

Title: A circulation-based hypothesis for vertebrate body plan evolution and endothermy

Title: A circulation-based hypothesis for vertebrate body plan evolution and endothermy

Author: William S. Peters

Correspondence and requests for materials should be addressed to:

William S. Peters MBChB, MD

Matai Medical Research Institute

Gisborne 4010

New Zealand

Email: w.peters@matai.org.nz

Key words/phrases

Vertebrate, body plan, circulation, heme, redox, endothermy, evolution, cardiogenesis

Abstract

The emergence of novel vertebrate body plans and endothermy remain central questions in evolutionary science. Although gene regulatory networks provide powerful explanatory frameworks, the contribution of systemic physiology to vertebrate evolution warrants further investigation. Here, a hypothetical circulation-based model is proposed that integrates the redox and magnetic properties of blood with circulatory architecture.

The circulation is modelled as a redox-balanced, one-way oxygen delivery scaffold that broadly reflects the vertebrate segmental body plan. It is hypothesized that an oxygenated shunt within an ancestral, fish-like single-loop circulation generates a kinematically coupled ‘loop-in-loop’ dynamic. The evolvable scaffold adjusts to maintain a balanced state of redox eustress, influencing cardiorespiratory topology and the distribution of intersegmental blood flow. With greater air breathing dependence and strengthening of the loop-in-loop, transition from this archetypal tetrapodal circulatory format to the double-looped circuits of mammals and birds is achieved.

This circulation-based ecophysiological framework is examined in relation to extant vertebrate anatomy and comparative evolutionary and developmental evidence. Planck’s equation is used in calculating the thermogenic potential associated with heme oxygenation within the lungs as compared to the gills or with cutaneous oxygenation.

The model is restricted to the physical properties of circulating blood and does not explicitly incorporate mitochondrial metabolism, genomic regulation, or other biological processes. It is presented as a testable hypothesis rather than a causal explanation of vertebrate evolution. If supported by empirical investigation, this framework may complement existing evolutionary and

developmental models by identifying potential physiological mechanisms relating to vertebrate body plan organization and thermal physiology. This knowledge may add to predicting how organisms may respond to climate change and may provide further insights into evolutionary medicine and developmental disorders.

Introduction

The closed, one-way circulation of redox-active blood is fundamental to vertebrate life (Monahan-Earley et al. 2013). Oxygen is delivered by blood in a biophysically optimised manner to fuel intracellular redox processes (Forjaz et al. 2026). With oxygen dissociation, blood switches from diamagnetic to paramagnetic, dramatically altering its visible light absorption properties, and thus its outward colour (Pauling and Coryell 1936). These characteristics of blood reverse with reoxygenation in the pharyngeal-based gills, buccocutaneous system and/or lungs.

From ectothermic fishes to endothermic mammals and birds, the living organism is actively maintained in a state far from thermodynamic equilibrium, and a whole-of-body, spatiotemporal redox eustress exists (Jones 2024). Notably, estimates based on whole-body cell counts indicate that red blood cells comprise approximately 70-80% of all cells in the human body (Bianconi et al 2013; Hatton et al. 2023). It is therefore postulated that the circulation of redoxing blood plays a significant role in whole-body redox balance and the evolving body plan.

In fishes, the heart and gills, like the body, are sagittally bisymmetric. Deoxygenated blood from the body drains to a central atrium and is then ejected through the single ventricle heart to the gills. Newly oxygenated, the blood runs on to perfuse the body - it is not reaccelerated (Graham 1997). Notionally, it is a single-looped circuit.

In mammals and birds, the four-chambered heart is suspended asymmetrically within the thorax. Deoxygenated blood from the body drains to the right atrium and is ejected from the right ventricle to the lungs (Al-Ghazal 2002). Oxygenated within the thorax, blood loops back through

the left heart and is re-accelerated, now in a spiral manner, to perfuse the body. Harvey (1628) described the ventricles as bellows, the blood running in series through the two loops, with lungs interposed, to complete one circuit of the body.

The widely accepted theory of evolution recognises that mammals and birds share common ancestry with ancient fish-like vertebrates (Darwin 1859, Ahlberg and Milner 1994). Given the fundamental nature of the circulation of blood in vertebrates, this manuscript focuses on how a single-looped circuit may have evolved to become a double-looped circuit and how the shift in oxygenation from external gills to internal lungs may underlie the emergence of endothermy.

Hypothesis

It is hypothesised that the bulk physics of redoxing blood, which switches polarity with oxidation state, influences evolution of the vertebrate circulatory system. From this blood-based hypothesis, several subplots are developed, including the emergence of lungs, limbs, bipedalism and endothermy. The physiological model is evaluated against extant anatomical and evolutionary evidence. The calculation of potential heat generation with heme oxygenation is provided. From a developmental perspective, the model is further evaluated against cardiogenesis and the role of the genome is also considered.

Blood basics

The model incorporates the magnetohydrodynamic characteristics of blood and the redox potential of heme, properties which are exploited in technologies such as electromagnetic flow meters (Boccalon et al. 1978), magnetic resonance imaging (Li and van Zijl 2020) and plethysmography (Nordlund and Hoffmann 2019).

Because hemeoglobin and other plasma constituents carry electrical charge, the movement of blood through the geomagnetic field induces internal electrical currents (Tenforde 2005; Tzirtzilakis 2005). These currents interact with the external magnetic field to generate an electromotive Lorentz force. By definition, this force acts perpendicular to both the axial stream and the external magnetic field. Fully oxygenated blood flowing in the presence of the geomagnetic field is electrically homogeneous and is slightly more diamagnetic than water.

With oxygen dissociation in the peripheral tissues, unpaired electrons are exposed on the iron (Fe) centres of heme molecules. Although oxyhemeoglobin and deoxyhemeoglobin contain the same total number of electrons, the high-spin state of deoxyhemeoglobin results in two additional unpaired electrons. Consequently, deoxygenated blood becomes strongly paramagnetic (Rollemma 1975; Jain et al 2012). The presence of unpaired electrons creates local magnetic heterogeneity within and around the deoxygenated bloodstream. As a result, deoxygenated blood exhibits a tendency to align with, and be attracted by, an external magnetic field.

Oxygen dissociation also alters the optical properties of heme. Deoxygenated heme strongly absorbs red light (around 660nm) and appears dark as a result. With a conformational shift induced by the binding of oxygen, oxyhemeoglobin has a significantly greater affinity to absorb near-infrared light (around 940nm), and blood switches to a bright red colour as a result (Nordlund and Hoffmann 2019).

The single-looped circulation and the surrogate body plan

Starting with a simplified fish circulation, dorsally positioned cephalad and caudal cardinal veins drain deoxygenated blood via bilateral ductus Cuvieri into the venous pole of the midline heart (Satchell 1991). From the central atrium, blood enters the ventricle before it is ejected at a reverse acute angle through the arterial pole to the pharyngeal gill arches. The inflow atrio-ventricular valve is bicuspid and attached to ventricular papillary muscles, while pocket-like semilunar outflow valves are arranged circumferentially around the muscular ventricular outflow tract of the truncus arteriosus (Sans-Coma et al. 2022).

The historical numbering of I-VI (first-sixth) is used to describe the pharyngeal gill arches in non-amniotes, numbered from cephalad to caudal (Congdon 1922). In the model, only arches III-VI, which are common to amniotes also, are referred to (**Fig. 1**). As blood perfuses the capillary beds of the gill arches, deoxygenated heme binds oxygen acquired from the aquatic environment and blood switches from dark to bright.

Newly oxygenated blood from the arches enters the paired dorsal aortae which supply the head and upper body, and converge caudally as one to supply the lower body and tail. Paired intersegmental arteries arising from the dorsal aortic system perfuse the body walls bilaterally (Jacobson, A. G. 1988). Cervical intersegmental branches adjacent to the fourth pharyngeal arches supply the pectoral fins and are homologous to the mammalian subclavian arteries (Paulissen et al. 2022). Deoxygenated blood returns to the dorsal cardinal veins via intersegmental venae comitantes, veins which run counter-current to the arteries, to complete the circuit.

