered throughout the oxygen cascade between environment and cells (Fig. 1.1d).

1.3 Gas Diffusion

Gas molecules at higher concentration move towards the region of lower concentration until a dynamic equilibrium is reached. Nonuniform gases tend towards uniformity because the motion of a particle has less chance to be disturbed when it is heading towards a region with fewer particles. At equilibrium, the probabilities of movement are the same for all the gas particles so that there is no net displacement in any direction. Other factors being constant, the time required to reach equilibrium depends on the diffusion coefficient D of the gas. In ideal conditions, D is inversely proportional to the square root of the molecular weight w (Graham's Law). Hence, O_2 with $w=32$ has a higher D than CO_2 with $w=44$. In real conditions, an additional factor for D is the weak electrical intermolecular repulsive and attraction forces (van der Waals' forces). For CO_2 , the attractive forces are more important than they are for O_2 , which further exacerbates the differences in D between the two gases. In fact, D of O_2 (~ 0.2 cm²/sec) is 1.3 times that of CO_2 (~ 0.15 cm²/sec), a difference larger than expected simply from their respective w ($\sqrt{44}/\sqrt{32}=1.17$). D is inversely proportional to the barometric pressure P_b and, in the temperature range 30–40 °C, increases $\sim 0.8\%$ for every °C.

1.3.1 Fick's Laws of Diffusion

A gas x with different concentrations separated by a surface A of thickness θ will diffuse from the region with higher to that with lower concentration. The quantity Q^3 of the gas x diffusing per unit time, or diffusion rate Q_x/t , at any point through the barrier depends on the diffusion coefficient of the gas D_x and its concentration gradient $\delta C_x/\delta\theta$. If we assume for simplicity that the gradient is linear, $\delta C_x/\delta\theta$ can be expressed by the difference in concentration over the barrier $\Delta C_x/\theta$, and

² Differently, PO_2 cannot remain constant in a respiratory system with tidal ventilation like that of mammals. In the mammalian respiratory system, the PO_2 in the alveoli is lower than the inspired PO_2 because the inspired air, during its progression from the large airways to the gas exchange region, accumulates water vapour and carbon dioxide.

³ Volumes of gases are at standard temperature, pressure and dry conditions (STPD). 1 mol contains the Avogadro's number of particles. 1 mMol $O_2=22.4$ ml O_2 and 1 ml $O_2=0.0446$ mMol O_2 .

$$Q_x/t = \Delta C_x \times (A/\theta) \times D_x, \quad (1.1)$$

known as the Fick's first law of diffusion after the enunciation in the middle of the nineteenth century by the German physician and physiologist Adolf Fick (who, incidentally, developed the methodology to measure cardiac output that bears his name). In essence, Eq. 1.1 states that the net movement of a quantity Q of substance x over time equals the product of the area A through which x is diffusing, the diffusion coefficient D and the concentration gradient $\Delta C/\theta$.

The dimensions for Q_x/t and $\Delta C/\theta$ are, respectively, moles/min and (moles cm^{-3})/cm, from which D has the dimensions of cm^2/min (Table 1.1).

From Dalton's law, each gas x has a partial pressure P_x proportional to the product of its concentration C_x and barometric pressure P_b

$$P_x = C_x \cdot P_b. \quad (1.2)$$

Therefore, Eq. 1.1 can be written as

$$Q_x/t = \Delta(P_x / P_b) \cdot (A/\theta) \cdot D_x. \quad (1.3)$$

Fick had likened the flux of a gas under a concentration gradient to the proportionality between a flux of heat and the temperature gradient, a relationship discovered by Joseph Fourier some years earlier. These relationships follow the general pattern 'flux = pressure/resistance', equivalent to the familiar Ohm's law of current = voltage/resistance ($I=V/r$); resistance is the reciprocal of 'conductance' and in the case of molecules or small particles, conductance refers to 'diffusivity'.

