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INTERNATIONAL WORKSHOP ON PROTEOMICS: PROTEIN STRUCTURE, FUNCTION AND INTERACTIONS

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"Towards a noncontingent biology: the proteins folds as natural forms"

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Towards a non contingent biology: Physical law as a major determinant of organic form

What is the essential nature of organic form? Are organisms machines? Is life a substrate neutral phenomenon? Can the vitalist doctrine be redefined and redefended?

FIG II-1

The Nature of Organic Form

1. Contingent assemblages of matter (machines - LEGO assemblages)

2. Lawful [emergent] arrangements of matter (atoms or crystals)

The Contingent model

pre Socratic atomists

Descartes

Newton

Paley

Darwin

Weismann

von Neumann

Watson and Crick

I suppose the body to be nothing but a machine ..... We see clocks, artificial fountains, mills, and other such machines which, although only man made, have the power to move on their own accord in many different ways .....one may compare the nerves of the machine I am describing with the works of these fountains, its muscles and tendons with the various devices and springs which set them in motion.....the digestion of food, the beating of the heart and arteries.....respiration, walking .....follow from the mere arrangement of the machine's organs every bit as naturally as the movements of a clock or other automaton follow from the arrangements of its counterweights and wheels.

Descartes *Treatise on Man*

17th Century English Mechanism

The Royal Society

Hooke

Boyle

Ray

Newton

Every indication of contrivance , every manifestation of design which existed in the watch exists in nature with the difference, on the side of nature, being greater and more, and that in a degree which exceeds all computation . . . yet in a multitude of cases, are **not less evidently mechanical, not less evidently contrivances . . . than are the most perfect productions of human ingenuity**.

Paley's *Natural Theology*

If a man were to make a machine for some special purpose, but were to use old wheels, springs and pulleys, only slightly altered, the whole machine, with all its parts, might be said to be specially contrived for its present purpose. Thus throughout nature almost every part of each living being has probably served in a slightly modified condition, for diverse purposes, and has acted in **the living machinery of many ancient and distinct forms**.

Darwin (1862) *On Orchids*

It seems clear to me that the species **is not a life crystal in that it *must*, like a rock crystal, *take form in a particular way* and in no other for purely internal reasons and by virtue of its physical constitution**; the species is essentially a complex of adaptations, of modern adaptations which have been recently acquired, and inherited adaptations handed down from long ago—***a complex which might well have been other than it is***, and indeed must have been different if it had originated under the influence of other conditions of life.

[my emphasis]

August Weismann *The Evolution Theory* (1904)

When we find in all species of plants and animals a thousand characteristic peculiarities of structure continued unchanged through long series of generations . . . we naturally ask for the causes of such a striking phenomenon . . . I have attempted to explain heredity by supposing that in each ontogeny, **a part of the specific germ–plasm contained in the parent egg is not used up in the construction of the offspring but is reserved unchanged** for the formation of the germ cells of the following generation.

August Weismann *Essays on Heredity and Kindred Biological Problems* (1885)

Living organisms are very complicated aggregations of elementary parts, and by any reasonable theory of probability or thermodynamics highly improbable. That they should occur in the world at all is a miracle of the first Magnitude.

Von Neumann *Theory of a self reproducing automaton* (1966)

All complex organic form is contingent and specified in the genes

All the unique properties of living things are the result of cleverly contrived arrangements of matter.

[Basic axioms of the current *Gene Centric* view of biological form]

The forms and properties of organisms arise like artifacts [machines] from contingent arrangements of basic elements

- jumbo jet, watch, computer, LEGO assemblage.

The forms and properties of natural products arise emergently from the lawful intrinsic properties of matter

- galaxy, crystal, water, iron, chlorine, alcohol

Life as ‘clever contrivance’: Mechanism as the defining idea of our time

Darwinism

DNA centric view of life

Artificial intelligence

Artificial Life

Science Fiction - Androids, Cyborgs

Empowerment of men (Eucken)

The lawful [*vital*] model of organic form

Plato/Aristotle

naturphilosophie

Goethe

von Baer

Geoffroy

Owen

Pre Darwinian biology

The idea of Lawful form has vitalist implications

- If organic forms arise from the intrinsic properties of certain categories of matter [the 19th C 'Crystal model']

- then the properties of organic forms are like other natural forms [iron, chlorine, water, alcohol etc whose properties also arise from the basic properties of matter] but not like those of machines which arise from contingent arrangements of matter.

