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Frank-Starling law and Bowditch phenomenon may have the common theoretical grounds.

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Abstract

Formalized description of heterometric and homometric regulation was obtained while modeling of circulation on the basis of several principles; the leading one is defined as follows: concept of circulation presumes that the part of pressure which ventricle produces for propelling of blood must be left, as guaranteed part, for producing of deformation of the next ventricular filling. The relationship between the force of contraction, F, and linear deformation, L, was deduces as function $F = f(L^2)$ which does not deny approximation to direct proportionality at the operating region of Frank-Starling law (ascending limb cut out from parabola). Another function determines the force of contraction when the sizes of deformation drop below the domain of Frank-Starling function: $F = f(1/t_{syst})$, where t_{syst} is the duration of systole. Bowditch staircase is explained as repeated (cyclic) transitions from one function to another because "a resting muscle" (condition of Bowditch experiment) can be equalized with too small deformations (below the limit of domain of Frank-Starling function).

Introduction

Heterometric regulation (Frank-Starling law) and homometric regulation (Bowditch phenomenon) belong to the same phylogenetic level that justifies the attempt to formulate both of them in some general form and look for theoretical model of combination. There is also some specificity of description concerning the above biological laws – the high degree of formalization: a force (of contraction), linear sizes, volumes, precise time intervals, approximation to direct proportionality (Frank-Starling law). That is why it is reasonable to chose the approach appropriate to physical theory: firstly, - to define the basic axiomatic statements and then, - to use the ordinary methods of mechanic and hydrodynamic description in order to deduce the equations that express the observing laws. But elements of modeling are indispensable because beforehand it is necessary to formalize some physiological parameters and condition simplifications of some physiological processes which are subordinate and play the role of instruments (although such conditions resemble axioms either).

Methods

The model of ventricle is presented by cylindrical syringe and such model is convenient for our speculations due to coincidence of numerical values:

- of the distance of travel of the piston l (the size in 1-dimensional space) and the volume V (the size in 3-dimensional space);

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- of linear velocity U of rectilinear motion of the piston and the volume flow rate Q cased by the motion of the piston.

The transition from l to V, either from U to Q accomplishes by means of coefficient equal to 1 which changes the dimension of quantity only.

One more advantage of the model presented by cylindrical syringe is the following. We may numerically equalize l and the duration of diastole (with correction by means of the coefficient) when the steadiness of volume flow rate of ventricular inflow is stipulated.

As far as ventricular filling is the process that participates almost everywhere at our thought experiment it is necessary to define the mode of deformation the wall of ventricle imitates. We assume that the relaxing ventricular wall behaves like viscous material and it is pertinent to remind that viscous process is the function of two variables – stress (pressure) and duration of stress. (Details of the approach concerning the viscous deformation can be found in our previous work [1].)

The inquiries of further formalization and simplification will arise while introducing the axioms.

The first postulate. Concept of circulation presumes that the part of pressure which ventricle produces for propelling of blood must be left, as guaranteed part, for producing of deformation of the next ventricular filling.

Let us denote the pressure mentioned as "guaranteed part": it is the minimal venous pressure sufficient for diastolic deformation of ventricle (minimal guaranteed stress) $P_{ven.min}$. The volume flow rate of ventricular outflow can be determined as $Q_{outflow}=\frac{P_1-P_2}{R}$ and simplified if $R=const=1$; the pressure P_1 at the initial part of pipe is the arterial pressure P_{art} and the pressure P_2 at the final part of pipe is the above $P_{ven.min}$. We introduce some pressure damper that converts the difference between P_{art} and $P_{ven.min}$ into the time interval during which $P_{ven.min}$ can be maintained due to exploiting of the energy of $P_{art}-P_{ven.min}$ and this time interval must be directly proportional to $P_{art}-P_{ven.min}$. Diastolic deformation of ventricle, - as we consider it a viscous deformation which is the function of two variables (stress and time), - is organized by minimal sufficient stress $P_{ven.min}$ and time interval (duration of diastole) proportionate to $P_{art}-P_{ven.min}$ and also proportional to $Q_{outflow}$. Therefore, the volume flow rate of the ventricular outflow is directly proportional to the duration of ventricular diastole.