Because of the proportionality between C_x and P_x (Eq. 1.2), usually no distinction is made between ΔC_x and ΔP_x , that is, between Eqs. 1.1 and 1.3. However, it is important to be aware that the latter, not the former, is responsible for diffusive transport (1.3.2). At high altitude, even though the O_2 concentration remains the same as at sea level, O_2 diffusion decreases because of the lower P_b and lower partial pressure of O_2 .

Equation 1.1 applies to a steady condition with time stability in $\delta C/\delta \theta$, that is, when the rate of change in C does not vary over time ($\delta C/\delta t=0$). However, precisely because of diffusion, often the concentration gradient decreases over time ($\delta C/\delta t \neq 0$). Fick's second law addresses this issue and indicates that the rate of Q does not depend on the gradient $\delta C/\delta \theta$ itself but on the *rate of change* of the gradient. One advantage of introducing the element of time in the analysis of the diffusion process is that it permits to compute the time t that a particle needs in order to diffuse a given distance L , simplified as

$$t = L^2/(2D), \quad (1.4)$$

where D stands for the diffusion coefficient (cm^2/sec) and 2 is a numerical constant that depends on the dimensionality of the diffusion process. The main point of Eq. 1.4 is that, differently from the familiar concept of motion at constant speed

where t is proportional to the travelled distance L , in diffusive motion t is proportional to square of L . The reason for it is in the essence of the diffusion process itself, with particles continuously changing directions as the result of random collisions. On statistical grounds, the actual distance travelled by a particle with diffusive motion in steady conditions is nil, because a step in one direction gets offset by another in the opposite direction. However, as the number of random steps increases with time, the dispersion (or variance) of the distance travelled at each step increases, whatever its direction may be. Diffusion time is proportional to the variance, or mean square displacement (L^2), rather than to the average displacement. This means that the distance travelled by a particle with diffusive motion increases ever more slowly the greater the displacement. Hence, a particle that requires a time t to diffuse a distance d needs $4t$ to diffuse distance $2d$ and $100t$ to diffuse $10d$. Diffusion is therefore extremely efficient for a molecule to travel very short distance, but becomes an inefficient way to move for long distances.

1.3.2 Gas Diffusion in Liquids

The passage of gases through the BGB of the vertebrate respiratory system invariably involves diffusion of gases into liquids according to their partial pressure gradient. Equilibrium is reached when the net movement of particles leaving the liquid toward the gaseous phase is the same as that in the opposite direction, meaning that the gas partial pressure is the same at both sides of the BGB. Hence, in condition of equilibrium, when many gases are dissolved into the same liquid, the sum of their individual partial pressures is equal to the total pressure of the gaseous phase. For example, the total pressure of the gases in the arterial blood is the same as that of the pulmonary alveoli because in normal conditions blood and alveoli reach equilibrium.

Although liquids are fluids just like gases, their intermolecular cohesive forces are stronger, which explains why gases can be compressed while liquids practically cannot. In a liquid, the interactive forces confine the freedom of movement of the molecules, and diffusion coefficients D are several fold lower ($\sim 10^{-4}$) than in gases (Table 1.2). For example, by application of Eq. 1.4, a molecule of O_2 to diffuse 0.1 mm into water ($D=2.5 \cdot 10^{-5} \text{ cm}^2/\text{sec}$) will take about 2 s and to diffuse 1 mm will take more than 3 min.

The volume of gas x dissolved in a liquid depends on the product between its solubility coefficient α ($\text{mlx} \cdot \text{ml}^{-1} \cdot \text{Px}^{-1}$)⁴ and its partial pressure P_x ; therefore, the rate of diffusion of a gas x in a liquid differs from what expressed by Eq. 1.3 and becomes

$$Q_x/t = (\Delta P_x \cdot \alpha) \cdot (A/\theta) \cdot D_x. \quad (1.5)$$

⁴ The solubility α of gases in liquids depends on temperature and concentration of solutes.

