Homeostatic regulation in physiological systems: A versatile Ansatz

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Abstract

A generic modelling formalism is described for homeostatic dynamics in physiological systems. The method is particularly suited where the peripheral, physiological system itself is well-characterised, but the details of the central, regulatory component (the nervous and endocrine systems) have not necessarily been characterised in full detail. The method is applied to temperature regulation in Cardinalis cardinalis, C. sinuatus, Lepus alleni, and Passer domesticus, and furthermore to hydromineral regulation in Lymnaea stagnalis. These case studies demonstrate that the method allows a comprehensive analysis and integration of the available data and is capable of furnishing physiologically relevant predictions. We discuss the method in relation to optimal control theory as well as more conventional modelling approaches.

Keywords
Homeostasis; Cardinalis cardinalis; Lymnaea stagnalis; Body temperature; Water and salt balance

1. Introduction

A common situation in the study of homeostasis at the whole-organism level can be schematically represented in the language of dynamical systems:

\[ \dot{x} = f(x, z); \]

\[ \dot{z} = g(x, z), \]
where \( \mathbf{x} \in \mathbb{R}^n \) denotes the constitutive physiological state, e.g. blood glucose concentration, body temperature, \( \text{pH} \) of the blood, glycogen density in the liver, and so on. The dimensionality of the state, \( n \), may be low (e.g. \( n = 1 \), \( \mathbf{x} \) is a scalar \( x \)) or high, depending on the level of detail and spatial structuring that we wish to account for in the theoretical treatment. The function \( f \) represents the dynamics of \( \mathbf{x} \). Basic principles of physics, along with ingenious physiological measurements, often go a long way to the specification of the dynamics \( f \). To close the dynamics, additional state variables are almost always required; let us call these *actuator variables*. These are collected in the vector \( \mathbf{z} \in \mathbb{R}^m \). This portion of the state can be regarded as the regulatory component of the homeostatic feedback loop (see refs. [19], [22], and [23] for accounts of physiological control and homeostasis). Examples of actuator variables include blood plasma concentrations of the relevant hormones, levels of enzymes and transporters in the tissues that carry out physiological fluxes and transformations, as well as membrane potentials of the relevant neurones and endocrine cells. The dynamics of \( \mathbf{z} \) is represented by \( g \). This partitioning of the state into two components \( \mathbf{x} \) and \( \mathbf{z} \) is somewhat arbitrary (after all, neuroendocrinology is physiology *sensu lato*) and much might in fact be known about the latter—perhaps we should call the components ‘accessible state’ and ‘inaccessible state’ but ‘physiological/constitutive’ and ‘regulatory/actuator’ correspond more closely to the conventions of the physiological literature.

The problem we consider in this paper is how to model the regulatory/actuator component. From an experimental point of view, physiologists often have much readier access to \( \mathbf{x} \) as compared to \( \mathbf{z} \), and where it comes to the specification of \( f \), modellers can rely on basic principles to a much greater extent as compared to \( g \). Specification of \( \mathbf{x} \) and its dynamics may be regarded as almost routine [3] and [16], especially when compared to the much harder problem of doing the same for \( \mathbf{z} \) and its dynamics. One approach is to formulate plausible empirical relationships, which is feasible when a wealth of supporting data is available, as is the case for the human energy metabolism system (e.g., refs. [10], [25]). Another approach is to close dynamics at the level of \( \mathbf{x} \) and \( f \), for instance by appealing to generality arguments (e.g., ref. [17]), an approach which may be more suitable when the theory is intended to give a good approximation over a wide range of species.

Here, we explore a third option. The idea is to posit a potential function \( V(\mathbf{x}, \mathbf{z}) \) and let the dynamics of \( \mathbf{z} \) be determined by the gradients of this function, as follows:

\[
\dot{\mathbf{z}} = -\kappa(\mathbf{x}, \mathbf{z}) \cdot \frac{\partial}{\partial \mathbf{x}} V(\mathbf{x}, \mathbf{z}) - \mu \cdot \frac{\partial}{\partial \mathbf{z}} V(\mathbf{x}, \mathbf{z}) \tag{3}
\]

where \( \frac{\partial}{\partial \mathbf{x}} V \) denotes a vector in \( \mathbb{R}^n \) the components of which are \( \frac{\partial V}{\partial x_i} \) for \( i = 1, \ldots, n \), and \( \frac{\partial}{\partial \mathbf{z}} V \) denotes a vector in \( \mathbb{R}^m \) whose components are \( \frac{\partial V}{\partial z_j} \) for \( j = 1, \ldots, m \), \( \mu \) is a positive constant, and \( \kappa \) is an \( m \times n \) matrix that satisfies the sign condition

\[
\text{sgn}(\kappa_{ij}) = \text{sgn}(\frac{\partial f_i}{\partial z_j}) \tag{4}
\]

where \( \dot{\mathbf{z}} = \mathbf{f}(\mathbf{x}, \mathbf{z}) \). In other words, \( \kappa \) must agree sign-wise with the transpose of the Jacobian matrix of the constitutive dynamics \( f \). The model thus obtained is non-linear in general, barring special choices for \( \kappa \) and \( V \).

It is probably clear that Eqs. (3) and (4), which we shall call the *physiological potential Ansatz*, will work (they generalise the familiar concept of integrating control, e.g., ref. [14]). We propose that this Ansatz is a suitable generic model which can serve as default in those cases where data to support the classical approaches are scarce or altogether lacking. To demonstrate that it ties in well with the way physiologists formulate functional ideas about homeostatic systems, and that it provides a good template for complex systems in which there are several interlocking control loops, we present two case studies: in Section 2 we consider body temperature control in homeothermic (‘warm-blooded’) vertebrates and in Section 3 we study the interactions between water balance...
and salt balance in an aquatic invertebrate. Finally, in Section 4, we consider how our approach may complement other approaches.

2. Temperature homeostasis in homeothermic vertebrates

If an animal’s body is to maintain a constant core temperature, heat must be lost from the body at the same rate as it is being produced by metabolic activity. This can be achieved in three ways: conduction coupled to convection, radiation, and evaporation of water [23]. The first two processes require that the animal’s environment, or some part of it, be at a lower temperature than the surface of the body.

The physics of heat transfer between the body and the environment involves several effects. Conductive heat loss is proportional to the temperature, so that the net heat gain to the body is proportional to the temperature difference $T_0 - T_c$ where $T_0$ is the ambient temperature and $T_c$ is the core temperature. The proportionality constant depends not only on the conductivity of the skin and the fur or scales covering the integument, but also on the convection patterns in the fluid (air or water) surrounding the animal, which are themselves determined by the shape of the animal’s body and by prevailing wind conditions [20].