This is a formalized version of **the first postulate** appropriate for application and let us apply it to syringe model of ventricle in order to reveal some numerical peculiarities that follow the above direct proportion.

But one consequence must be mentioned just now. Since the damper maintains some constant level of pressure and this level is sufficient to enlarge the volume of the chamber each time unit, - and there is no elasticity as a component of deformation (enlargement of volume of chamber) which will result in

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appearance and growth of resistance, - we may state, firstly, that the flow exists and, secondly, that the volume flow rate of ventricular inflow is steady.

For simplification, let the above direct proportionality has the coefficient of proportionality equal to 1, i.e., the value of $Q_{outflow}$ is equal numerically to the duration of diastole which this $Q_{outflow}$ generates being converted into the time interval.

Second postulate. Duration of ventricular systole and duration of ventricular diastole are variable parameters but systole is less variable; certain diapason of rhythms (more slow rhythms) permits us to consider the duration of ventricular systole constant and the rest diapason of rhythms (more rapid rhythms) claims to consider it variable. But we have no criterion of transition from one consideration to another. Nevertheless, we are sure that shortening of duration of systole is associated with acceleration of rhythm, i.e., any rising of frequency of rhythm indicates that shortening of duration of systole has happened. And vice versa, any transition to more rare rhythm denotes that systolic shortening is absent.

Third postulate. There is a lower limit of deformation of relaxing ventricle (lower limit of linear elongation of muscle or lower limit of end-diastolic volume) which prevents to distinguish the difference between deformations below this limit - that results in disappearance of functional linkage (biunique relation) of deformation with the force of contraction. Certainly, the existence of the function "deformation – force" ought to be put first but the postulate is accentuated on physiological domain of function.

It would be wrong to state that hydrodynamic process of filling alters dramatically when deformation (independent variable of the function "deformation - force") quits physiological domain of the function. The ventricle keeps on contracting but the biunique relation disappears, i.e., diastolic deformations may vary below the limit but the function will consider all of them equal to each other and equal to the lowest value of distinguishable deformation; consequently, the response of contractile force will be – as if – ventricle has perceived the smallest distinguishable deformation.

Results

Frank-Starling law

Let the duration of diastole is equal to A and duration of systole is equal to 4; hence, $Q_{outflow}$ is equal to A/4 and the next diastole (generated by $Q_{outflow}$ equal to A/4) is shortened and is equal to A/4; shortening of next duration of diastole will go on progressively: A/16, A/64 etc. and it can be interpreted as progressive acceleration of rhythm - together with progressive deceleration of $Q_{outflow}$. Let us vary the initial duration of diastole, i.e. vary the initial rhythm. When we shorten the initial duration of diastole, - now it is equal to A/2, - $Q_{outflow}$ is equal to A/2 : 4 = A/8 and it corresponds to the duration of the next diastole. Symmetrically, when we elongate the initial duration of diastole, - now it is equal to 2A, - $Q_{outflow}$ is equal to 2A : 4 = A/2 and it corresponds to the duration of the next diastole either. Therefore,

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shortening or elongation of diastole (initial rhythm) results only in degree of acceleration of rhythm – under condition that duration of systole is constant (and is equal to 4 at this example).

Let us repeat the experiment where we conserve the initial duration of diastole equal to A but shorten the duration of systole – which is now equal to 2; hence, $Q_{outflow}$ is equal to A/2 and the next diastole (generated by $Q_{outflow}$ equal to A/2) is also shortened and shortening will go on progressively: A/4, A/8, etc. and again it can be interpreted as progressive acceleration of rhythm together with progressive deceleration of $Q_{outflow}$. Let accelerate initial rhythm: diastole shortens down to A/2 and, consequently, $Q_{outflow}$ will be A/2 : 2 = A/4, i.e., rhythm will be accelerated. Let us decelerate initial rhythm: diastole elongates up to 2A and $Q_{outflow}$ becomes 2A/2 = A which is shorter than 2A and it means the acceleration of rhythm either; therefore, the durations of the next diastoles will demonstrate progressive shortening, like at the previous example, and it also results in progressive acceleration of rhythm.