Table 1.2 Representative physicochemical properties of respiratory gases in air and water

	In air (~20°C, 1 atm)			In water (20°C, 1 atm)		
	O ₂	CO ₂	CO ₂ /O ₂	O ₂	CO ₂	CO ₂ /O ₂
Diffusion (D) (cm ² /sec)	0.198	0.155	0.8	2.5·10 ⁻⁵	1.8·10 ⁻⁵	0.7
Capacity (β) (nMol ml ⁻¹ torr ⁻¹)	54.7	54.7	1	1.8	51.4	28
Permeation (K=Dβ) (nMol cm ⁻¹ sec ⁻¹ torr ⁻¹)	10.9	8.5	0.8	4.5·10 ⁻⁵	9.3·10 ⁻⁴	21

These values are approximate figures for temperatures around 20°C, 1 atm. Differences among values reported in the literature can be substantial (e.g. MacDougall and McCabe 1967). In air, the permeation coefficient K equals D·β or D·α, because β and α are the same. In water, β and α are the same for O₂, while for CO₂ β and α usually differ greatly, unless the water is carbonate free

Often, the terms D and α are lumped together into a ‘permeation coefficient’ (or Krogh’s constant) K=D·α, with dimensions mlx cm⁻¹ sec⁻¹·mm Hg⁻¹ (Piiper et al. 1971), so that Eq. 1.5 simplifies into

$$Q_x/t = (\Delta P_x \cdot (A/\theta)) \cdot K_x. \quad (1.6)$$

The permeation coefficient of CO₂ (KCO₂=9.3·10⁻⁴) is some 20 times higher than that of O₂ (KO₂=4.5·10⁻⁵) because, despite the slightly lower D, α for CO₂ is about 28 times higher than for O₂ (Table 1.2).

In essence, Eq. 1.6 states that the quantity of a gas x that diffuses per unit time is the product between the pressure gradient that drives diffusion and the gas diffusive conductance

$$Q_x/t = \Delta P_x \cdot G_x, \quad (1.7)$$

where G_x, with the units of mlx min⁻¹ mm Hg⁻¹, represents the product between geometric factors (A/θ) and the gas physical characteristics (K=D·α). Hence, the conductance (G) of the BGB for a gas x can be computed physiologically, by measuring ΔP and Q/t (Eq. 1.7), or can be computed from Eq. 1.5 with the knowledge of the morphological features of the BGB (A/θ) and the gas physicochemical properties (α·D). However, it should be noted that Eq. 1.7 is valid in conditions of steady state for the two media from which the gas is diffusing through. This is often not the case. For example, the alveolar-capillary PO₂ and PCO₂ gradients continuously change; hence, equilibrium may be reached only towards the end of the transit time, when the partial pressure values at the capillary and alveolar sides coincide. These dynamic events complicate the accurate computation of the diffusive G.

An increase in temperature influences the permeation coefficient K (Eq. 1.6) on two grounds; it raises D and slightly decreases the solubility α. The net effect of a rise in temperature on gas diffusion in liquids is ~1% increase for every °C.

1.3.3 Gas Capacitance

It is important to recognise that the partial pressure P of a gas in a liquid is solely determined by the gas physically dissolved; the chemically bound gas (like O_2 bound to haemoglobin or CO_2 as bicarbonate) does not contribute to P . Hence, in respiratory gas exchange, it is common to consider the total capacitance β of a liquid for a gas. This parameter, which has the same units as the solubility α (moles ml^{-1} mm Hg $^{-1}$), includes both the chemically bound and the physically dissolved forms.