Heat transfer by radiation is proportional to the fourth-power of the temperature of the source [19]. The proportionality involves the emissivity of the source’s surface, which is different at various wavelengths; for instance, the animal emits mostly in the infrared and thus coloration in the visible spectrum is irrelevant, animals generally being highly emissive—black—in the infrared region whereas the sun emits half its energy in the visible range, so the colour of the animal does influence the heat gain via this route [23]. Moreover, radiation reaches the animal not only from the sun directly, but also from the ground and from the sky, the latter being diffracted solar radiation [20].

Schmidt-Nielsen ([23]) gives a compelling argument to the effect that conductive and radiative heat transfer can be summarised in a single term $C(T_0 - T_c)$ where the factor $C$ combines all the constants that enter into the transfer equations. Replacing the fourth power by a simple proportionality is warranted since the physiological range of temperatures, from $\sim 270$ K to $\sim 310$ K, is relatively narrow. This is the Scholander–Irving model [19] and the constant $C$ is known as the conductance [11].

Evaporative heat loss exploits the latent heat of vaporization of water [23], which is considerable and allows the animal to shed large amounts of heat using relatively small amounts of water. Even though the heat of vaporization does depend slightly on the ambient temperature, the heat loss is usually taken to be proportional to the amount of water committed to heat loss via sweating, panting, or both [23].

Core body heat content $Q$ and core body temperature $T_c$ are related by the formula $Q = \gamma T_c$ where $\gamma$ is the effective heat capacity of the tissues. If the animal generates metabolic heat at a rate $\Phi_{mb} > 0$, and loses heat through an evaporative term $\Phi_{ev} \geq 0$, the heat balance can be represented by the following ordinary differential equation:

$$\dot{Q} = \Phi_{mb} + C \left( T_0 - \frac{Q}{\gamma} \right) - \Phi_{ev}. \quad (5)$$

The metabolic term $\Phi_{mb}$ can be further decomposed into a contribution from muscular activity and a contribution from metabolic processes. The former comprises both the physical exercise that is an unavoidable part of the animal’s activities and shivering thermogenesis, whereas the latter comprises a basal term plus a non-shivering thermogenesis (decoupling) term.

2.1. Basic single-control treatment

To put Eq. (5) in the general form of Eq. (1), we define a dimensionless constitutive state variable $x$: 
This is the core temperature relative to the physiological optimum temperature \( T_{\text{opt}} \) (no teleological connotations are implied by the term ‘optimal’; this is simply the point where the physiological potential function has its global minimum). Let us also define a dimensionless regulatory state variable \( z \):

\[
\bar{z} = \frac{\Phi_{\text{BMR}} - \Phi_{\text{BMR}}}{\Phi_{\text{BMR}}},
\]

where \( \Phi_{\text{BMR}} \) denotes the basal metabolic rate (BMR). Finally, we express time in units of 
\[
\gamma T_{\text{opt}}/\Phi_{\text{BMR}}
\]
and define a scaled ambient temperature as 
\[
\xi = T_{0}/T_{\text{opt}}.
\]
The dynamics can then be written as follows:

\[
\dot{x} = C^*(\xi - x) + z \tag{8}
\]

\[
\dot{z} = -\kappa V_x(x, z) - \mu V_z(x, z) \tag{9}
\]

where \( \kappa > 0 \) in accordance with the sign condition, and \( C^* = CT_{\text{opt}}/\Phi_{\text{BMR}} \). For a typical mammal, the heat production corresponding to \( \Phi_{\text{BMR}} \) balances a heat loss rate across a gradient of 4 K [23], which implies \( \Phi_{\text{BMR}}/C = 4 \, \text{K} \), and \( T_{\text{opt}} = 310 \, \text{K} \), so that \( C^* = 310/4 = 77.5 \).

The physiological potential function \( V \) can be formulated in several ways. Perhaps the simplest method is to decompose \( V \) as a sum of terms, each of which depends on one state variable. Thus we have a term \( \propto (x - 1)^2 \) to express the drive towards maintaining the optimum \( x = 1 \). In addition, for \( z \) we have to include a ‘stop’ term of the type shown in Fig. 1. These terms are added together to yield the function \( V \).

During strenuous muscular activity, the metabolic rate can become ten times higher than the resting level [7], which implies \( z_{\text{max}} = 10 \) (this figure is sensible for animals of the...
size under consideration; $z_{\text{max}}$ can be up to $\sim 36$ in larger birds and mammals, cf. refs. [6, 9]). Evaporative heat loss is capable of matching a heat load of about ten times the BMR [23]; accordingly, let us put $z_{\text{min}} = -9$.

A steady state in which the physiological optimum $x = 1$ is maintained must satisfy the following condition:

$$z = C^* (1 - \xi).$$

Since $z \in [z_{\text{min}}, z_{\text{max}}]$ it follows that this condition can only be satisfied at steady state when

$$\xi_{\text{lo}} \leq \xi \leq \xi_{\text{hi}} \quad \text{where} \quad \xi_{\text{lo}} = 1 - \frac{z_{\text{max}}}{C^*} \quad \text{and} \quad \xi_{\text{hi}} = 1 - \frac{z_{\text{min}}}{C^*}.$$

For the values given, this works out as $\xi_{\text{lo}} \approx 0.871$, corresponding to 270 K or $\sim -3^\circ \text{C}$ and $\xi_{\text{hi}} \approx 1.116$, corresponding to 346 K or $\sim 73^\circ \text{C}$. These values are reasonable, with the following caveats. First, mammals adapted to polar conditions have $C$-values that can be a third of those pertaining to typical mammals adapted to a moderate climate [24]. This takes the lower limit down to $\sim -80^\circ \text{C}$. Second, these limits represent outer tolerance limits that cannot be sustained for prolonged periods of time. The lower limit presupposes maximal muscular activity (shivering thermogenesis) which would soon deplete energy reserves. Furthermore, the upper limit corresponds to a water loss that is equivalent to about a quarter of the blood volume per hour, and the animal would rapidly dehydrate.

Simulations of the dynamics described by Eqs. (8) and (9) are shown in Fig. 2 for various values of the regulatory rate parameter $\kappa$, which can be interpreted as a 'reactivity' parameter. If we set the latter to higher values, we find that the system is better able to keep $x$ close to the optimum 1 under step-wise perturbations in the scaled ambient temperature $\xi$. The general trajectory of the regulated state variable $v$ is a rapid excursion towards either $z_{\text{min}}$ or $z_{\text{max}}$, followed by a damped oscillation about the final values, as indicated by the local analysis in Section 4.1.