Let us repeat experiment once more. We again conserve the initial duration of diastole (A) and shorten the duration of systole down to 1. To our surprise, $Q_{outflow}$ is now equal to A and the next diastole will be equal to the previous one, i.e., equal to A. Let us accelerate the initial rhythm by shortening initial duration of diastole down to A/2; $Q_{outflow}$ will be A/2 : 1 = A/2, i.e., no acceleration is observed and it will not appear after repetitions of cardiac cycle. Let us decelerate initial rhythm: elongated initial diastole is equal to 2A and, consequently, $Q_{outflow}$ will be 2A : 1 = 2A, i.e., no acceleration is observed again.

We may call the examples with fixed duration of systole - which value is more than 1 - the imbalance relating it to the application of principle of direct proportionality (between $Q_{outflow}$ and duration of diastole) – with coefficient of proportionality equal to 1 as it was conditioned. On the contrary, the example with fixed duration of systole – which duration is equal to 1 – demonstrates the equipoise that is evidently associated with the number 1. Symmetrically, when shortenings of duration of the systole are the fractures (½, ¼ - symmetrically to 2,4) we observe not total acceleration of rhythm (as it is when 2,4) but total deceleration – and we omit this excessive illustration.

Let us see in numbers – and in concise form - the linkage between $Q_{outflow}$ and duration of diastole.

Systole 4, initial diastole A

$Q_{outflow}$ A**1/2**, next diastole A/2 deceleration of initial rhythm (diastole **2**A)

$Q_{outflow}$ A**1/4**, next diastole A/4 initial rhythm (diastole A/**1)**

$Q_{outflow}$ A**1/8**, next diastole A/8 acceleration of initial rhythm (diastoleA**1/2)**

Systole 2, initial diastole A

$Q_{outflow}$ A/**1**, next diastole A/1 deceleration of initial rhythm (diastole **2**A)

$Q_{outflow}$ A**1/2**, next diastole A1/2 initial rhythm (diastole A/**1)**

$Q_{outflow}$ A**1/4**, next diastole A/4 acceleration of initial rhythm (diastole A**1/2)**

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Systole 1, initial diastole A

$Q_{outflow}$ **2**A next diastole 2A deceleration of initial rhythm (diastole **2**A)

$Q_{outflow}$ A/**1**, next diastole A/1 initial rhythm (diastole A/**1)**

$Q_{outflow}$ A**1/2**, next diastole A1/2 acceleration of initial rhythm (diastole A**1/2)**

Compare left and right columns of bold figures at each example. When $Q_{outflow}$ is two-fold smaller – diastoles are two-fold smaller; and the example with systole 1 has no difference with other examples. It means that each example demonstrate the same direct proportionality with coefficient of proportionality equal to 1 as it was conditioned before. How does systole with duration equal to 1 originate equipoise?

Surely there is no some magic "1" but there is a linkage between the duration of systole and the force that the systole generates. When systole is equal to 1 its force is adequate to generate $Q_{outflow}$ which is numerically equal to the next diastole <u>and to the previous one</u>. When systole is longer, i.e., equal to 2, its force is smaller and it can generate $Q_{outflow}$ which is also numerically equal to the next diastole (the claim of direct proportionality with coefficient 1) but this diastole is shorter then the previous one, i.e., the direct proportionality is not a sufficient condition for equipoise. Therefore, we must find the linkage between the force and duration of diastole – the next and the previous – because both must be equal. In other words, we are looking for some factor which converts any duration of systole into 1 – and we are looking for it on the basis of physical explanation; it means that it is necessary to add some more force if we want not only to maintain direct proportionality but also to enlarge value of $Q_{outflow}$. (Symmetrically: to distract some force in order to diminish $Q_{outflow}$ when durations of systole are fractional.) Thus, we are looking for the linkage between force and duration of diastole.