In air, from the general gas law,

$$P \cdot V = M \cdot R \cdot T, \quad (1.8)$$

it is apparent that the capacity β of a gas (moles M ·volume V^{-1} ·pressure P^{-1}) equals $1/(R \cdot T)$, or

$$\beta = (M/V)/P = 1/(R \cdot T), \quad (1.9)$$

where R is the gas constant and T the temperature in Kelvin; hence, in air the capacitance β is the same for all gases. In water, O_2 is present only in the dissolved form; hence, $\beta_{O_2} = \alpha_{O_2}$, while in the arterialised blood, the presence of haemoglobin raises β_{O_2} as much as 70 times. For CO_2 , in distilled and carbonate-free water $\beta_{CO_2} = \alpha_{CO_2}$. However, in most waters and in blood CO_2 is found both physically dissolved and bound to bicarbonates and other buffers, according to the pH of the water (Dejours 1988). Hence, usually in water and blood β_{CO_2} largely exceeds α_{CO_2} (Table 1.2), with implications on the partial pressures that result from the O_2 – CO_2 exchange (1.4.3).

1.4 Some Considerations

Despite the simplicity and often intuitive nature of the laws governing diffusion, it may be useful to emphasise some aspects with respect to gas exchange through the BGB.

1.4.1 Thickness (θ) and Area (A) of the BGB

The flux of a gas through the BGB is favoured by a short diffusive distance θ and a large surface A (Eqs. 1.1 and 1.3). Indeed, large exchange surfaces and very short diffusive distances are the most obvious characteristics of all structures involved in gas exchange, from gills and placentas to alveolar-capillary or chorioallantoic membranes. The risk of membrane fragility imposes a lower limit on how thin the

gas-exchange barrier can be. In mammals, where the lungs are organs with a high degree of volume change and subjected to the distortion and conformational changes of the chest wall, the minimum θ of the BGB is of the order 0.2–1 μm . In birds, where the lungs are rather rigid structures with air capillaries protected by a scaffold of surrounding vascular capillaries, the barrier is thinner than in mammals, possibly down to 0.1 μm . Values below these limits would jeopardise the integrity of the barrier, which seems to have reached its optimal limits with no room for further improvement. Indeed, species of different body sizes and metabolic requirements present large differences in BGB surface area but only minute differences in BGB thickness (Maina 2005). Furthermore, within each individual the possibility exists for the gas exchange area to increase further, as in the case of gills in conditions of hypoxia (Sollid and Nilsson 2006).

The physiological role of the gas exchange area needs to be considered not in absolute terms but in relation to the metabolic needs of the organism. For this reason, gas exchange through the body surface may be adequate even in organisms with small surface-to-mass ratio,⁵ as long as O_2 needs are low such as many invertebrates and a few vertebrates, like the lungless salamander. In the majority of vertebrates, the tegument as the sole means of gas exchange is insufficient because of the large body size and the high metabolic demands. Hence, specialised organs have evolved to provide gas exchange areas much larger than body surface, both during prenatal development (the chorioallantoic membrane and the placenta) and postnatally (gills and lungs). In adult humans, the lung surface area is estimated at about 10 cm^2 per gram of body weight, which exceeds by 50–100 times the body surface area. In small-size species, especially those with high metabolic scope, the lung surface area can be much larger, like the $\sim 100 \text{ cm}^2 \text{ g}^{-1}$ of the flying bats. Among birds and mammals, only some of the smallest newborn marsupials can use the skin as BGB. The newborn Julia Creek dunnart survives for weeks almost entirely by skin gas exchange because, in addition to the small body mass ($\sim 17 \text{ mg}$) and the extremely thin tegument, it has very low weight-specific needs for O_2 (Mortola et al. 1999). In the high humidity of the maternal pouch, these newborns do not risk dehydration which is a serious challenge to any terrestrial organism that uses the tegument as BGB.