![Fig. 2. Example of the dynamics described by Eqs. (8) and (9) for various values of the regulatory rate parameter $\kappa$ as indicated. The top shows the scaled core body temperature $x$; the bottom row shows the regulated heat flux $z$. Scaling is explained in the text. At times $t = 0.05, 0.2$, and 0.4 the scaled external temperature $\xi$ undergoes step changes, from 1 initially to 0.89, then to 1.1, and finally to 0.99. The term $V_z$ was as indicated in Fig. 1. In the simulations shown, $\epsilon$ was set to 0.0005 and $\mu = 1$.](image)

2.2. Advanced multiple-control treatment

Eqs. (8) and (9) are a minimal representation of temperature control which, although it has the virtue of illustrating the basic idea of a homeostatic control loop, lumps together two processes that may be controlled in different ways (e.g., with different reactivities). Moreover, the conductance can be modulated by the animal: it may fluff its feathers or raise its fur, change its body shape from spherical to elongated (domestic cats routinely provide dramatic demonstrations of this fact), and regulate the blood flow to appendages.
(ears, flippers, and the like). Accordingly, we represent the evaporative heat loss term \( \Phi_{ev}/\Phi_{BMR} \) as a second actuator variable \( z_2 \geq 0 \) and replace \( C^* \) by a third actuator variable \( z_3 > 0 \). The metabolic rate is now analysed as follows:

\[
\frac{\Phi_{mb}}{\Phi_{RMR}} = 1 + z_1 + \alpha z_2
\]

where \( z_1 \geq 0 \) represents additional thermogenesis. The term \( \alpha z_2 \) with \( \alpha \in (0, 1] \) (a dimensionless constant) is introduced to account for the additional muscular action required to achieve evaporative heat loss (such as panting and pumping blood along the sweat-moistened skin). The following equations describe this refined model:

\[
\dot{x} = 1 + z_1 - (1 - \alpha) z_2 + z_1 (\xi - x)
\]

\[
\dot{z}_1 = -\kappa_1 V_x(x, z) - \mu_1 V_{z_1}(x, z)
\]

\[
\dot{z}_2 = -\kappa_2 V_x(x, z) - \mu_2 V_{z_2}(x, z)
\]

\[
\dot{z}_3 = -\kappa_3 V_x(x, z) - \mu_3 V_{z_3}(x, z).
\]

The condition \( \alpha < 1 \) is imposed because, if \( \alpha \) were to exceed 1, the muscular action involved in evaporative heat loss would generate more heat than is shed via this route. The sign condition now yields:

\[
\kappa_1 > 0; \quad \kappa_2 < 0; \quad \text{sgn}(\kappa_3) = \text{sgn}(\xi - x).
\]

The last of these suggests that the animal would require sensors in the skin to determine the direction of the temperature gradient; the first two conditions only require internal sensors that monitor the core temperature.

Again we compose the physiological potential function as a sum of separate terms corresponding to the state variables, with a quadratic term for \( x \). We take into account the additional physiological potential associated with energy expenditure, which is expressed for \( z_1 \) and \( z_2 \) by the functions shown in Fig. 5. The minima in these functions at \( z_i = z_{i,\text{mid}} \) close to the minimal values contribute to a tendency to keep energy expenditure minimal. The 'stops' for \( z_3 \) are modelled as in Fig. 1.

The steady-state behaviour is shown in Fig. 3 for Northern Cardinal Cardinalis cardinalis (which was identified by Dawson (8) as Richmondena cardinalis, its then-current binomial nomenclature). This passerine bird has the impressive ability to maintain its body temperature over a range of \( \sim 55 \text{ K} \). The graph of the total metabolic rate, Eq. (11), versus ambient temperature is divided into three regions: a central region where both \( z_1 \) and \( z_2 \) are minimal and the animal regulates the heat balance by matching the basal metabolic heat production against the conductance \( (z_3) \); a region at lower ambient temperatures where additional heat is produced \( (z_1 > 0) \) to maintain the heat balance at minimal conductance; and a region at higher ambient temperatures where heat is actively being dumped by means of evaporation \( (z_2 > 0) \). The middle region is known as the thermoneutral zone. These phenomena emerge naturally in the context of our Ansatz, which combines constitutive equations expressing basic physics with a physiological potential encoding regulatory drives.
Temperature regulation in the Northern Cardinal *Cardinalis cardinalis*, at steady state acclimatised to different ambient temperatures. Data from Dawson [8], recalculated for a 40 g bird, assuming that the production of 1 l O$_2$ is equivalent to 20.112 kJ; solid lines represent theoretical results. Left: metabolic rate as given by Eq. (11). Middle top: heat production over basal metabolic rate as a dimensionless multiple $z_1$ of the basal metabolic rate ($\Phi_{BMR}$). Middle bottom: non-dimensionalised conductance assuming that the evaporation of 1 g H$_2$O is equivalent to the dissipation of 2.427 kJ. Right: water evaporation rate. Parameters were set to the following values: $\alpha=0.318; z_{1,\text{min}}=0; z_{1,\text{mid}}=0.231; z_{1,\text{max}}=5.244; z_{2,\text{min}}=0; z_{2,\text{mid}}=0.189; z_{2,\text{max}}=2.164; z_{3,\text{min}}=13.95; z_{3,\text{max}}=27.85; \mu_1=1.518; \mu_2=4.363; \mu_3=1; |\kappa_1|=|\kappa_2|=10^4; |\kappa_3|=10^6; \epsilon=0.05$. The scaled model was linked to dimensional (unit-bearing) data via $T_{opt}=316$ K and $\Phi_{BMR}=1.697$ kJ/h.

The steady-state response of the scaled conductance $z_3$ shows a gradual increase from the minimum to the maximum value across the thermoneutral zone. The data fit suggests that the maximum conductance is twice that of the minimum. This prediction is in accordance with the finding by Herreid and Kessel ([11]) that heat loss in defeathered birds is two to three times higher than in intact birds. Not only does the air trapped under the feathers create an insulating effect, the animals can modulate the passive conductance by adjusting the 'set' of the feathers and by redirecting blood flow to appendages uncovered by feathers [20].

A direct comparison between $z_3/z_{3,\text{min}}$ as predicted from the Dawson data [8] and as calculated by Hinds and Calder [12] from observations in *C. cardinalis* (the Arizona population) and the closely related species *C. sinuatus* (Desert cardinal or Pyrrhuloxia) is shown in Fig. 4. The agreement is satisfactory (the parameter values were adjusted to the Dawson data [8] so the curve shown is a prediction relative to this data set) and confirms the factor $\sim 2$ between minimum and maximum conductance.