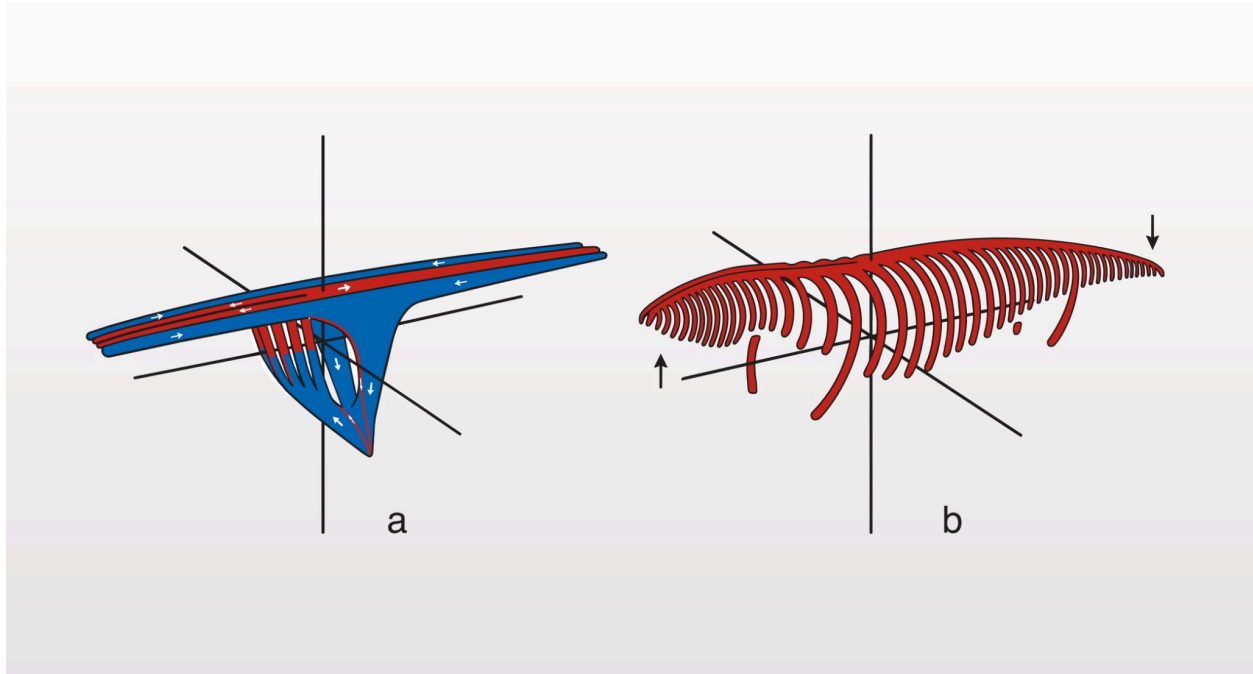


Figure 1: Single-looped circulation model. (a) Stylised 3D representation of the blood within the heart and great vessels. Deoxygenated blood (blue) drains from paired cardinal veins into the midline heart and is ejected out into the paired pharyngeal arches III-VI. Oxygenated blood (red) perfuses the body via the dorsal aortic system. A post-pharyngeal oxygenated shunt bypasses the dorsal aortic system and gets caught into the venous return, setting up an intra-cardiac loop-in-loop (shunt origin shown as a white dot). Arrows indicate the one-way direction of flow in the circuit and highlight the co-current relationship of the loop-in-loop in the heart and the counter-current arrangement of oxygenated and deoxygenated blood flow in the body. (b) Stylised 3D representation of the bilateral intersegmental arterial distribution from the dorsal aortic system. The developing loop-in-loop sets off an instability in the circuit, compensated for by precession and pentameric intersegmental redistribution to maintain angular momentum and a net-zero redox eustress.

It is hypothesised that the one-way circulation of blood induces a rotational moment that maintains the bodily perfusion scaffold in a horizontal disposition relative to gravity (**Fig. 1a**). Blood cycles from the body, through the heart and arches, back to the body. Within the central and intersegmental arteries and veins of the body, oxygenated and deoxygenated blood runs counter-current, and by their opposite polarities, these flows are counter-moment also. This

arrangement is hypothesised to create a multiplier mechanism and an additive, co-moment compulsion to the one-way cycling of blood. In addition, the left-right, head-tail arrangement of the redox-active circuit is proposed to establish a net-zero centre of eustress.

This circulatory scaffold is used as a surrogate for the body plan in its broadest sense. The body walls fuse ventrally in the midline to enclose the oral–anal passage and coelomic cavities, including the abdominal and pericardial cavities. For simplicity, the dorsally positioned nervous system and the enteric aorto-portal circulation are acknowledged but are not further detailed in this dissertation.

The systemic shunt and the transitional loop-in-loop circulation

This ideal circulation cannot exist, however. It represents an inert state. Anatomically, the pharyngeal gill bed responsible for oxygen uptake is embedded within the systemic capillary network responsible for oxygen delivery. Consequently, a region of overlap exists between these oxygen ingress and oxygen egress pathways; there is no physiological boundary between the two. This provides an opportunity for a slip of post-pharyngeal gill-oxygenated blood to bypass the dorsal aortic pathway and shunt instead into the central venous return (**Fig. 1b**). The anterior, or inferior jugular vein, which drains the lower pharyngeal region in some fishes, provides an example of a post-pharyngeal oxygenated shunt into the single ventricle heart (Graham 1997, Ishimatsu 2012).

Caught in with the paramagnetic stream at the venous pole, it is hypothesised that the nascent diamagnetic shunt rotates axially on its polar opposite host as they slip-stream through the heart together. The oxygenated streamlet twists beneath the deoxygenated stream as they exit through the truncal outlet and into the pharyngeal arches, setting up a ‘loop-in-loop’. Influenced by

mutually repellent Lorentz forces, the co-current streams want to scissor apart, the valved outlet where the streams cross acting as the fulcrum, and with the separation forces greatest closest to the fulcrum. The nascent oxygenated stream dog-legs rightward and winds selectively through the third and fourth arches while the deoxygenated blood is nudged leftward into the sixth arches.

Between the divergent third-fourth and sixth arch loops, it is proposed that the fifth-arch gill filament network begins to involute. Like gloves pulled inside out, gill filaments iteratively remodel, insufflating into bilateral thoracic coelomic cavities as primitive alveolar beds.

Attracted by lower vascular resistance and access to aerated oxygen, left and right pulmonary arterial tendrils splint from the burgeoning sixth-arch flows to tail the internalising fifth-arch capillary beds. Newly oxygenated, neo-pulmonary venous blood traverses centrally, dorsal to the longitudinally disposed cardinal veins, and adds to the nascent oxygenated shunt, an interposed pulmonary circulation now established.

With greater ambient oxygen, the loop-in-loop strengthens and valve elements are co-opted at the point of scissoring in the widening truncal outlet. As the red loop grows, the circuitry scaffold precesses to preserve angular momentum and the head comes up. The nascent spiralled oxygenated outflow into the dorsal aorta incrementally replaces the ancestral laminar flow and distribution of blood via the intersegmental arteries morphs toward a pentameric patternation to maintain a bisymmetric bodily redox balance. As in classical geometry, in nature, left- and right-handed logarithmic spirals achieve bilateral balance within a pentagram (Bredder 1955; Ghyka 1946). Cephalic, lower cervical, and lower lumbar segments grow with increased intersegmental flow while under-nourished segments shrink; fins become limbs and tail segments compact.

The loop-in-loop circulation described by the model retains a state of whole body eustress and is reflective of the salamandrid body plan and circulation (Francis 1934). It is representative of an neotenic, archetypal tetrapod circulation from which extant amphibian and reptile circulations can be derived.

The model versus extant amphibian and reptilian anatomies

In all amniotes, the first and second gill arch structural elements get heavily modified and repurposed into vital structures of the jaw, neck, and inner ear.

In semi-aquatic salamanders, derived from the remaining arches, there is a mix of gills, a buccocutaneous circulation and rudimentary lungs, with a patent ductus arteriosus and the fifth arches variably retained (Victor et al 1999; Grimes and Kirby 2009). Fins have iteratively evolved to become limbs (Adachi et al 2016). A partial interatrial septum is present, creating left and right atria. Atrial septal formation appears directly related to pulmonary development and the separate passage of oxygenated atrial blood (Lewis and Hanken 2017). The ventricle is defined as single, though an interventricular foramen is a functional channel shaped by an intraventricular fold that directs oxygenated blood into the outflow trunk. Within the trunk, the oxygenated outflow tract, or cavum aorticum, is incompletely separated from the cavum pulmocutaneum by an intraluminal spiral fold (Icardo et al. 2005; Carrasco-Medina et al. 2024). These findings are consistent with the loop-in-loop model.

Within the context of the loop-in-loop model, it is proposed that the first and second gill capillary filaments are extravagated dorsally and deoxygenated blood from the sixth arch pulmocutaneous branches pursues this cutaneous oxygen-ingress capillary network in a manner not unlike with the pulmonary arteries pursuing the internalizing fifth arch capillary beds. In support of this

proposal, it is noted in amphibians that the cutaneous arteries pass bilaterally in the groove between the depressor mandibulae and temporalis muscles to exit the thorax and perfuse the cutaneous capillary beds spread across the dorsum and flanks (Carrasco-Medina et al. 2024). These muscles derive from the second and first arches, respectively (Ziermann and Diogo 2024).

As an extension to the basic blood model, the in-parallel cutaneous perfusion bed provides a flexible, auxiliary blood oxygenation avenue to accommodate a semi-aquatic lifestyle. However, unlike lung-based oxygenation, the skin-oxygenated blood drains directly into the systemic venous return via the musculocutaneous veins. This transitionary circulatory set-up provides gill, cutaneous and pulmonary oxygenation circuits that run in parallel and that are accommodative of a wide range of habitats and oxygenation levels.

Variations of this archetypal tetrapod loop-in-loop model are seen in the circulations of frogs and toads. As they transition from a tetrapodal larval form to an adult, the gills are lost, replaced by lungs. The hearts remain three chambered, though the ductus arteriosus has closed and fifth arches are no longer present. The buccocutaneous respiration circuit is greatly embellished and runs in parallel with the pulmonary circuit, but drains to the right heart rather than the left. This arrangement allows tolerance of hypoxic aquatic environments, with shunting of blood away from the lungs coupled with a physiological lowering of the body metabolic rate.