At the microscopic level, biological membranes are structurally irregular. From the view point of gas diffusion, they could be compared to a mesh where regions with high G are spaced by others with low G . Extreme examples of such unevenness are the pores of the avian eggshell or the stomata of a plant leaf, which are the sole pathways out of the whole structure permitting diffusion. Indeed, any BGB, owing to unavoidable structural requirements, must be characterised by regions of low and high diffusive G . What matters for diffusive G (Eq. 1.7) is the cumulative A of the diffusive paths, irrespective of the number, distribution and size of the paths. In other words, whether a diffusive A of 1 cm^2 originates from the cumulative sum of 100 passages of 1 mm^2 each or from a single one of 1 cm^2 has hardly any

⁵ Based on simple geometric considerations, as the size of an organism increases, its body surface-mass ratio rapidly decreases, because surfaces increase with the square of the linear dimension while volumes increase with the cube of the linear dimension ('Surface Law').

consequence on *diffusive* G . This is very different from the concept of G applied to convective transport, where a G of 100 1 mm^2 pores would be much lower than the G of one single 1 cm^2 passage. As an example, let us consider the diffusive G of an egg, which is usually measured from the daily weight loss caused by water evaporation⁶. The water vapour conductance (*diffusive* G) of chicken eggs is in the range 10–20 $\mu\text{l day}^{-1} \text{ mm Hg}^{-1}$. This value originates from the diffusive paths of some 10^4 eggshell pores, which all combined provide a diffusive A of 2.2 mm^2 . On the other hand, if one had to measure the *convective* conductance of the eggshell by forcing gas through a piece of eggshell, the value would be $\sim 1700\text{--}3900 \mu\text{l day}^{-1} \text{ mm Hg}^{-1}$, or some 200 times higher (Paganelli 1980).

The application of Fick's law (Eq. 1.3) becomes less valid when the pathways of diffusion through a structure are very crowded together or the thickness of the barrier θ is very short in relation to its cross section (Rahn et al. 1987). Either condition creates interference between the diffusive flows because of a boundary layer that lowers the conductance G . Under these circumstances Stefan's law applies, where diffusion is more closely proportional to the diameter, rather than the area, of the diffusive path. An additional factor that can functionally complicate the application of Fick's laws to the BGB is the formation of unstirred boundary layers. These are unlikely to alter the diffusive G in air breathers, but can offer a substantial diffusive resistance in water breathers. It was estimated that up to 90% of the total diffusive resistance at the level of the fish gill secondary lamella was produced by the unstirred film of water (Hills and Hughes 1970). Various mechanisms are in place to lower the boundary diffusive resistance, for example, locomotion as in the case of ram ventilation, or the waving movements of the gills or cilia movements. From these examples, it is apparent that G can have quite different values when obtained by a physiological approach (Eq. 1.7) or by a computation based on the morphological features (A/θ) of the BGB (Eq. 1.5).

1.4.2 Diffusion (D) and Permeation (K) Coefficients

Diffusion of gases, whether within gases or liquids, depends on the partial pressure difference ΔP , not on the concentration difference ΔC . As mentioned above, the distinction has no practical importance for diffusion in air because of the direct proportionality between concentrations and partial pressures (Eq. 1.2), but it becomes relevant for gas diffusion in liquids. Because the solubility α of a gas can vary greatly among liquids, it is not unconceivable that ΔC and ΔP may have opposite sign, in which case the gas diffuses along ΔP and against ΔC .

The fact that the values of D for gases in liquids are very low (by comparison to the values in gaseous solutions) implies that equilibrium between air and liquid can take long, or very long, time to reach. For example, some waters can differ greatly

⁶ The egg daily weight loss due to water evaporation permits to compute the conductance of water vapour, $G_{\text{H}_2\text{O}}$, from which G_{O_2} is calculated from the molecular weight of H_2O and O_2 .

in O_2 partial pressure (PO_2) from the air they are in contact with. The PO_2 of a pond can oscillate daily between 30 and >400 mmHg (Truchot and Duhamel-Jouve 1980) depending on the prevalence of photosynthesis over animal respiration, and during the sunniest hours the waters may be hyperoxic even at high altitude! With respect to CO_2 , similar differences between aquatic and aerial partial pressures are unlikely to occur because of the large capacitance β for CO_2 (1.3.3). On a similar note, body compartments such as tissues and blood can present important differences in PO_2 because they never have sufficient time to reach diffusion equilibrium, while differences in partial pressure of CO_2 (PCO_2) are small. In mammals, the PCO_2 has similar values in the alveolar regions, in the pulmonary capillaries, systemic capillaries and in tissues.