Let the piston of the syringe travels (imitating a diastole) at distance l_1 , for the first example; and for the second example, the distance is l_2 and $l_2 > l_1$, i.e., l_1 and l_2 are the one-dimensional sizes of the operating chamber of syringe. During systole the piston moves the mass m_1 at the distance l_1 (and the mass m_2 at distance l_2 , respectively). In terms of rectilinear motion (alternatively to hydrodynamics) we may imagine a solid m_1 attached to the internal surface of the piston; the imaginary high density material of it permits to fancy the minimal size of m_1 and trace its travel at distance l_1 ; the analogous solid m_2 travels at distance l_2 .

The combination of **the second and the third postulates** arrange the limitation which warrants the term "shortening of duration of systole" only for the systole coupled with diastole that deforms ventricle (together with $P_{ven.min}$) below the critically small deformation. It is the deformation below which the ventricle can not distinguish the difference between deformations and, hence, can not respond with adequate contraction. Besides, acceleration of rhythm will be linked with shortening of duration of systole factually – only when deformations become indistinguishable.

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This part of analysis deals with diapason of deformations above the critically small ones which indicate the border between shortened systoles and systoles that can be considered all equal. Referring to previous speculations, we deal with one abstract duration of systole equal to abstract 1. Consequently, duration of each systole t_{syst} is identical to the duration of another one and deformations l_1 and l_2 are far from lower limit of distinguishing of deformation.

According to Newton second law:

$$F_1 = m_1 a_1 \quad \text{and} \quad F_2 = m_2 a_2 \quad ,$$

where F_1 and F_2 denote the forces which are applied to the piston in order to move m_1 and m_2 during the systole, respectively. As far as $a = \frac{U}{t}$ and the duration of systole is fixed we may write:

$$F_1 = m_1 \frac{U_1}{t_{syst}} \quad \text{and} \quad F_2 = m_2 \frac{U_2}{t_{syst}} \quad ,$$

and after equating we get:

$$\frac{m_1 U_1}{F_1} = \frac{m_2 U_2}{F_2} \quad .$$

Now we change small traveling solids to liquids by replacement of densities and volumes due to $m = \rho V$ and after substitution we achieve the equation

$$\frac{\rho V_1 U_1}{F_1} = \frac{\rho V_2 U_2}{F_2}$$

which can be transformed to proportion

$$\frac{F_2}{F_1} = \frac{V_2 U_2}{V_1 U_1} \quad .$$

The final transition to hydrodynamic terminology can be done by substitution of Ql instead of VU because $VU = \left[m^3 \frac{m}{s} = \frac{m^3}{s} m \right] = Ql$:

$$\frac{F_2}{F_1} = \frac{Q_2 l_2}{Q_1 l_1} \quad .$$

According to **the first postulate**: $Q_2 = Q_1 \frac{t_{diast\,2}}{t_{diast\,1}}$. The steadiness of volume flow rate of ventricular inflow (it is the consequence of **the first postulate** mentioned above) permits to equalize the duration of diastole and the distance of travel of the piston (via some coefficient k) at syringe model of ventricle:

$$Q_2 = Q_1 \frac{k\, l_2}{k l_1} = Q_1 \frac{l_2}{l_1} \quad .$$

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After substituting of such presentation of Q_2 to the final proportion concerning forces we get rid of the volume flow rate in $\frac{F_2}{F_1}=\frac{Q_1 l_2 l_2}{Q_1 l_1 l_1}$ and come to the conclusion that

$$\frac{F_2}{F_1}=\frac{l_2^2}{l_1^2} \quad .$$

Numerically the two-fold increasing of F_2 comparing to F_1 can be illustrated by example:

$\frac{F_2}{F_1}=\frac{l_2^2}{l_1^2}=\frac{7^2}{5^2}=\frac{49}{25}\approx\frac{2}{1}$, i.e., the length of fiber must be enlarged from 5 to 7.

Miscellaneous diagrams picturing the dependance of tension (or the contractile force) and the length of myocardial fiber, - cited as data of different experiments, - demonstrate non-linearity of the linkage. If roughly: the shallow slope at small lengths and steeper slope at larger lengths, i.e., the operating range of Frank-Starling curve resembles very much the ascending limb cut out from parabola. And if at some references the curvature can be hardly discerned – the steepness of such direct proportionality claims significant numerical coefficient before the argument: that makes the linear graph close to the ascending portion of parabola.