Within the context of the loop-in-loop model, it assumed the evolved morphospace of frogs and toads provides a balanced, blood-based state of whole body eustress, albeit with a wide degree of tolerance to fluctuating ambient oxygen and aquatic environments.

Progression of the archetypal tetrapod loop-in-loop model is also seen in reptiles, but with a trajectory separate to amphibians. Lungs have more fully developed and any in-parallel gill and

cutaneous circulations have completely regressed. The neck is narrowed and limbs are more robust, positioned directly beneath the body. There are two atria and a distinct, spiralled intra-ventricular ridge has developed. The spiralled aortic outflow is physically separated from the pulmonary trunk (Poelmann et al 2017; Hicks).

Within the partially divided ventricle of non-crocodilain reptiles, functionally separated oxygenated and deoxygenated blood streams can be variably distributed via the paired aortic arches to the body and through the pulmonary trunk to the interposed pulmonary circulation. This mixed arrangement allows for considerable physiological flexibility, with central shunts to accommodate changing metabolic and environmental demands (Burggren et al 2020).

The model versus evolutionary history

Applying a general attribution of atmospheric oxygen concentration to vertebrate evolutionary stages, the transitional nature of the loop-in-loop model is seen reflected in the evolution of early tetrapods, from when fishes dominated marine environments approximately 500 million years ago. During a period of rising atmospheric oxygen levels, the first tetrapods appeared around 390 million years ago (mya). The amphibian crown group branched early, at approximately 375 mya and Synapsida and Sauropida reptilian clades first appeared approximately 320 mya.

Atmospheric oxygen concentrations reached an estimated peak of 30–35% at this time (Huey and Ward 2005; He et al. 2019). It is postulated that the transitional loop-in-loop circulation of early amphibians and reptiles was influenced by this luxuriant oxygen environment, allowing some species to stem to fill this niche while other species remained relatively unchanged.

A sharp decline in oxygen to approximately 10–12% over the next 50-70 million years coincided with a massive shake-down in terrestrial vertebrate life. Relative hypoxia, compounded by

extreme warming, may have imposed significant physiological and ecological constraints on larger-bodied amphibians and reptiles (Huey and Ward 2005). Subsequent to this extinction event came the rise of mammals and birds from the Synapsida and Sauropida reptilian clades, respectively (He et al. 2019). In the context of the blood hypothesis, the atmospheric oxygen peak provided a facilitative environment for evolution from single to double-looped circulations.

Transitioning to the double-looped circuit - a predictive kinematic model

Greater air-breathing dependence strengthens flow through the low resistance pulmonary circuit, driving loop-in-loop divergence, and interventricular septation and aorto-pulmonary division completes. All deoxygenated blood from the body is now committed to loop through the interposed pulmonary pathway, the double-looped circuit established.

Kinematics of the loop-in-loop model

Geometrically, the pivot–precession relationship of the loop-in-loop circulation may be conceptualised as an articulated flat-pack frame with an axle through its central convergence (**Fig. 2**). Within this coupled mechanism, the primary deoxygenated loop is depicted as a blue plane and the oxygenated loop a red plane. The head-tail hinge-line between the planes corresponds to the sagittal midline axis of the body. As the oxygenated trajectory strengthens, the planes pivot apart (θ) while the entire assembly precesses (Ψ), degree for degree, toward a perpendicular parity. In its simplest form, the relationship may be expressed as:

$$\theta \mapsto \Psi(\theta), \text{ where } \theta, \Psi \in (0^\circ, 90^\circ)$$

The transitional loop-in-loop circulation of an archetypal tetrapod may be loosely modelled as twenty degrees unpacked (**Fig. 2a**). Conceptually, the threshold at which ventricular septation

completes and commitment to the double-looped circuit occurs may exist at around forty-five degrees. As pivoting increases, precession matches, limited by perpendicularity of the planes. With unpacking of the kinematic model, there is a coupled spiral outflow influence on bisymmetric intersegmental arterial redistribution toward a pentameric format in a way that retains a net zero centre of redox eustress. The model predicts progressive reorientation of the head–tail axis and the central loops toward orthogonality (**Fig. 2b**).

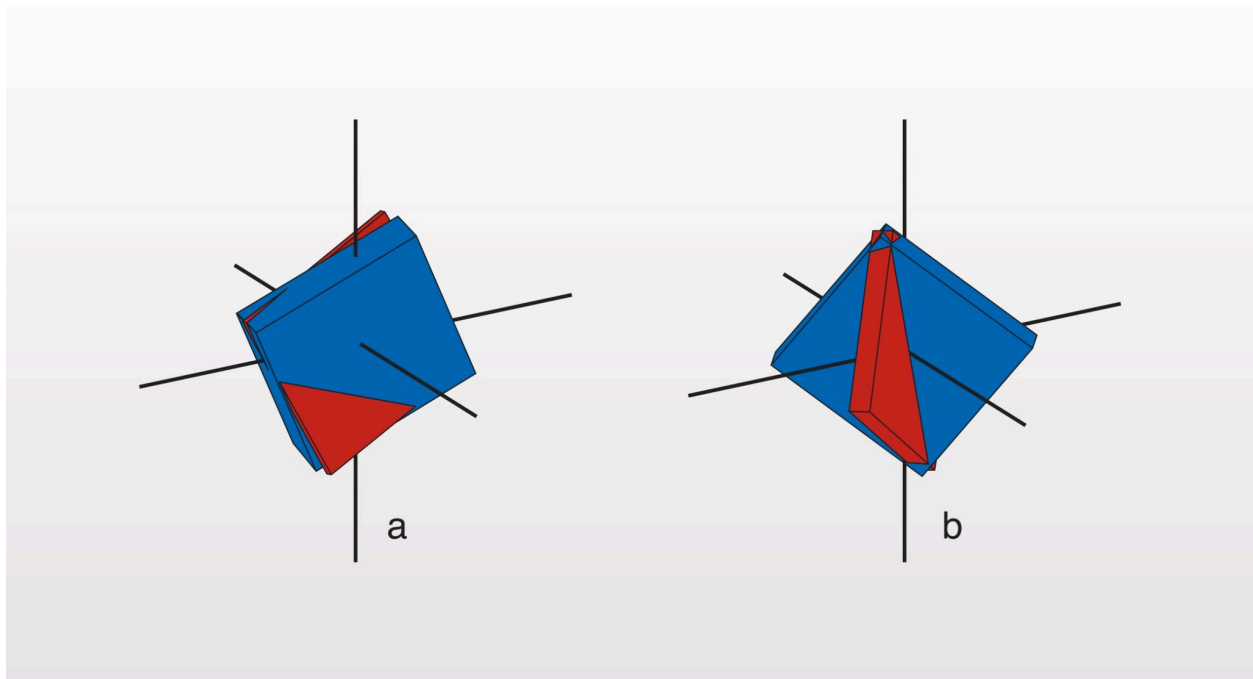


Figure 2: Kinematic ‘loop-in-loop’ model. Coupled spatial mechanism illustrating the relationship between pivoting of the loop-in-loop and precession of the vascular scaffold at (a) 20 degrees deployed and (b) 80 degrees deployed.

The double-looped circuit and the promise of bipedalism

From an evolutionary perspective, progression from a transitional tetrapod circulation to the double-looped circulation of mammals and birds is also accompanied by remodelling of the

double aortic arch system. In all mammals, the left fourth arch persists as the definitive aortic arch through to the dorsal aorta, passing to the left of the trachea and oesophagus, while the right fourth arch regresses dorsally. In stark contrast, in all birds it is the right fourth arch that is retained and the left fourth arch regresses dorsally (Balkaya 2016). The relationship between aortic arch sidedness and the body plan is considered below and reviewed within the context of the kinematic model.

Comparative anatomy of the body plans and of the aortic and pulmonary outflows in mammals and birds

In quadrupedal mammals, the bisymmetric body plan is pronograde and pentameric, typically with a tail. The chest is deep and narrow, with the forelimbs forward on the chest wall. Digital pentadactylism is present but not well delineated. From a ventral perspective, the pulmonary trunk overlies and obscures the relatively short ascending aorta and the aortic arch branches.

In ruminants, a single innominate trunk off the aortic arch divides into all the upper body branches, namely the bilateral carotid and subclavian arteries (Elster 2008), whereas in cats and dogs, there are two arch branches; a large innominate trunk giving rise to the right subclavian artery and both common carotid arteries, the left subclavian artery arising separately. The quadruped descending (dorsal) aorta is relatively straight, sitting on the vertebral column, and it divides into the common iliac arteries, with the medial sacral artery - as the attenuated continuation of the caudal dorsal aorta - supplying the tail.

In bipedal primates and humans the body plan is orthograde and pentameric. There is no tail. The chest is broad, the shoulders back, the hips open, and there is well-defined pentadactylism in the digits of the hands and feet. The left ventricular apex sits obliquely in the left chest. The

ascending aorta and main pulmonary artery appear widely splayed, sitting side-by-side. In humans, the aortic and pulmonary valves associated with the respective outflow pathways have a near-orthogonal relationship (Bhatia 2016; Saremi et al. 2017).