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**Fig. 4.**

Normalised conductance $z_3/z_{3,\text{min}}$ as a function of ambient temperature. Data recalculated from Hinds and Calder ([12]), who reported the conductance $C$ as the 'dry heat transfer coefficient' for the Arizona population of the Northern Cardinal *Cardinalis cardinalis* (circles) and the Desert Cardinal *C. sinuatus* (triangles). The solid curve is the prediction from the fit to the data from Dawson ([8]). All parameter values as in **Fig. 3.**
Fig. 5.
Terms added to the physiological potential function $V$ to implement 'stops' to constrain a controlled state variable $z_1$ (scaled heat production, solid line) and $z_2$ (scaled evaporation, dashed line). The functions are asymptotically steep at $z_{i,\text{min}}$ and $z_{i,\text{max}}$ and have a minimum at $z_{i,\text{mid}}$ ($i=1,2$). This expresses the need to keep energetic expenditure as low as possible. Curves can be shown on a common scale since the $z$-variables are dimensionless after scaling. Parameter values as in Fig. 3.

The theoretical prediction has an interesting feature, namely the discontinuous step down (at steady state) to the minimum value as the ambient temperature exceeds the body temperature. This is a direct consequence of the sign condition for $\kappa_3$ as displayed in (16). A switch back to minimal conductance makes intuitive sense: when the heat load comes from passive conductance, minimising the flux minimises the amount of heat that must be shed.

Whereas the data obtained by Hinds and Calder [12] do provide some support for this behaviour at ambient temperatures higher than body temperature, more conclusive evidence is provided by data in the Antelope Jackrabbit $Lepus alleni$ (a North-American species of hare) from Dawson and Schmidt-Nielsen [7]. The linear regression lines to the steady-state response of $z_2$ (evaporative heat loss) show a decrease in slope, which is predicted by the theory, which states that this slope is proportional to $z_2$ (Fig. 6). This phenomenon cannot be observed in the Cardinal data set, Fig. 3, simply because ambient temperatures higher than the body temperature were not attained in this study.

Fig. 6.
Cooling by evaporation as a fraction of basal metabolic rate ($z_2 = \Phi_{ev}/\Phi_{BMR}$) in the Antelope Jackrabbit (desert hare) $Lepus alleni$ as a function of the temperature difference between the environment and the body core. Data from Dawson and Schmidt-Nielsen ([7]). The lines are separate independent linear regressions against the data below and above the point of temperature equality, respectively.
The values of $T_{opt}$ and $\Phi_{BMR}$ are subject to diurnal fluctuations. As a result, the steady-state response during the day differs from that at night, as is shown in Fig. 7, which compares data obtained in the House Sparrow \textit{(Passer domesticus)} by Hudson and Kimzey \cite{13} during day time and night time. The theoretical curves are for the same model, with the same parameter values, except that the basal metabolic rate was assumed to be 52.38\% lower at night, and the temperature set point was assumed to be 3.16\% lower at night (in terms of absolute temperature).

![Figure 7. Temperature regulation in the House Sparrow \textit{Passer domesticus}, at steady state acclimatised to different ambient temperatures. Data from Hudson and Kimzey \cite{13}, recalculated for a 35 g bird, assuming that the production of 1 l $O_2$ is equivalent to 20.112 kJ; solid lines represent theoretical result based on the metabolic rate as predicted by Eq. (11). Data obtained during daytime are indicated as circles, data obtained at night are indicated as triangles. Parameters were set to the following values: $\alpha=0.235$; $z_{1,\min}=0$; $z_{1,\text{mid}}=0.344$; $z_{1,\max}=3.075$; $z_{2,\min}=0$; $z_{2,\text{mid}}=0.178$; $z_{2,\max}=17.42$; $z_{3,\min}=18.51$; $z_{3,\max}=48.15$; $\mu_1=1.512$; $\mu_2=6.049$; $\mu_3=1$; $|\kappa_1|=|\kappa_2|=104$; $|\kappa_3|=106$; $\epsilon=0.05$. The scaled model was linked to unit-bearing data via $T_{opt}=316$ K and $\Phi_{BMR}=1.786$ kJ/h. At night, the basal metabolic rate was assumed to be 52.38\% lower and the temperature set point was assumed to be 3.16\% lower.]

3. Hydromineral metabolism in the pond snail, \textit{Lymnaea stagnalis}

In the analysis of temperature homeostasis, the 'constitutive' state $x$ (i.e., the 'physiological plant') was one-dimensional, while its dynamics was governed by actuator variables (collected in the vector $z$). The modularity of living systems implies that homeostatic loops will often operate more or less independently in parallel, and can each be analysed independently using a scalar constitutive state. However, there are also cases where two or more such variables are enmeshed. As a good example of such a system we shall study the salt and water metabolism of the pulmonate freshwater snail, \textit{Lymnaea stagnalis} (the Great Pond Snail), an air-breathing aquatic gastropod which is a hyperosmotic regulator \cite{18,27} and \cite{29}. This means that the animal maintains the osmolarity of its coelomic fluid at a higher value than the ambient medium, ranging from fresh water with near-zero salinity to fairly brackish water, as shown in Fig. 8; this is the \textit{homoiosmotic} range. However, as this figure also shows, at higher salinities the animal behaves as an osmoconformer, with the coelomic fluid regulated at nearly the same value as the surrounding medium; this is the \textit{poikilosmotic} range.
Fig. 8.
Relationship between external and haemolymph sodium concentrations in *Lymnaea stagnalis* acclimatised to different external salinities. Data from De With and Van der Schors ([34]). Solid line shows the model prediction. Parameters were set to the following values: \( \omega = 1.5; \chi_0 = 0.73; \chi = 0.002; \eta = 2.235; z_1,\text{min} = 0.318; z_1,\text{mid} = 0.637; z_1,\text{max} = 0.701; z_2,\text{min} = 0; z_2,\text{max} = 2.936; z_3,\text{min} = 0; z_3,\text{max} = 1.874; \mu_1 = 10^{-3}; \mu_2 = 1; \mu_3 = 1; \kappa_1 = 0.1; \kappa_2 = 10; \kappa_3 = -20; \kappa_4 = -2000; \kappa_5 = 100; \epsilon = 0.25 \). The scaled model was linked to unit-bearing data via \( [Na^+]_{opt} = 51 \text{ mM} \) and 
\[
H_{cp} P_{H_2O} [Na^+]_{opt}^{-1} = 30_{h}.
\]

We first express the physiological processes and then will non-dimensionalise the equations to bring them into the \((x, z)\) formalism. The pond snail has an *open circulation* lacking capillaries but having major vessels that pump an interstitial fluid around the body; this haemolymph enters interstitial cavities [15]. The dynamics of \( H \), the haemolymph volume, is as follows:

\[
\dot{H} = P_{H_2O}(\eta [Na^+]_h - 2[Na^+]_ex) + \Phi_{oral} - \Phi_{excr}. \tag{17}
\]

The first term represents passive exchange of water due to osmosis: the osmotic value of the ambient medium can be taken to be twice that of the ambient sodium concentration \([Na^+]_ex\). The osmotic value of the haemolymph is represented here as \( \eta [Na^+]_h \) where \([Na^+]_h\) is the haemolymph sodium concentration. Data from De With ([29]) and De With and Van der Schors ([34]) indicate that \( \eta \approx 2.235 \). The factor \( P_{H_2O} \) represents the total water permeability of the skin. The final two terms in Eq. (17) represent active movements of water: \( \Phi_{oral} \) represents oral water ingestion, which has been shown to make a major contribution to the water balance [30] and the term \( \Phi_{excr} \) represents the excretion of water via the kidney; the urine is derived from an ultrafiltrate which is thought to be produced in the heart [1]; the pro-urine being drained from the pericardial cavity without interfering with cardiac refilling [2].