The diffusion coefficient D increases with a drop in barometric pressure P_b . To a minor extent, this improves the O_2 availability for those organisms relying on gas diffusion at high altitude, where ΔP is low (Eq. 1.3). Of course, the effect of P_b on D applies to all gases, meaning that at high altitude the advantage of higher D for O_2 diffusion has to be weighed against the risks of losing water in the form of water vapour. Avian eggs laid above sea level have eggshells with reduced G (Eq. 1.7) and small pore areas (A of Eq. 1.3), which limit water loss. Above ~ 3000 m, though, the needs for O_2 become imperative and the eggshell G rises above the sea level value by an increase in pore areas (Mortola 2009). Incidentally, this is another example of the plasticity of the BGB, where greater diffusion needs are accommodated by changes in A with no alterations in θ (1.4.1).

1.4.3 The Environmental Side of the BGB

Whether the environmental side of the BGB is air or liquid (Fig. 1.1), it makes a big difference on the ventilatory work and on the partial pressure of the expired gases and arterialised blood. The low β_{O_2} , coupled to the high density and viscosity of water⁷, implies that animals ventilating water must perform greater respiratory work than animals ventilating air. In some fish, water pumping may take up to 50% of metabolic rate, compared to 10% or less for air ventilation in air-breathing vertebrates. In hypoxia, the cost of the hyperventilation for a fish may be so high as to increase its metabolic rate, in contrast to the hypometabolic response to hypoxia commonly observed in many air breathers.

Because all molecules of gases occupy approximately the same volume (22.4 L at standard temperature, pressure and dry (STPD) conditions), in air the values of α and β coincide and are the same for O_2 and CO_2 (Table 1.2). This means that in air breathers, as the result of O_2 - CO_2 exchange, the drop in PO_2 will correspond to the increase in PCO_2 , the only difference being due to respiratory exchange ratios (RER) different from one. For example, with $RER=0.8$, the 50 mmHg drop in PO_2 (from 150 mmHg inspired to 100 mmHg alveolar) corresponds to a $50 \cdot 0.8=40$ mmHg

⁷ At 20 °C water is about 1000 times denser and about 100 times more viscous than air.

increase in P_{CO_2} . Indeed, these are the P_{O_2} and P_{CO_2} values in the mammalian lungs and in the air cell of avian eggs towards the end of incubation. In water, O_2 is carried only in its dissolved form; hence β_{O_2} is the same as α_{O_2} and both values are much lower than in air because of the lower O_2 solubility (Table 1.2). Differently, β_{CO_2} is ~ 30 times larger than β_{O_2} (1.3.3). The consequence of $\beta_{CO_2} > \beta_{O_2}$ is that, differently from air-breathing, in water-breathing the O_2 – CO_2 exchange causes only minor increases in P_{CO_2} for the same decrease in P_{O_2} . On theoretical grounds, even if a water-breather were successful in extracting all the O_2 , its expired P_{CO_2} would be only 5 mmHg⁸. The difference between β_{CO_2} and β_{O_2} in water, not present in air, explains why arterial P_{CO_2} in mammals is about 40 mmHg, while in many fish is just a few mmHg (Scheid and Piiper 2011).

In air, changes in temperature have only modest effects on gas capacitance, because the changes in temperature within the biologically significant range have little impact on absolute temperature (Eq. 1.9). Differently, in water the increase in temperature reduces β . This can pose a serious challenge to fish and other water-breathing ectotherms, the metabolic rate of which depends on ambient temperature. In fact, a rise in water temperature increases the animal's metabolic activity and O_2 requirements while at the same time reduces the water O_2 capacitance β_{O_2} .

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⁸ With water $\beta(CO_2)/\beta(O_2) \approx 30$, a drop in P_{O_2} of 150 mmHg raises P_{CO_2} by only $150/30 = 5$ mmHg.

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