The human left ventriculo-aortic flowline is seen to spiral in a logarithmic fashion from the left ventricle to perfuse the body in a bisymmetric manner (**Fig. 3**). The columella, or central spiral axis of the outflow is orientated obliquely relative to the bisymmetric body. The carotid and subclavian branches to the head and upper limbs derive from a characteristic three-branch arch pattern. The descending (dorsal) aorta sweeps through the left thoracic paravertebral gutter before trending back to the anterior aspect of the lumbar vertebral column where it divides terminally into the bilateral common iliac arteries supplying the pelvis and lower limbs. The vestigial median sacral artery supplies the coccyx.



Figure 3: Distribution pattern of human systemic oxygenated blood. The image is derived from a cardiac MRI scan and is presented as viewed from a left anterior oblique aspect. The centreline of blood flow is depicted in white. The flowline originates in the left ventricle

and runs through the ascending to the descending aorta with a normal three branch pattern off the arch giving rise to bilateral carotid and subclavian arteries (terminal iliac branches off the descending aorta not shown).

In comparison, in birds there is a relatively limited variation in both body plan and cardiac morphology (Kroneman 2019). The body plan is pentameric, but blunted, with a broad-based tail, or pygostyle (Rashid et al. 2018). Though the head-tail axis lies somewhere short of orthograde, birds are bipedal (Abourachid et al. 2023). Within the barrelled chest, the ascending aorta and pulmonary trunk are seen relatively side-by-side in ventral projection, though the left ventricular apex is more caudally orientated than in humans (Beaufrère et al. 2010).

The avian aortic arch gives rise to two arch branches, the left and right innominate trunks. Each divides into its respective common carotid and subclavian artery. The carotid arteries are elongate and ascend posteriorly along the neck. The subclavian arteries are short and support the pectoral flight muscles and wings. The descending aorta continues caudally before giving off paired iliac and ischiatic arteries. The ischiatic arteries constitute the principal arterial supply to the hindlimbs, with variable contributions from the iliac/femoral arteries (Midtgård 1982). The median sacral artery extends into the pygostyle.

These findings are consistent with the predictive model. As compared to tetrapods, in mammals and birds the head is elevated and there is further progression toward a pentameric body plan. Splaying of the aorto-pulmonary outflows is more evident in bipedal mammals and birds, with the aorto-pulmonary offset seen to be near-orthogonal in bipedal humans.

Arch sidedness provides a punctuated distinction between mammals and birds. As compared to the diversity of mammals, it is postulated that in birds the spiral outflow line defined by the the

more caudally orientated left ventricular apex and the right-sided aortic arch might constrain the degree of aorto-pulmonary outflow pivoting and segmental redistribution to a much narrower range of balanced vascular scaffold configurations and that this situation may predispose both flight and bipedal locomotion.

Heart and great vessel topology

The arrangement of the left and right blood flow pathways within the four-chambered heart might also be reflective of the model. Growth of the oxygenated, spiralled loop predicts progressive co-option and shaping of the left ventricular chamber and its inflow and outflow valves from the ancestral common ventricle. This is illustrated by viewing a staged sequencing of the model, looking at a cross section of the base of the heart through the venous and arterial poles from a dorsal perspective (**Fig. 4**).

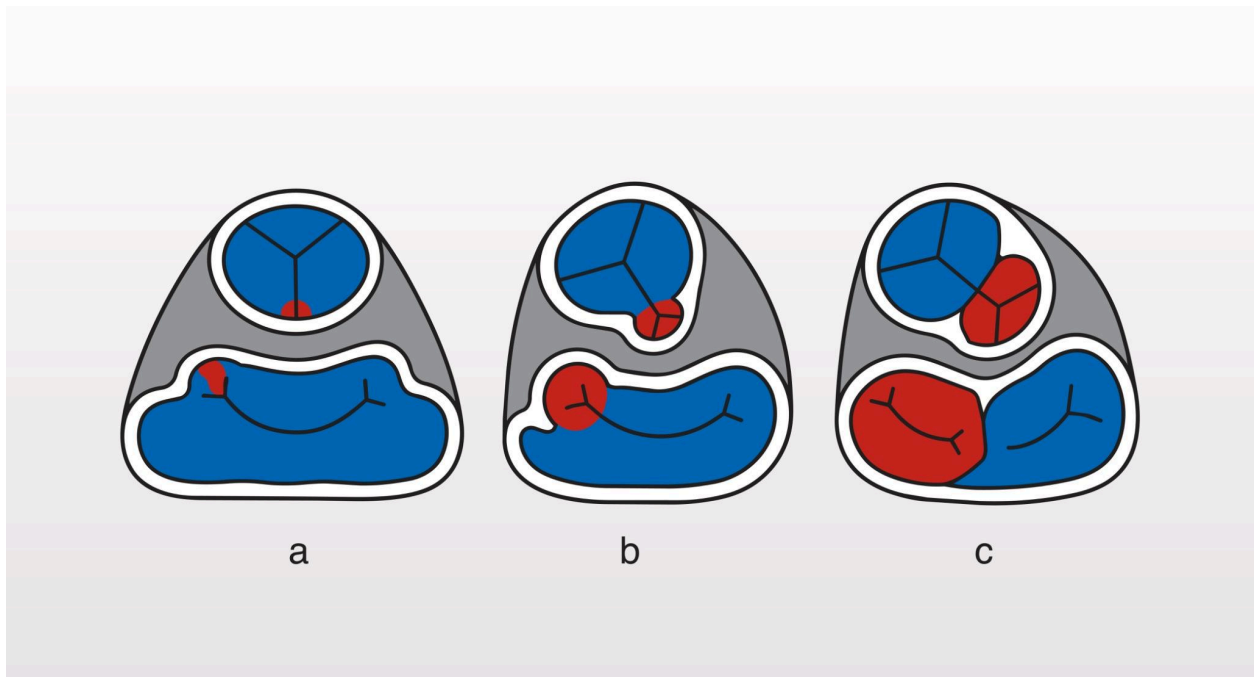


Figure 4: Evolution of the four-chambered vertebrate heart. Dorsal cross-sectional view of the base of the vertebrate heart in evolution per the loop-in-loop model. Atrio-ventricular and truncal valve components are

co-opted as the loop-in-loop develops and intracardiac septation forms between the separately streaming loops. The transverse pericardial sinus (grey) persists between the venous and arterial poles (white) with growth of the oxygenated loop. (a) Single looped heart (b) Archetypal tetrapod heart (c) Double looped heart

Consistent with the model, the mature human heart remains suspended within the pericardial sac by singular venous and arterial poles. The transverse pericardial sinus persists between them. The aortic valve commissures are seen as a mirror of the pulmonary commissures (Bhatia 2016). The right ventricular inflow and outflow regions are spread by the anterior aspect of the aortic root (Goor and Lillehei 1975). The fanned out right ventricle retains the reverse angle, inflow–apex–outflow relationship characteristic of the ancestral single-ventricle condition (Henein et al 2011). Muscular trabeculae in the left ventricle have a pronounced right-handed helical course from the apex to the base (Pettigrew 1864; Berman et al. 2010; Lunkenheimer et al. 2013). Helical organisation is also evident in blood flow through the left ventricle and ascending aorta (Morbiducci et al. 2009; Tanaka et al. 2010).

Pulmonary respiration and endothermy

With elevation of the mouth, the saline tide that passed over the gills has given way to the tidal volume of air-based pulmonary respiration, and associated with it, the shift from ectothermy in fishes to endothermy in birds and mammals. With pulmonary respiration, oxygen binds to heme within the body rather than at the external gill surface. As heme becomes oxygenated, its optical properties change, and blood switches from dark to bright.

Using clinical oximetry wavelengths of 940 nm and 660 nm as the molecular peak absorption values for oxygenated and deoxygenated blood, respectively (Nordlund and Hoffmann 2019), the single photon energy difference between these two states can be calculated. Applying Planck's

equation (Planck 1901), the difference in photon energy (E) is given by the product of Planck's constant (h , 6.626×10^{-34} J.s) and the speed of light (c , 3×10^8 m/s), divided by the difference in peak wavelengths ($\Delta\lambda$, m):

$$\begin{aligned}
 &= (h \text{ J.s} \times c \text{ m/s}) / \Delta\lambda \text{ m} \\
 &= (6.626 \times 10^{-34} \times 3 \times 10^8) / (280 \times 10^9) \\
 &= 7.10 \times 10^{-19} \text{ J}
 \end{aligned}$$

Factoring in the Soret band differential (approximately 317 nm and 330 nm for oxygenated and deoxygenated blood, respectively), the net photonic energy differential is calculated:

$$\begin{aligned}
 &= (7.10 \times 10^{-19}) - (0.15 \times 10^{-19}) \\
 &= 6.95 \times 10^{-19} \text{ J}
 \end{aligned}$$

Assuming one photon per heme molecule, and using normal values* for cardiac output, percentage saturation of oxygenated and deoxygenated blood, hemeoglobin concentration and the molar mass of a hemeoglobin tetramer (containing four heme groups), the total number of heme molecules that transition from a deoxygenated to an oxygenated state every second is calculated:

$$\begin{aligned}
 &= ((\text{CO L/s} \times \text{Hb g/L}) / M_{\text{Hb}}) \times 4 \times (\text{SaO}_2 - \text{SvO}_2) \times N_A \\
 &= ((0.0833 \times 150) / 64,458) \times 4 \times (0.98 - 0.75) \times (6.022 \times 10^{23}) \\
 &= 1.074 \times 10^{20} \text{ molecules/s}
 \end{aligned}$$