Total sodium content of the haemolymph is represented by the product \( H [Na^+]_h \). Its dynamic balance sheet works out as follows:

\[
\frac{d}{dt}(H[Na^+]_h) = P_{Na}([Na^+]_ex - [Na^+]_h) + \Phi_{oral}[Na^+]_ex
\]

\[
-\Phi_{excr}[Na^+]_{urine} + \frac{[Na^+]_ex}{K_m + [Na^+]_ex} \nu_{max}
\]

where the first term again represents passive exchange by diffusion of sodium ions through the skin, thought to make a quantitatively minor contribution to the sodium...
balance [32], and the final three terms are related to active uptake or loss of sodium. In particular, \( \Phi_{\text{oral}}[\text{Na}^+]_{\text{ex}} \) is sodium uptake concomitant with the ingestion of water, \( \Phi_{\text{excr}}[\text{Na}^+]_{\text{urine}} \) is the loss of sodium via the urine, and \( V_{\text{max}}/(1+K_m/[\text{Na}^+]_{\text{ex}}) \) represents an active transport of sodium ions by specialised cells in the skin. The latter quantity \( K_m \) is a saturation constant, estimated as \( K_m \approx 0.1 \text{ mM} \) by De With and Van der Schors ([33]). The maximum uptake rate \( V_{\text{max}} \) is known to be under neuroendocrine control; the so-called Yellow Cells in the central nervous system secrete a hormone, the sodium influx-stimulating peptide, that modulates \( V_{\text{max}} \) [35] and [36]. These cells are most active at low values of \([\text{Na}^+]_{\text{ex}}\) [26].

De With and Van der Schors ([34]) propose the following form for the urine sodium concentration:

\[
[\text{Na}^+]_{\text{urine}} = [\text{Na}^+]_h - [\text{Na}^+]_o \quad \text{when} \quad [\text{Na}^+]_h > [\text{Na}^+]_o \quad \text{and} \quad [\text{Na}^+]_{\text{urine}} = 0 \quad \text{otherwise},
\]

where \([\text{Na}^+]_o\) is a threshold value estimated by these authors as 38 mM. The existence of such a threshold is believed to be associated with the existence of a maximum capacity for renal absorption of the ions [23].

To scale the equations, we introduce \( H_{\text{op}} \) and \([\text{Na}^+]_{\text{op}}\) as the ‘optima’ (i.e. the values where the physiological potential function attains its minimum) and adopt these as the natural units:

\[
x_1 = \frac{H}{H_{\text{op}}} \quad \text{and} \quad x_2 = \frac{[\text{Na}^+]_h}{[\text{Na}^+]_{\text{op}}},
\]

The quantity \( H_{\text{op}} [H_{\text{H}_2\text{O}} [\text{Na}^+]_{\text{op}}]^{-1} \) is chosen as unit of time. The actuator variables can then be defined as follows:

\[
z_1 = \frac{\Phi_{\text{oral}}}{P_{\text{H}_2\text{O}} [\text{Na}^+]_{\text{op}}}; \quad z_2 = \frac{\Phi_{\text{excr}}}{P_{\text{H}_2\text{O}} [\text{Na}^+]_{\text{op}}}; \quad z_3 = \frac{V_{\text{max}}}{P_{\text{H}_2\text{O}} ([\text{Na}^+]_{\text{op}})^2}.
\]

Finally, the parameters are scaled as follows:

\[
\sigma = \frac{P_{\text{Na}}}{P_{\text{H}_2\text{O}} [\text{Na}^+]_{\text{op}}}; \quad \gamma = \frac{[\text{Na}^+]_o}{[\text{Na}^+]_{\text{op}}}; \quad \kappa = \frac{K_m}{[\text{Na}^+]_{\text{op}}};
\]

\[
\xi = \frac{[\text{Na}^+]_{\text{ex}}}{[\text{Na}^+]_{\text{op}}}.
\]

The scaled system is as follows:

\[
\dot{x}_1 = \eta x_2 - 2 \xi + z_1 - z_2
\]

\[
\dot{x}_2 = \frac{\sigma (\xi - x_2)}{x_1} + \frac{\xi z_1}{x_1} - \max\{0, x_2 - \gamma \} z_2
\]

\[
+ \frac{z_3}{1 + \kappa / \xi} x_1 - \frac{\dot{x}_1}{x_1} x_2
\]

\[
\dot{z}_1 = -\kappa_{11} V_{x_1}(x, z) - \kappa_{12} V_{x_2}(x, z) - \mu_1 V_{x_1}(x, z)
\]

\[
\dot{z}_2 = -\kappa_{21} V_{x_1}(x, z) - \kappa_{22} V_{x_2}(x, z) - \mu_2 V_{x_2}(x, z)
\]

\[
\dot{z}_3 = -\kappa_{31} V_{x_1}(x, z) - \kappa_{32} V_{x_2}(x, z) - \mu_3 V_{x_3}(x, z)
\]

with the following sign structure:

\[
\kappa_{11} > 0; \quad \kappa_{12} > 0; \quad \kappa_{21} < 0; \quad \kappa_{22} = 0 \quad \text{for} \quad x_2 \leq \gamma; \quad \kappa_{22} < 0 \quad \text{for} \quad x_2 > \gamma; \quad \kappa_{31} = 0; \quad \kappa_{32} > 0.
\]

It may be seen from Eqs. (24) and (25) why volume and haemolymph salinity concentration are thoroughly intertwined: any changes in volume alter the electrolyte
concentration of salt as well, and oral water ingestion and urine production affect both volume and salinity.

The physiological potential function is formed in the usual manner, adding together a term $\propto (x_1 - 1)^2$, a term $\propto (x_2 - 1)^2$, 'stop' terms of the type shown in Fig. 1 for $z_2$ and $z_2$, and a more complex term for $z_1$ (oral water intake) as shown in Fig. 9. Unlike urine production, oral ingestion of water is not solely connected to hydromineral regulation but an inadvertent secondary effect of the animal's normal foraging behaviour. The general eco-physiological conditions define a rate of movement of the feeding apparatus appropriate to those conditions, and deviations above and below that rate incur an additional cost; this motivates the use of the form shown in Fig. 9. $L.\ stagnalis$ is a perfect volume regulator, but the animal tolerates a range of haemolymph salinities without ill effect [31]. To account for this in the model, the term in $V$ corresponding to $x_1$ was set to be $100 \times$ higher than the term corresponding to $x_2$.