The function $F=f(l^2)$ must be restricted to a subset of its physiological domain and the corresponding image of function, - the above mentioned ascending limb cut out from parabola, - can be really approximated to the function of direct proportionality restricted to the same physiological domain. The image of latter function, - as a whole codomain, - will have the coefficient of proportionality more than unit as far as the slope of the linear function is relatively steep. That is, the operation of cutting out the certain part of square function determines the coefficient of proportionality of linear function – for approximate calculations. Consequently, physiological experiments – which are always accompanied by statistical deviations, - may obtain data close to linearity. And we may not exclude that just the mechanism of contractile response is programmed on the basis of such approximation to linearity – but slope characteristics of such direct proportionality has inevitably been taken from square function.

Bowditch phenomenon

Obligatory condition of the revealing of homometric regulation is “a resting muscle”, i.e., the muscle which is not loaded sufficiently to reveal Frank-Starling law. This condition of “resting” we equalize with the range of deformations below the level of distinguishing of deformations. As soon as mechanism of contractile response receives the information about too light load it associates it with shortening of duration of systole, i.e., it receives only indirect information about it (via diastolic deformation)(the combination of **the second and the third postulates**). The reserved condition is that rhythm of stimulation can be compared to more frequent rhythm or to less frequent rhythm (**the second postulate**), i.e., totally indirect information about shortening of duration of systole is receiving from two sources – from Frank-Starling

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function (that quits its domain and does not distinguish diastolic deformations any more) and from essential relation between duration of systole and frequency of rhythm. However, the first variant of Bowditch phenomenon - which we begin with (the stepwise growth of contractile force in response to rhythmical stimulation), - concerns the rhythmical stimulation the muscle has nothing to compare with.

Let us start repeating the previous thought experiment and realize where the difference appears. Let the piston of the syringe travels (imitating a diastole) at distance l_1, for the first example; and for the second example, the distance is l_2 and $l_2 > l_1$. During systole the piston moves the mass m_1 at the distance l_1 (and the mass m_2 at distance l_2, respectively). Thus, according to Newton second law:

$$F_1 = m_1 a_1 \quad \text{and} \quad F_2 = m_2 a_2 \quad ,$$

where F_1 and F_2 denote the forces which are applied to the piston in order to move m_1 and m_2 during the systole, respectively. As far as $a = \frac{U}{t}$ and the durations of systole are now considered different let us denote durations of systole as $t_{syst\,1}$ and $t_{syst\,2}$, and that $t_{syst\,2}$ is shorter than $t_{syst\,1}$. Hence,

$$F_1 = m_1 \frac{U_1}{t_{syst\,1}} \quad \text{and} \quad F_2 = m_2 \frac{U_2}{t_{syst\,2}} \quad .$$

We remind that combination of **the second and the third postulates** refers now the analysis out of the operating range of deformations of Frank-Starling law; here the mechanism of contractile response does not distinguish the difference between deformations. After transition of masses from mechanical representation to hydrodynamical one we understand that if the difference between deformations l_1 and l_2 can not be found – the difference between masses of liquid m_1 and m_2 can not be found either. Consequently,

$$m_1 = F_1 \frac{t_{syst\,1}}{U_1} \quad \text{and} \quad m_2 = F_2 \frac{t_{syst\,2}}{U_2} \quad \text{can be equated:}$$

$$\frac{F_1 t_{syst\,1}}{U_1} = \frac{F_2 t_{syst\,2}}{U_2} \quad \text{or} \quad \frac{F_1 t_{syst\,1}}{Q_1} = \frac{F_2 t_{syst\,2}}{Q_2}$$ as far as syringe-model of ventricle permits to interchange linear speed of piston and volume flow rate easily.