*Cardiac output (CO) 5.0 L/min, or approx 0.0833 L/s, hemeoglobin concentration (Hb) 150 g/L, arterial oxygen saturation (SaO₂) 0.98, mixed venous oxygen saturation (SvO₂) 0.75, molar mass of hemeoglobin tetramer (M_{Hb}) approx 64,458 g/mol, heme groups per tetramer (n) 4, Avogadro's Number (N_A) 6.022x10²³ molecules/mol

Multiplying the total number of heme molecules transitioning per second by the net photonic energy change per transitioning heme molecule (E) gives the wattage produced in the lungs in a normal adult human at rest:

$$= \text{molecules/s} \times E \text{ (J)}$$

$$= 1.074 \times 10^{20} \times 6.95 \times 10^{-19}$$

$$= 74.6 \text{ W}$$

It is thus hypothesised that the photonic energy released with oxygenation - a phenomenon here termed 'photoscission' - is transferred to the surrounding serum as heat. In fishes with gill-based oxygenation the energy derived from heme-based photoscission is lost externally to the environment whereas in birds and mammals with pulmonary-based oxygenation, this phenomenon may confer a basal source of endothermy; radiator cooling versus central heating.

Cardiogenesis as an evolutionary corollary

There is a strong interplay between evolutionary patterns and developmental mechanisms in vertebrates (Raff 2012). Owing to the evolutionary repeatedness of cardiac development, observations made in nonamniote and amniote species have classically been used to extrapolate

to human development. Consequently, observations derived from surrogate cardiogenesis models are used to further interrogate the blood-based model.

The model as related to the classical stages of cardiogenesis

Cardiogenesis follows a well-defined developmental sequence (**Fig. 5**) and it proceeds under contractile blood flow conditions (Hove et al. 2003; Courchaine et al. 2018). The primitive heart tube forms early in embryonic development and blood begins to flow one-way (Männer et al. 2010). In amniotes, an extra-embryonic external oxygen source is established, and oxygenated blood enters via the sinus venosus into the developing heart tube. Blood flow is laminar in the contractile heart tube and streams do not mix (Hogers et al. 1995; Yoshida et al. 1983).

Ventral, or C- looping of the heart tube occurs and brings the inflow and outflow poles of the heart into close approximation (**Fig 5a**). With forward folding of the heart tube, the dorsal mesoderm between the two poles breaks down. This creates the transverse pericardial sinus (Le Garrec et al. 2017). As a result, the ventricular apex assumes a ventral position, with the outflow tract arising at a reverse acute angle relative to the inflow tract (Jenkins et al 2007). Per the model, the nascent spiralled red stream is establishing the loop-in-loop at this stage.

The C-loop then bends and twists into a characteristic S-shaped configuration - S-looping - that sets the stage for the four chambered heart (**Fig 5b**). Invoking the model, the developing allantoic oxygenated blood supply may fuel the heart tube loop-in-loop and help drive differentiation toward a four-chambered heart with separate aortic and pulmonary outflows. Emerging evidence suggests that oxygen availability early in vertebrate embryogenesis may function as an active developmental regulator (Zhu 2026).

Following S-looping, atrioventricular septation and chamber expansion occurs (**Fig 5c**). The upper and lower pharyngeal arches have undergone a patterned reformation into the branched aortic arch and pulmonary trunk, respectively (Congdon 1922). The loop-in-loop is seen as fully developed at this stage, with the ductus arteriosus pathway wide open. Following birth and the onset of pulmonary respiration, the ductus closes and the lungs assume the oxygenation role previously provided by the amnion.

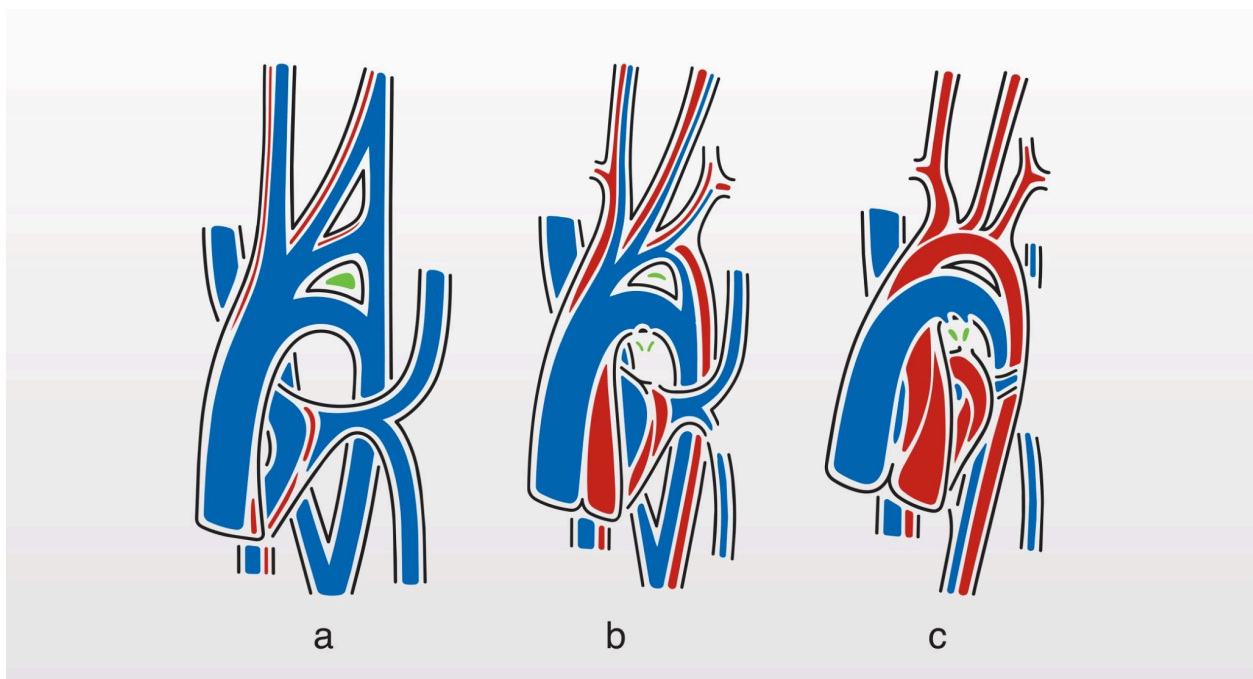


Figure 5: Cardiogenesis and the loop-in-loop model. Stylised left anterior oblique view of the developing four-chambered heart in embryogenesis. The endothelium is shown as black and the fifth arch structures are indicated in green. Allantoic oxygenated blood (red) is seen streaming into the heart via the right caudal cardinal vein (blue). (a) C-looping (b) S-looping (c) Septation and chamber enlargement.

Selected observations from developmental studies

Developmental studies demonstrate that within the single ventricle, a muscular ridge develops from the ventricular apex and forms between the separately streaming inflow bloodlines (Grimes

and Kirby 2009; Sizarov, et al. 2012). Notably, the structures underpinning ventricular septation retain the properties of the primary myocardium of the heart tube (Keith and Flack 1907). The crest of the muscular ventricular septum is the most primitive part: “The ventricles are outgrowths; or bulgings from the primitive heart tube; the septum is that part of the tube which remains between the outgrowths”. These findings are consistent with the proposed ventricular loop-in-loop divergence leading to ventricular ballooning and septation.

The aortic and pulmonary roots develop from the intermediate component of the ventricular outflow tract (van Praagh 2016). The funnel-shaped, muscular conus wall gives way to accommodate the oxygenated stream, co-opting valvular structures as it proceeds. The conus remodels to enclose the pulmonary outflow in its own muscular turret, the aortic root effectively budded off and its commissures a mirror of the pulmonary valve. Within the blood-based model, this point of separation between the mirrored aortic and pulmonary valve commissures corresponds conceptually to the pivot point between the scissoring outflow streams.

The fifth arches make but a brief appearance in birds and mammals (Wang et al 2024). Simultaneously, a deepening laryngopharyngeal diverticulum develops within the ventral pharyngeal endothelium immediately caudal to the fourth arch pouches and subsequently buds bilaterally to form the lungs (Hiruma and Hirakow 1995; de Mello and Reid 2000)

The larynx and its cartilages arise largely from mesenchymal derivatives of the fourth and sixth pharyngeal arches that border this region. The dorsal branchial structures are seen repurposed and the associated “inner fish” genomic regulatory network here subverted (Poopalasundaram 2019). Within the context of the model, these developmental events are interpreted as the involution and repurposing of ancestral fifth arch elements to support pulmonary respiration.

Cardiogenesis gone wrong

The model (as adapted to cardiogenesis) can be extended to account for the conotruncal malformation patterns observed in Transposition of the Great Arteries (TGA) and Tetralogy of Fallot (ToF). Within this framework, TGA is interpreted as arising from under-rotation of the developing oxygenated loop. Rather than cross beneath, the co-current streams run in parallel into the arches, and they boomerang apart. The spatial connections between the ventricles and the aortic and pulmonary outflows are reversed and this produces two single-looped circuits in parallel, as is the clinical condition.