![Figure 9](image)

**Term added to the physiological potential function $V$ to implement 'stops' to constrain $z_1$ (scaled oral water ingestion).** The function is asymptotically steep at $z_{1,\text{min}}$ and $z_{1,\text{max}}$ and has a minimum at $z_{1,\text{mid}}$. Parameter values as in Fig. 8.

The steady state response of $x_2$ is shown as the solid curve in Fig. 8. The accompanying steady-state response of other quantities is shown in Fig. 10. In the top-right panel of this graph, the response of the excretion rate is compared to observed rates of ultrafiltration. In assessing the agreement between theory and data, it should be borne in mind that these two quantities are not necessarily identical, since the animal is capable of water reabsorption [34] and the rate of ultrafiltration may be up to $\sim 60\%$ higher than the rate of final urine production [31]. The bottom-right panel of Fig. 8 shows the steady-state response of the haemolymph volume ($x_1$), to confirm that the animal is adequately represented as a near-perfect volume regulator.
The steady-state oral water uptake curve shown in the top-left panel of Fig. 8 shows a less marked variation than is suggested by the data. A possible explanation for this discrepancy is that oral water uptake varies considerably from moment to moment: the model is concerned with the long-time average whereas the data tend to show the mean over the period of experimental observation.

The steady-state response curve for active sodium uptake ($z_3$) is shown in the bottom-left panel of Fig. 8. It can be seen that the perfect regulation achieved over the homoiosmotic portion of the salinity steady-state curve (Fig. 8) correlates with a gradual decrease of this variable, which apparently plays a similar role to the heat conductance in the temperature control, as was discussed in Section 2. The results agree with the finding by De With et al. ([28]) that lower values of $V_{max}$ correlate with higher values of haemolymph salinity across specimens acclimatised to different ambient salinities.

In addition to steady-state observations, transient responses have also been observed in this system; these are shown in Fig. 11, together with independent theoretical predictions. The agreement is fair, although for the experiment in which animals were transferred to higher salinities, the model predicts a more rapid acclimatisation than the data would suggest. Short-term variations in oral water ingestion may here, too, be responsible for the minor anomaly.
4. Connections to other approaches

The physiological potential Ansatz is proposed here as a complement to, not a replacement for, alternative methods. Two well-established approaches warrant particular attention.

4.1. Optimal control theory

To relate the Ansatz, Eqs. (1) and (2), to classic optimal control theory [14] and [21], let us specialise to the case \( n = m = 1 \) and let us suppose that the dynamics \( f \) is such that there exists a point \((x_0, z_0)\) where we have

\[
 f_x(x_0, z_0) < 0 \quad \text{and} \quad f(x_0, z_0) = V(x_0, z_0) = V_z(x_0, z_0) = 0
\]

with \( V(x_0, z_0) \) being a global minimum. Linearising the dynamics, rescaling, and translating the point \((x_0, z_0)\) to the origin, we obtain the following form to describe the dynamics locally:

\[
 \dot{x} = -x + z. \tag{28}
\]

By the same scaling/linearisation, and assuming that \( V \) is approximately quadratic in \( x \), to leading order, around the operating point (which was formerly \((x_0, z_0)\) but brought to the origin \((0, 0)\) by scaling) we find that the Ansatz prescribes \( \dot{z} \propto -x \) (which implies that \( \dot{z} = 0 \) at the stationary point). We enquire whether the conventional optimal control approach leads to a compatible conclusion. To this end, we set

\[
 \dot{z} = u \tag{29}
\]

where \( u \) is the control input. The stationary point corresponds to the physiological optimum. Let us assume that the dynamics is confined to a sufficiently small neighbourhood of this point and compare the physiological potential Ansatz to the optimal control solution for the following problem:

\[
 J[u(\cdot)] = \int_0^{\infty} (q x^2 + u^2) dt \rightarrow \min_{u(\cdot)} \tag{30}
\]

where \( q > 0 \) is a free parameter. Of interest is the case \( q \gg 1 \), since under this assumption the term \( x^2 \), corresponding to \( V \), will dominate the cost integral \( J[u(\cdot)] \). The theory of problems of this type is well-developed [14] and states that the optimal solution assumes the following form:

\[
 u = [-0, 1] \cdot P \cdot \begin{bmatrix} x \\ z \end{bmatrix} \tag{31}
\]

where \( P \) is a symmetric matrix that satisfies a matrix-algebraic Ricatti equation:

\[
 \begin{pmatrix} q & 0 \\ 0 & 0 \end{pmatrix} + P \cdot \begin{pmatrix} -1 & 1 \\ 0 & 0 \end{pmatrix} + \begin{pmatrix} -1 & 0 \\ 0 & 0 \end{pmatrix} \cdot P = P \cdot \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix} \cdot P. \tag{32}
\]
Letting
\[
P = \begin{bmatrix}
\xi & \zeta \\
\xi & \eta
\end{bmatrix},
\]
we find that Eq. (32) reduces to three equalities, which follow from element-wise comparison of the matrices on the left and on the right in the Ricatti equation:

\[q - 2\xi = \zeta^2; \quad \xi - \zeta = \xi\eta; \quad 2\zeta = \eta^2.\]  

The solution of this system is

\[\eta = \sqrt{1 + 2\sqrt{q} - 1}; \quad \xi = (\eta^3 + \eta)/2; \quad \zeta = \eta^2/2.\]

Furthermore, Eq. (31) gives:

\[\dot{z} = -\zeta x - \eta z.\]

For \(q \gg 1\), we have \(\zeta/\eta \gg 1\), and thus the first term on the right-hand side of Eq. (36) dominates. In this sense, optimal control accords well with the Ansatz \(u \propto -x\). As for stability of the equilibrium point, the linear dynamical system (28) and (36) has characteristic polynomial

\[P(\lambda) = \lambda^2 + (1 + \eta)\lambda + \eta + \zeta = 0\]

from which it can be deduced that the stationary point at the origin is stable even when we drop the term \(-\eta z\) in Eq. (36). For large \(q\) the roots of \(P(\lambda)\) are complex.