After transformation we get:

$$\frac{F_1}{F_2} = \frac{Q_1 t_{syst\,2}}{Q_2 t_{syst\,1}} \quad .$$

As far as the difference between deformations l_1 and l_2 is not distinguishable the durations of diastole $t_{diast\,1}$ and $t_{diast\,2}$ lose any sense to determine direct proportionality presented in **the first postulate** $Q_2 = Q_1 \frac{t_{diast\,2}}{t_{diast\,1}}$. Moreover, the response of contractile force (value of the function) to such

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indistinguishable deformations will be equal and will correspond to lowest point of domain of Frank-Starling function. Therefore, we may put down that $Q_1 = Q_2$ and, hence

$$\frac{F_1}{F_2} = \frac{t_{syst\,2}}{t_{syst\,1}}$$

Thus, what happens when the resting muscle is undergone to rhythmical stimulation? The first contraction – influenced by stimulus and information about too small deformation (resting condition) – is assessed as contraction with shortened systole. The contraction is weak because the lack of perceptive deformation may refer the response at least to minimal perceptive deformation (the lowest point of domain of Frank-Starling function). But information about shortened duration of systole marks the starting point for reading of the next contraction as contraction with shortened systole relatively to the previous. Therefore, second contraction will be associated with $t_{syst\,2}$ which is shorter (for instant, equal to 2) than $t_{syst\,1}$ (for instant, equal to 3), and according to the above proportion:

$$\frac{F_1}{F_2} = \frac{t_{syst\,2}}{t_{syst\,1}} = \frac{2}{3}$$ the second contraction will be more intensive $F_2 = F_1 \frac{3}{2}$.

The achievement of some limit of force of contraction and forming of plateau is worth notice. Certainly, it is nothing but exhausted reserve, i.e., physiological limit, - but it imitates the response which is adequate to some real very large deformation of ventricle since the force is extremely high. In other words, the plateau imitates the recurrence to Frank-Starling law.

We have approached to the second variant of Bowditch phenomenon [2]. Videlicet: stimulation of resting muscle by some initial rhythm results in stepwise increasing of force of contraction until the force reaches some plateau; while keeping on stimulation - but with more frequent rhythm – the resuming of staircase happens (first contraction is weak and then the one observes stepwise growth of contractile force up to the plateau again).

Acceleration of rhythm associates with shortening of duration of systole but not with deceleration (**the second postulate**). Hence, if we accelerate rhythm when staircase still continue – we send signal similar to the one that controls the linking of each contraction with shortening of systolic duration. But when imitation of Frank-Starling law appears the regulating signal from indistinguishable deformation may disappear due to association of extremal force with – as if – substantial deformation. That is why the signal from another source (essential shortening of duration of systole while accelerating of any rhythm) may trigger the refreshment of signal from the first source (signal concerning inability to distinguish deformation if it is too small). As a result, the false signal about – as if – substantial deformation (conjugated with plateau of force values) will be substituted by prevalent signal from two sources which will start up a staircase again. Evidently, the signal about decelerating of rhythm will not influence the refreshment of signal from indistinguishable deformation and plateau will remain intact.

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Homometric regulation can hardly be compared to heterometric one as regulatory mechanism. Physiologic meaning of homometric response of contractile force is an extraordinary measure when the main feedback is lost. It seems so because the functional linkage between force and duration of systole is not expressed as previous regulation - when argument varies to both sides and the function is a biunique value (heterometric regulation). Here any subsequent contraction assesses the duration of previous contraction as the longer one than its own duration – and what is the criterion of shorter? The duration may drop significantly – and the force will raise enormously – but we observe the staircase. It means that the difference is small and the only criterion for "small" is the minimum necessary for perception. That is, the moment we lose the perception of deformation – we gain the ability to perceive the duration of systole. Consequently, the difference between systoles appear as a perceptive limit and it can not be large. The next contraction is the repetition of the above transition from one mode of regulation to another, i.e., it is not the functioning of $F = f(\frac{1}{t_{syst}})$ but it is a transition to it; and it happens repeatedly. Nevertheless, the duration of systole grows shorter factually as far as the force of contraction demonstrates stepwise increasing.

Recapitulation of the results is the following. The model itself, together with the basic principles marked out, tries to explain how the intrinsic mechanism of cardiac muscle is programmed if it participates not only in adequate responding to the external loading but if it maintains circulation, i.e., if it is responsible for loading itself either. Besides, the controlling of such mechanics excludes reflexes which belong to the higher phylogenetic level.

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