Conversely, ToF is interpreted as resulting from over-rotation, and over-scissoring of the oxygenated loop, impinging on the remodelling pulmonary outflow tract and inhibiting complete interventricular septation. The clinical phenotype is compatible with this proposal, with the defining pathology an antero-cephalad deviation of the interventricular muscular outlet septum, narrowing of the right ventricular outflow tract and the ascending aorta enlarged and dextro-rotated, over-riding a ventricular septal defect.

Outside of recognised syndromic developmental disorders, in these congenitally acquired conditions the overall body plan is generally preserved despite the substantial disturbance in aortic outflow dynamics. This is contrary to the evolutionary blood-based model, where it is proposed that over millennia the aortic outflow trajectory acts in reciprocity with intersegmental flows and segmental growth and differentiation.

This dichotomy infers embryonic establishment of the inherited segmental body plan arises from a hierarchically deeper regulatory framework than cardiogenesis. Notably, the vertebrate segmentation clock is a pre-somitic mesodermal oscillating genetic network that regulates timing

and formation of paired somites from head to tail. This process is accompanied by a robust and regular bilateral sprouting of intersegmental vessels connecting with the axial trunk vessels (Jacobson 1988, Diaz-Cuadros et al. 2020; Geudens et al. 2019). The heart tube forms following the first somites (Kaufman and Navaratnam 1981).

In surrogate developmental models, experimental manipulation of intracardiac blood flow during cardiogenesis is known to selectively influence the cardiac phenotype (Courchaine et al. 2018). It is important to note that blood flow diameters in the developing heart tube are of the order of 100-500 microns (Jenkins et al. 2007). At these microfluidic diameters, viscous forces dominate and can influence cellular behaviour and gene expression (Hove et al. 2003; Courchaine et al. 2018). It is proposed that electromotive forces generated by the oxygenated and deoxygenated blood streams are also relevant at this scale. These forces can be influenced by the blood composition, oxygen carrying capacity, flow rate and temperature (Tzirtzilakis et al. 2005; Jain et al 2012). Externally applied magnetic fields also influence microfluidic blood flow dynamics (Okazaki et al. 1987; Formicki and Winnicki 1998). Accordingly, the adapted model suggests disturbances in blood physiology or environmental conditions at a critical juncture in the cardiogenic window may be sufficient to perturb the central bloodline trajectories within the heart and result in misaligned ventriculo-truncal topology independent of any genetic program. These congenitally acquired cardiac disorders occur sporadically and do not demonstrate simple patterns of familial inheritance (van Praagh 2016; Fahed et al. 2013).

Once the cardiogenic window has closed and embryonic development gives way to foetal growth, cardiac topology is set in place and microfluidics gives way to classical hemeodynamics. Although strong magnetic fields can induce measurable electrical potentials

within the aorta of large animals, they do not appear to produce significant alterations in cardiac function or systemic hemodynamic parameters (Tenforde 2005).

What about the genome?

Life depends on biologically mediated redox reactions (Jelen et al. 2016). Operating under continually changing environmental conditions, cells modify their functional state through dynamic interactions among genetic, epigenetic, metabolic, and environmental processes. Variations in redox status at nested levels, from intracellular to whole organs to systemic, can influence gene expression, genome stability, and epigenetic regulation (Allen and Tresini 2000). Developmental and evolutionary change may also arise through organism–environment interactions (Odling-Smee et al. 1996) while some environmentally induced effects can persist across generations through epigenetic mechanisms (Soubry et al 2014). In this sense, the genome may be viewed not as a static blueprint but as part of a dynamic biological system capable of responding to changing developmental and environmental conditions (Shapiro 2013). Others have proposed the idea that a cell will differentiate in a specific way by interpreting its position in the body, a two-way translation of genetic information into spatial patterns of differentiation and regulation (Wolpert 1969).

Vertebrate evolution has unfolded over hundreds of millions of years within the physical and ecological constraints of the biosphere, and cellular metabolism is seen to be vectorial (Saier 2000). However, the reciprocal manner in which the heritable genome, developmental regulatory networks and cellular differentiation may interact with changes in circulatory organisation and cellular metabolism remains unclear.

Of note, lungfishes and salamanders, as living representatives of an archetypal tetrapod model circulation, have the largest nuclear genomes among vertebrates (Mohlhenrich and Mueller 2016). Within the context of the model, this genomic volume may reflect greater flexibility tolerated by the transitional loop-in-loop blood circuit in maintaining eustress and the opportunity for many heritable reconfigurations to be selected.

Discussion

The circulation is modelled as an evolvable redoxing system that distributes energy throughout the organism in a topologically constrained way and is centred on the maintenance of a whole-body redox eustress. Furthermore, the light absorption properties of redoxing heme are used to develop the notion of photoscission and develop the proposal that the evolution of pulmonary-based respiration might underlie the emergence of endothermy in mammals and birds.

The physiological model extends the principle that biological form emerges through coherent interaction with the physical laws governing the biosphere (Thompson 1942). Consistent with concepts of punctuated equilibrium (Eldredge and Gould 1972; Duran-Nebreda et al. 2024), the model also offers a mechanism for how vertebrate body plans might remain remarkably stable over long evolutionary intervals, while retaining the capacity for comparatively rapid change.

However, the model lacks any consideration of the cells of the body other than as representing a mitochondrion that requires a continuous supply of oxygen. The genome is not accounted for other than as a potential buffering system for intra-organismal redox flux. No consideration is given to germ cells, modes of inheritance or any concept of consciousness or agency. As such,

the model is viewed as constraining the morphospace of vertebrate species, rather than acting as a direct driver of evolution *per se*.

Other than to highlight a previously unheralded potential mechanism for vertebrate thermogenesis and how this may relate to ectothermy in fishes and the emergence of endothermy with the evolution of mammals and birds, no attempt is made to assimilate the notion of photoscission within the blood-based model with known thermal regulatory systems. In particular, it is noted that in amphibians and reptiles, with their species-specific variations of mixed circulations and ancillary, in-parallel pulmocutaneous connections, that a range of oxygenation and thermal regulatory strategies are deployed (Taylor et al. 2021).

More broadly, the model invites consideration of the evolutionary product of a living organism as a result of the active distribution of an externally sourced energy to maintain the redoxing corporeal and its ability to adapt to changing conditions. Looking across other clades, evolutionary analogies are apparent. For example, the signature gastropod body plan is of a spiral shell organised around a central axis, or columella that is oriented obliquely relative to the bisymmetric ‘stomach foot’ that meets and moves through the world to which it has adapted (Grande and Patel 2009). Variations on this underlying architectural theme permit adaptation to diverse ecological niches while preserving a recognisable body-plan framework. For example, a wider enveloping angle dictates a flatter body-shell habitus, an adaptive configuration more suited to seashells attached to rocks.

However, description alone cannot underpin a mechanistic hypothesis (Clark 2016). The model lends itself to investigation and experimental interventions that can determine whether and how the loop-in-loop mechanism can help to predict novel character origins. To test this model

empirically, topological analysis of the central blood-flow trajectories and vascular distribution patterns across vertebrate species using 3D axial imaging is envisaged, as is 4D analysis of embryonic chick heart tube blood streams using next-generation, single-photon avalanche diode image sensors and ultra-high-speed recording. The pulmonary-based concept of endothermy invites further empirical calculations and investigative studies.

Studying deep constraints to vertebrate evolution and endothermy, and what limits or directs biological change, is useful to predict how organisms may adapt—or fail to adapt—to rapidly changing modern environmental and climate pressures. If found to be broadly applicable, the blood hypothesis may add an ecophysiological component to the emergence of a 21st century evolution narrative (Noble 2024) and may provide further insights into evolutionary medicine and developmental disorders (Williams and Nesse 1991).

Acknowledgements

This research was originally funded by a competitive grant from the Australasian Society of Cardiothoracic Surgeons Research Foundation (2006) with the purpose of investigating spiral flow in the ascending aorta. Thanks to Peter Hunter and David Ladd (Auckland Biomedical Institute, NZ) for hosting the original research grant and for the generation of Fig 3, and to Michael Markl (University Hospital Freiburg, Germany) for providing the 4D cardiovascular MRI dataset from which Fig. 3 was derived.

Thanks also to Paget Milsom, Campbell Emmerton and John Windsor (Auckland City Hospital, NZ), Kirsten Finucane and John Artrip (Starship Hospital, NZ), Wenbo Li and Peter van Zijl (Johns Hopkins University School of Medicine, Baltimore, MD), and James Shapiro (Chicago, IL) for discussion and debate which helped shape this manuscript, to Don Campbell (Matrix

Applied Computing, Auckland, NZ) for creating the algorithmic animation from which Fig. 2 was derived and to Rees Morley (Morley Degin Group, Wānaka, NZ) for preparing Figs. 1, 2, 4 and 5 for publication.

Statements and Declarations

No conflicts of interest

Literature cited

Abourachid, A., C. Chevallereau, I. Pelletan, and P. Wenger. 2023. An upright life, the postural stability of birds: a tensegrity system. *J R Soc Interface* 20:20230433

<https://doi.org/10.1098/rsif.2023.0433>

Adachi, N., M. Robinson, A. Goolsbee, and N.H Shubin. 2016. Regulatory evolution of Tbx5 and the origin of paired appendages. *Proc Natl Acad Sci USA* 113:10115–10120.