4.2. 'Detailed' regulatory models

Next, we consider whether the Ansatz \(\dot{z} = -\kappa(x, z)V_1(x, z) - \mu V_2(x, z)\) can be compatible with detailed models that account, more or less explicitly, for the processes that effect physiological fluxes and transformations, and the neural and endocrinological systems that regulate these processes. Suppose, for the sake of the argument, that we are presented with a physiologically detailed model of the regulatory system. We imagine that this model is extremely detailed and well-documented, accommodating for instance all the afferent and efferent signals and the relevant biophysics of the neural and endocrine tissues. We will call this a 'good' model; its constituents are the state \(s \in \mathbb{R}^{m'}\) (with \(m' \in \mathbb{N}^+\) where we anticipate \(m' \gg 1\)) and dynamics \(\dot{s} = \psi(x, s)\) (Even even when the model involves PDEs, integro-differential equations, and so on, an arbitrarily precise approximation in ODEs may be constructed; the details need not detain us here.) If there are compatible biological interpretations of the variables in both representations, the detailed model can be linked to the Ansatz by a map \(h : \mathbb{R}^{m'} \mapsto \mathbb{R}^m\), such that \(z = h(s)\). The variables in \(z\) will generally be key physiological quantities so it is reasonable to assume that they have a representation in the detailed model, such that one or several (or indeed many) variables in \(s\) correspond to each of the elements of \(z\).

In order that the detailed model and the Ansatz be compatible, the 'bridge' map \(h\) must satisfy a compatibility requirement: its Jacobian matrix \(h_s\) must obey the following relationship:

\[\kappa \cdot V_x + \mu \cdot V_z = -h_s \cdot \psi\]

which follows directly by differentiating \(z = h(s)\) with respect to time. If we are given some 'good' model \(\dot{s} = \psi(x, s)\), Eq. (38) is essentially a PDE for the physiological potential function and solving the latter may be helpful in exploring the 'design logic' of the detailed model. Conversely, if we began our study of the biological system with the Ansatz, we have a guide for future detailed modelling.

To illustrate the approach, we specialise to \(n = m = 1\) and consider an endocrinological model involving just two hormones (not overly 'good'). The blood plasma concentrations
of these two hormones are denoted \( s_1 \) and \( s_2 \) and they have the following dynamics:

\[
\dot{s}_i = \phi_i(x, s_i) - \lambda s_i \quad \text{for } i = 1, 2
\]

(39)

where \( \lambda \) is a positive parameter. The term \( \phi_i(x, s_i) \) represents the secretion of the hormone into the bloodstream and the term \( -\lambda s_i \) represents clearance of the hormone (e.g., uptake into target cells, renal clearance, or breakdown by blood-borne enzymes). Furthermore, the actuator variable \( z \), representing a flux or a rate of a compensatory process, depends on these hormones through a function \( h(\cdot, \cdot) \), so that \( z = h(s_1, s_2) \). This function is assumed to satisfy

\[
h_1 h_2 \leq 0
\]

(40)

where \( h_i \) denotes the partial derivative of \( h \) with respect to \( s_i \), that is, \( \partial h/\partial s_i \equiv h_i \) for \( i = 1, 2 \). Fig. 12 shows an example of such a function. The fundamental compatibility condition, Eq. (38), here becomes:

\[
-\kappa V_x - \mu V_z = h_1 \phi_1 + h_2 \phi_2 - \lambda (h_1 s_1 + h_2 s_2).
\]

(41)

At the 'stops' where \( z \) equals \( z_{\min} \) or \( z_{\max} \), we have \( h_1 = h_2 = 0 \) which is consistent with \( V_z/V_x = -\kappa/\mu \), so we focus on the regulatory working range where \( z_{\min} < z < z_{\max} \). We consider the following term-by-term identifications:

\[
\kappa V_x \leftrightarrow -h_1 \phi_1 - h_2 \phi_2 \quad (\ast) \quad \text{and} \quad \mu V_z \leftrightarrow \lambda (h_1 s_1 + h_2 s_2) \quad (\ast\ast).
\]

Let us adopt the following expression for the hormone secretion rates:

\[
\phi_i = \max\{0, -\kappa V_x/h_i\}
\]

(42)

for \( i = 1, 2 \). The maximum operator is included here because \( \phi_i \) represents a hormone secretion rate, which cannot be negative. From the condition \( h_1 h_2 < 0 \), which applies when \( z_{\min} < z < z_{\max} \), it follows that exactly one of the two secretion rates \( \phi_1 \) and \( \phi_2 \) is non-zero at any given moment in time, and hence identification (\( \ast \)) is satisfied. As for identification (\( \ast\ast \)), the function \( h \) is locally described by the following equation:

\[
z = \tilde{z} + h_1 s_1 + h_2 s_2
\]

(43)

where \( \tilde{z} \) is a suitable constant. The identification therefore implies the differential equation \( V_z = \lambda \mu^{-1}(\tilde{z} - z) \) which is readily solved. Gradients of the physiological potential thus correspond to signals arising in the (neuro)endocrine system.

---

**Fig. 12.**

Hypothetical example of an actuator variable \( z \) in dependence on the concentrations of two hormones, \( s_1 \) and \( s_2 \). If \( z = h(s_1, s_2) \), this example satisfies the condition \( h_1 h_2 \leq 0 \), where \( h_1 \) and \( h_2 \) denote the partial derivatives with respect to \( s_1 \) and \( s_2 \), respectively; in particular, \( h_1 = h_2 = 0 \) when \( z = z_{\min} \) or when \( z = z_{\max} \) and \( h_1 = -h_2 \) when \( z_{\min} < z < z_{\max} \).
5. Discussion

Homeostasis is the collective term for the regulatory processes in biological systems that keep constant, or confined within a certain range of tolerance, a constellation of physico-chemical conditions within the body [22]. We have presented an Ansatz to analyse homeostatic regulation, which we believe equips physiologists with a flexible and intuitive approach that is congenial to the way in which such systems are discussed in the physiological literature. In such systems, we distinguish a constitutive and a regulatory component. The former is the basic physiology of the regulated system, which is relatively straightforward to represent as a dynamical system, since judicious application of the principles of physics and chemistry often suffices to formulate an adequate mathematical model of the constitutive component [3] and [16]. Such principles do not suffice to define the regulatory component, which is essentially the control loop composed of sensors that feed an afferent signal into an information-processing entity that produces the efferent signals that govern the relevant actuators; this entity may be a neural circuit or an endocrine gland, or a combination of both [5], [22] and [23]. Our Ansatz is not intended to replace the more detailed approach, but rather to provide a minimal model that can serve as a starting point for detailed analysis of the regulatory component. The formalism is tailored specifically to those cases where a wealth of data is available for the physiological system at the ‘organismal’ level, concurrent with a relative paucity of data on the wiring of the control system.