Ahlberg P.E. and A.R. Milner. 1994. The origin and early diversification of tetrapods. *Nature* 368:507–514.

Al-Ghazal S.K. 2002. The discovery of the pulmonary circulation: who should get the credit, Ibn Al-Nafis or William Harvey? *J Int Soc Hist Islamic Med* 1:46–48.

Allen, R.G. and M. Tresini. 2000. Oxidative stress and gene regulation. *Free Radic Biol Med* 28:463–499.

Balkaya, H. 2016. The arteries root from the aortic arch in the sparrowhawk (*Accipiter nisus*, *Falconiformes: Accipitridae*). *Int J Morphol* 34:110–115.

Beaufrère, H., R. Pariaut, D. Rodriguez, and T.N. Tully. 2010. Avian vascular imaging: a review. *J Avian Med Surg* 24:174–184.

Berman, M. A. Ali, E. Ashley, D. Freed, K. Clarke, S. Tsui, J. Parameshwar, and S. Large. 2010. Is stress cardiomyopathy the underlying cause of ventricular dysfunction associated with brain death? *J Heart Lung Transpl* 29:957–965.

Bhatia, A. 2016. Transesophageal echocardiography evaluation of tricuspid and pulmonic valves.

Bianconi E., A. Piovesan, F. Facchin, A. Beraudi, R. Casadei, F. Frabetti, L. Vitale, et al. 2013.

An estimation of the number of cells in the human body. *Ann Human Biol* 40:463–471.

Boccalon H. J., B.J. Candelon, H.G. Doll, P.F. Puel, and A.P. Enjalbert. 1978. Non-invasive electromagnetic measurement of the peripheral pulsatile blood flow: experimental study and clinical applications. *Cardiovasc Res* 12:66–68.

Breder, C.M. 1995. Observations on the occurrence and attributes of pentagonal symmetry. *Bull Am Mus Nat Hist* 106:173–220.

Burggren, W., R. Filogonio, and T. Wang. 2020. Cardiovascular shunting in vertebrates: a practical integration of competing hypotheses. *Biol Rev* 95:449–471.

Carrasco-Medina A.S., R.F. Salla, A. Sebben, H.R. da Silva, F.D. Passos, L.F. Toledo, and R. Rebouças. 2024. The cardiorespiratory system of miniature frogs. *J Anat* 244:232–248.

Clark, A.L. 2016. *Per Sanguinem Nostrum* by William S. Peters. *ESC Heart Fail* 3:299.

Congdon, E.D. 1922. Transformation of the aortic-arch system during the development of the human embryo. *Contrib Embryol Carnegie Inst Wash* 14:47–110.

Courchaine, K., G. Rykiel, and S. Rugonyi. 2018. Influence of blood flow on cardiac development. *Prog Biophys Mol Biol* 137:95–110.

Darwin C. 1859. *On the Origin of Species by Means of Natural Selection*. John Murray, London.

de Mello, D. E. and L.M. Reid. 2000. Embryonic and early fetal development of human lung

vasculature and its functional implications. *Pediatr Dev Pathol* 3:439–449.

Diaz-Cuadros, M., D.E. Wagner, C. Budjan, A. Hubaud, O.A. Tarazona, S. Donnelly, and A. Michaut, et al. 2020. In vitro characterization of the human segmentation clock. *Nature* 580:113–118.

Duran-Nebreda, S., R. Bentley. and B. Vidiella. 2024. On the multiscale dynamics of punctuated evolution. *Trends Ecol Evol* 39:734–744.

Eldredge, N. and S.J. Gould. 1972. Punctuated equilibria: an alternative to phyletic gradualism. Pp 82–115 in T.J.M. Schopf ed. *Models in Paleobiology*. Freeman, Cooper.

Elster, A.D. 2008. “Bovine” aortic arch. *AJNR Am J Neuroradiol* 29
<https://doi.org/10.3174/ajnr.A0861>

Fahed, A.C., B.D. Gelb, J.D. Seidman, and C.E. Seidman. 2013. Genetics of congenital heart disease: the glass half empty. *Circ Res* 112:707–720.

Forjaz A. M. Costa , C. Oliveira, P.A. Gensbigler, L. Dequiedt, V. Queiroga, S. Joshi, et al. 2026. Whole organism 3D mapping reveals universal branching topology and biophysical optimization governs vascular and nervous system development. Preprint. *bioRxiv*. 2026;2026.04.10.717729. doi:10.64898/2026.04.10.717729

Formicki, K. and A. Winnicki. 1988. Reactions of fish embryos and larvae to constant magnetic fields. *Ital J Zool* 65:479–482.

Francis, E.T.B. 1934. *The Anatomy of the Salamander*. Clarendon Press, Oxford.

Geudens, I., B. Coxam S. Alt, V. Gebala, A.C. Vion, K. Meier , A. Rosa, and H. Gerhardt. 2019.

Artery-vein specification in the zebrafish trunk is pre-patterned by heterogeneous Notch activity and balanced by flow-mediated fine-tuning. *Development* 146

<https://doi.org/10.1242/dev.181024>

Ghyka, M. 1977. *The Geometry of Art and Life*. Dover Publications, New York.

Goor, D.A. and C.W. Lillehei. 1975. *Congenital Malformations of the Heart: Embryology, Anatomy, and Operative Considerations*. Grune and Stratton, New York.

Graham J.B. 1997. *Air-Breathing Fishes: Evolution, Diversity, and Adaptation*. Academic Press, San Diego.

Grande, C. and N.H. Patel. 2009. Nodal signalling is involved in left-right asymmetry in snails. *Nature* 457:1007–1011.

Grimes, A.C. and M.L. Kirby. 2009. The outflow tract of the heart in fishes: anatomy, genes and evolution. *J Fish Biol* 74:983-1036.

Harvey W. 1993 (Original edition 1628). *De Motu Cordis: On the Motion of the Heart and Blood in Animals*. Prometheus Books, Frankfurt.

Hatton I.A. 2023. The human cell count and size distribution. *Proc Natl Acad Sci USA* 120.

He, T., M. Zhu, B.J.W. Mills, P.M. Wynn, A.Y. Zhuravlev, R. Tostevin, P.A.E. Pogge von Strandmann, A. Yang, S.W. Poulton, and G.A. Shields. 2019. Possible links between extreme oxygen perturbations and the Cambrian radiation of animals. *Nat Geosci* 12:468–474.

Henein, M.Y., Golden Ratio Collaborators, Y. Zhao, R. Nicoll, L. Sun, A.W. Khir, K. Franklin, and P. Lindqvist. 2011. The human heart: application of the golden ratio and angle. *Int J Cardiol*

150:239–242.

Hicks, J.W. 2002. The physiological and evolutionary significance of cardiovascular shunting patterns in reptiles. *Physiology* 17:241–245.

Hiruma, T. and R. Hirakow. 1995. Formation of the pharyngeal arch arteries in the chick embryo: observations of corrosion casts by scanning electron microscopy. *Anat Embryol* 191:415–423.

Hogers, B., M.C. DeRuiter, A.M.J. Baasten, A.C. Gittenberger-de Groot, and R.E. Poelmann. 1995. Intracardiac blood flow patterns related to the yolk sac circulation of the chick embryo. *Circ Res* 76, 871–877.

Hove, J.R., R.W. Köster, A.A. Forouhar, G. Acevedo-Bolton, S.E. Fraser, and M. Gharib. 2003. Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis. *Nature* 421:172–177.

Huey, R.B. and P.D. Ward. 2005. Hypoxia, global warming, and terrestrial late Permian extinctions. *Science* 308:398–401.

Icardo, J.M., E. Brunelli, I. Perrotta, E. Colvee, W.P. Wong, and Y.K. Ip. 2005. Ventricle and outflow tract of the African lungfish *Protopterus dolloi*. *J Morphol.* 265:43–51.

Ishimatsu, A. 2012. Evolution of the cardiorespiratory system in air-breathing fishes. *Aqua-BioSci Monogr* 5:1–28.

Jacobson, A.G. 1988. Somitomeres: mesodermal segments of vertebrate embryos. *Development* 104:209–220.

Jain, V., O. Abdulmalik, K.J. Probert, and F.W. Wehrli. 2012. Investigating the magnetic

susceptibility properties of fresh human blood for noninvasive oxygen saturation quantification. *Magn Reson Med* 68:863–867

Jelen, B.I., D. Giovannelli, and P.G.Falkowski. 2016. The role of microbial electron transfer in the coevolution of the biosphere and geosphere. *Annu Rev Microbiol* 70, 45–62.

Jenkins, M.W., D.C. Adler, M. Gargesha, R. Huber, F. Rothenberg, J. Belding , M. Watanabe , D.L. Wilson, J.G. Fujimoto, and A.M.Rollins. 2007. Ultrahigh-speed optical coherence tomography imaging and visualization of the embryonic avian heart using a buffered Fourier domain mode locked laser. *Opt Express* 15:6251–6267.

Jones N.P. 2024. Redox organization of living systems. *Free Radic Biol Med* 217:179–189.