We anticipate several criticisms that might be levied at such an approach, which we categorise as follows: (i) relevance to biology and experimental biologists—in particular whether the approach can lead to physiologically relevant predictions and whether the physiological potential function has a counterpart in biological reality; (ii) the validity of variational principles and the notion of optimality in a biological setting; (iii) compatibility with a more conventional approach that models the regulatory component in detail. Section 4.2 dealt specifically with the last question; therefore we restrict the present discussion to the first two kinds of objections.

The emphasis on the physiological potential function may engender the erroneous impression that the achievement of an internally coherent formalism is the primary goal of this paper, rather than the prediction of new physiological properties that might be experimentally verified in a further step. In fact, since the physiological potential function allows us to represent the key features of the regulatory component in an essentially geometric way, it is perhaps the most economical way of building comprehensive models in which various aspects of the homeostatic system can be brought together. As we have demonstrated in Sections 2 and 3, this yields physiological predictions. For instance, the solid curve in Fig. 4 is a theoretical prediction which is completely independent of the data set to which it is compared in this graph; the prediction is genuine as it was generated before we ever came across these data.

Another example is the discontinuity that can be discerned at the point of the zero temperature gradient in Fig. 6. This is a qualitative feature predicted by the analysis which is borne out by independent analysis of a data set that was not used in making the prediction. The success of our approach in making physiologically relevant predictions that can suggest further experiments, and be compared to independently obtained data sets, derives naturally from its ability to integrate data on different kinds of physiological quantities and processes in a consistent framework.

In Fig. 11, time course data are compared to an independent theoretical prediction. It is interesting that the flux and rate information obtained from steady-state data suffices to predict the behaviour of the biological system during transients. What is perhaps more salient is that the prediction deviates from the data in a systematic way: the model is too rapid for the exposure to high salinity and too slow for the exposure to low salinity. This is
suggestive of a physiological feature that remains to be discovered, such as the amount of integument exposed to the environment or acute adaptation of oral ingestion (the two may be tied together; an animal that retracts into its shell stops exposing itself and also stops foraging, which will automatically reduce oral uptake of water). In any event, the usefulness of our analysis in suggesting further experimental research will be clear.

One may question whether the physiological potential function corresponds to a biological reality. In Section 4.2 we argued that the answer is affirmative, the general idea being that the partial derivatives of $V$ essentially represent signals arising within the neural and endocrine systems. There is another point of view, which is ultimately connected to the signalling one via evolutionary thinking [4]. To explain this second point of view, let us consider the example of regulation of the blood plasma glucose level. Both high and low glucose concentrations are known to lead to a plethora of ill effects [5]. In principle, we can focus on one of these morbidities and reconstruct, from the data, a relationship between the blood plasma concentration and the statistical hazard rate of occurrence of this morbidity. Adding the hazard rates for the various morbidities, using weighting coefficients to represent how each impacts on fecundity, we obtain a function whose time integral is a natural representation of fitness (marginal to euglycaemia). In other words, we can construct the physiological potential function out of considerations of hazard rate and fecundity. Other homeostatic problems can be dealt with in a similar way, for instance those involving temperature, electrolytes and acidity, oxygen supply, or lipids and cholesterol [5], [19], [22] and [23].

Explanations that invoke teleology (purposefulness), or appear to do so, are generally considered improper by biologists, for many good reasons which can be left unsaid. It is nonetheless perfectly legitimate to enquire how animals succeed in surviving to reproductive age despite a hostile environment [19] and [23], a feat which manifestly involves homeostatic regulatory systems that share a basic structure with man-made control systems. To appreciate the adaptive value of maintaining a more or less constant internal environment for the body’s tissues, in the face of variations in the external environment, it suffices to consider the sensitivity of enzymes to variations in temperature, pH, osmolarity, and so on.

Closely related to reasoning in terms of controlled plants is the question whether or not set points are admissible parameters. Whether a detailed regulatory model features parameters that can be interpreted as set points is a red herring, for in any model of a system with homeostatic behaviour, this can trivially be achieved by a parameter transformation, that is, apparent set point parameters can be constructed as functions of underlying mechanistic quantities, such as rate variables, affinity constants, gene dosage, and so on [3]. In the above glucose example, let $G$ denote the blood plasma glucose concentration, $V^*$ the physiological potential constructed out of hazard rates and (marginal) fecundity effects, and consider the quantity $\widehat{G} = \inf_{G \in G} V^*(G)$ where $G$ is the set of physiologically possible values of $G$. This $\widehat{G}$ can now be deemed, by fiat, to represent a physiological optimum, without recourse to teleological reasoning or imputing purposefulness to living systems. In this sense, the reification of set points is a red herring, which is not to deny the importance of a genuinely profound question in homeostasis: how living beings manage to calibrate their regulatory circuits.

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References
[1] W.J. van Aardt
Quantitative aspects of the water balance in Lymnaea stagnalis (L.)
H.A. van den Berg

Model for mechanics of mollusc systemic heart

Article | PDF (1095 K) | View Record in Scopus | Citing articles (1)

H.A. van den Berg
Mathematical Models of Biological Systems Oxford University Press (2011)

H.A. van den Berg
Evolutionary Dynamics: The Mathematics of Genes and Traits Institute of Physics (2015)

C.G.D. Brook, N.J. Marshall
Essential Endocrinology Blackwell Science (2001)

T. Dawson, K. Schmidt-Nielsen
Effect of thermal conductance on water economy in the Antelope Jackrabbit, Lepus alleni

W.R. Dawson
Relation of oxygen consumption and evaporative water loss to temperature in the Cardinal

K.D. Hall
Computational model of in vivo human energy metabolism during semistarvation and refeeding

C.F. Herreid II, B. Kessel
Thermal conductance in birds and mammals

D.S. Hinds, W.A. Calder
Temperature regulation of the Pyrrhulox and the Arizona Cardinal

J.W. Hudson, S.L. Kimzey
Temperature regulation and metabolic rhythms in populations of the House Sparrow, Passer domesticus

O.L.R. Jacobs

H.D. Jones
The circulatory systems of gastropods and bivalves

J. Keener, J. Sneyd
Mathematical Physiology Springer (1998)

S.A.L.M. Kooijman

D. Kuhlmann, F. Feiden
Untersuchungen zur homöostatischen Regulation der Osmolalität der Hämolymphe von Lymnaea stagnalis L. (Gastropoda, Basommatophora)
[34] N.D. de With, R.C. van der Schors
Urine composition and kidney function in the pulmonate freshwater snail *Lymnaea stagnalis*

[35] N.D. de With, R.C. van der Schors
Neurohormonal control of Na\(^+\) and Cl\(^-\) metabolism in the pulmonate freshwater snail *Lymnaea stagnalis*

The bioelectrical activity of the body wall of the pulmonate freshwater snail *Lymnaea stagnalis*: effects of neurotransmitters and the sodium influx stimulating neuropeptides