Kaufman, M.H. and V. Navaratnam. 1981. Early differentiation of the heart in mouse embryos. *J Anat* 133:235–246.

Keith, A. and M. Flack. 1907. The form and nature of the muscular connections between the primary divisions of the vertebrate heart. *J. Anat. Physiol.* 41:172–189.

Kroneman, J.G.H., J.W. Faber, J.C.M. Schouten, C.F. Wolschrijn, V.M. Christoffels, and B. Jensen. 2019. Comparative analysis of avian hearts provides little evidence for variation among species with acquired endothermy. *J Morphol* 280:395–410.

Le Garrec, J.-F., J.N. Domínguez, A. Desgrange , K.D. Ivanovitch, E. Raphaël, J.A. Bangham, M. Torres, E. Coen, T.J. Mohun, and S.M. Meilhac. 2017. A predictive model of asymmetric morphogenesis from 3D reconstructions of mouse heart looping dynamics. *eLife* 6

<https://doi.org/10.7554/eLife.28951>

Lewis, Z. and J. Hanken. 2017. Convergent evolutionary reduction of atrial septation in lungless salamanders. *J Anat* 230:16–29.

Li W. and P.C.M. van Zijl. 2020. Quantitative theory for the transverse relaxation time of blood water. *NMR Biomed.* 33, e4207 <https://doi.org/10.1002/nbm.4207>

Lunkenheimer, P.P., P. Niederer., D. Sanchez-Quintana, M. Murillo. and M. Smerup. 2013. Models of ventricular structure and function reviewed for clinical cardiologists. *J Cardiovasc Transl Res* 6:176–186.

Männer, J., A. Wessel, and T.M. Yelbuz. 2010. How does the tubular embryonic heart work? Looking for the physical mechanism generating unidirectional blood flow in the valveless embryonic heart tube. *Dev Dyn* 239:1035–1046.

Midtgård, U. 1982. Patterns in the blood vascular system in the pelvic limb of birds. *J Zool* 196:545–567.

Mohlhenrich, E.R. and R.L. Mueller. 2016. Genetic drift and mutational hazard in the evolution of salamander genomic gigantism. *Evolution* 70:2865–2878.

Monahan-Earley R., A.M. Dvorak, and W.C. Aird. 2013. Evolutionary origins of the blood vascular system and endothelium. *J Thromb Hemeost* 11:46–66

Morbiducci, U., R. Ponzini, G. Rizzo, M. Cadioli, A. Esposito, F. De Cobelli, A. Del Maschio, F.M. Montecvecchi, and A. Redaelli. 2009. In vivo quantification of helical blood flow in human aorta by time-resolved three-dimensional cine phase contrast magnetic resonance imaging. *Ann Biomed Eng* 37:516–531.

Noble, D. 2024. It's time to admit that genes are not the blueprint for life. *Nature* 626:254–255.

Nordlund, T.M. and P.M. Hoffmann. 2019. *Quantitative Understanding of Biosystems: An Introduction to Biophysics*, 2nd edn. CRC Press, Florida.

Odling-Smee, F.J., K.N. Laland, and M.W. Feldman. 1996. Niche construction. *Am Nat* 147:641–648.

Okazaki, M., N. Maeda, and T. Shiga, T. 1987. Effects of an inhomogeneous magnetic field on flowing erythrocytes. *Eur Biophys J* 14:139–145.

Pauling L. and C.D. Coryell. 1936. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proc Natl Acad Sci USA* 22:210–216.

Paulissen, S.M., D.M. Castranova, S.M. Krispin, M.C. Burns, J. Menéndez, J. Torres-Vázquez, and B.M. Weinstein. 2022. Anatomy and development of the pectoral fin vascular network in the zebrafish. *Development* 149, dev199676 . <https://doi.org/10.1242/dev.199676>

Pettigrew, J.B. 1864. On the arrangement of the muscular fibres in the ventricles of the vertebrate heart, with physiological remarks. *Philos Trans R Soc Lond* 154:445–500.

Planck, M. 1901. Über das gesetz der energieverteilung im normalspektrum (On the law of the energy distribution in the normal spectrum). *Ann Phys* 309:553–563.

Poelmann, R.E., L.J. Wisse, R. Vicente-Steijn, M.A.G. de Bakker, F.J. Vonk, T. Hirasawa, S. Kuratani, and M.K. Richardson. 2017. Outflow tract septation and the aortic arch system in reptiles: lessons for understanding the mammalian heart. *EvoDevo* 8. <https://doi.org/10.1186/s13227-017-0072-z>

- Poopalasundaram, S., J. Richardson, A. Scott , A. Donovan , K. Liu, and A. Graham. 2019. Diminution of pharyngeal segmentation and the evolution of the amniotes. *Zool Lett* 5:6
- Raff, R.A. 2012. *The shape of life: Genes, development, and the evolution of animal form.* University of Chicago Press, Chicago.
- Rashid, D.J. K. Surya , L.M. Chiappe, N. Carroll, K.L. Garrett, B. Varghese , A. Bailleul , J.K. O'Connor, S.C. Chapman, and J.R. Horner. 2018. Avian tail ontogeny, pygostyle formation, and interpretation of juvenile Mesozoic specimens. *Sci Rep* 8:9014.
- Rollema, H.S, S.H. de Bruin, L.H. Janssen and G.A. and van Os. 1975. The effect of potassium chloride on the Bohr effect of human hemoglobin. *J Biol Chem* 250:1333–1339.
- Sans-Coma, V., B. Pozo-Vilumbrales, M.C. Fernández, M.Á. López-Unzu, M.T.Soto-Navarrete, A.C. Durán, J.M. Arqué, and B. Fernández. 2022. The medical versus zoological concept of outflow tract valves of the vertebrate heart. *J Cardiovasc Dev Dis* 9:318.
- Saremi, F., D. Sánchez-Quintana, S. Mori, H. Muresian, D.E. Spicer, C. Hassani, and R.H. Anderson. 2017. Fibrous skeleton of the heart: anatomic overview and evaluation of pathologic conditions with CT and MR imaging. *RadioGraphics* 37:1330–1351.
- Satchell, G.H. 1991. *Physiology and Form of Fish Circulation.* Cambridge University Press..
- Shapiro, J.A. How life changes itself: the read-write (RW) genome. 2013. *Phys Life Rev* 10:287–323.
- Sizarov, A. W.H. Lamers, T.J. Mohun, N.A. Brown, R.H. Anderson, and A.F. Moorman. 2012. Three-dimensional and molecular analysis of the arterial pole of the developing human heart. *J*

Anat 220:336–349.

Soubry, A., C. Hoyo, R.L. Jirtle. and S.K. Murphy. 2014. A paternal environmental legacy: evidence for epigenetic inheritance through the male germ line. *BioEssays* 36:359–371.

Taylor E.N., L.M. Diele-Viegas, E.J. Gangloff, J.M. Hall, B. Halpern, M.D. Massey, R. Rödder, N. Rollinson, S. Spears, B.J. Sun, and R.S. Telemeco. 2021. The thermal ecology and physiology of reptiles and amphibians: A user's guide. *J Exp Zool A Ecol Integr Physiol* 335:13-44.

Tanaka, M., T. Sakamoto, S. Sugawara, H. Nakajima, T. Kameyama, Y. Katahira, S. Ohtsuki, and H. Kanai. 2010. Spiral systolic blood flow in the ascending aorta and aortic arch analyzed by echo-dynamography. *J Cardiol* 56:97–110.

Tenforde T.S. 2005. Magnetically induced electric fields and currents in the circulatory system. *Prog Biophys Mol Biol* 87:279–288

Thompson, D.W. 1942. *On Growth and Form*, 2nd edn. Cambridge University Press, Cambridge.

Tzirtzilakis, E.E. 2005. A mathematical model for blood flow in a magnetic field. *Phys Fluids* 17:077103. <https://doi.org/10.1063/1.1992641>

van Praagh, R. 2016. Definition of conotruncal anomalies. Pp 1-25 in F. Lacour-Gayet., E. Bove, V. Hraška, V. Morell and T. Spray, eds. *Surgery of Conotruncal Anomalies*. Springer, Cham.

Victor, S., V.M. Nayak and R. Rajasingh. 1999. Evolution of the ventricles. *Tex Heart Inst J* 26:168–175

Wang, J., J. Liang, Y. Wang, and H. Tao. 2024. Evidence for the presence of the fifth pharyngeal arch during chick development. *Int J Morphol* 42:1322–1327.

Williams, G.C. and R.M. Nesse. The dawn of Darwinian medicine. 1991. *Q Rev Biol* 66:1-22.

Wolpert, L. 1969. Positional information and the spatial pattern of cellular differentiation. *J Theor Biol* 25:1–47.

Yoshida, H., F.J. Manasek, and R.A. Arcilla. 1983. Intracardiac flow patterns in early embryonic life: a reexamination. *Circ. Res.* 53:363–371.

Zhu, M. 2026. Re-examining the role of oxygen in mammalian embryogenesis. *Development* 153: dev205661 <https://doi.org/10.1242/dev.205661>

Ziermann, J.M. and R. Diogo. 2014. Cranial muscle development in frogs with different developmental modes: Direct development versus biphasic development. *J Morph* 275:398-413.