He was seeking to identify the inner law which presides over the formation of the skeleton throughout the animal kingdom. His system was . . . **an attempt to work out a geometry of the skeleton** . . . his thesis is that all forms of skeleton . . . can be deduced from a hollow sphere . . . every skeleton can be represented schematically by a number of hollow spheres suitably modified in shape and suitably arranged. We may expect then all skeletons to be composed of spheres, cylinders and dicones in diverse arrangements." [From Russell (1916)]

Carl Gustave Carus

The process of crystallization in inorganic nature . . **.is . .**

.the nearest analogue to the formation of cells . . .

should we not therefore be justified in putting forward the proposition that the formation of the elementary parts of organisms is nothing but a crystallization and **the organism nothing but an aggregate of such crystals** . . . if a number of crystals capable of imbibition [absorption] are formed, they must **combine according to certain laws** so as to form a systematic whole, similar to an organism

Schwann (1847) Microscopical Researches

19th C Biology

1. Organic Forms are Primary Givens of Nature (like crystals)

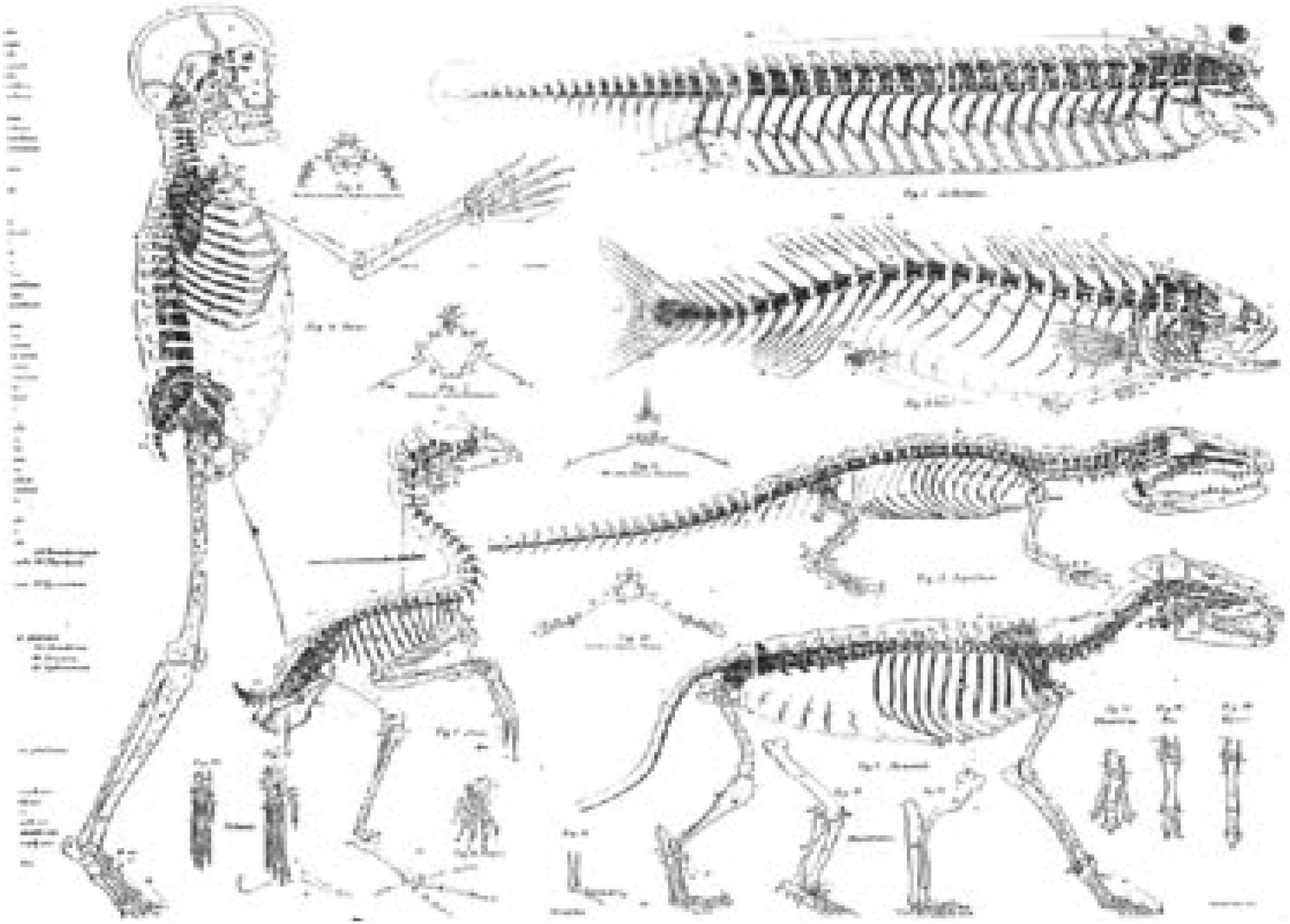
2. Functional adaptations as secondary modifications of primary Forms - “adaptive masks” (Owen)

19th C Biology as a Lawful/Form first biology

We must not suppose that a bull has horns in order to gore, but we must investigate the process by which it comes to have horns in the first place

Goethe

Functional adaptations as secondary modifications of primary forms (Figure from Owen's *On the Nature of Limbs*)



19th century Platonic (pre Darwinian) biology

Laws of form

Organic forms as abstract immutable patterns

***Form* first - *Function* second**
conception of form: Adaptations as secondary modifications of primary givens of physics

Challenges to the Contingent conception of form

1. Examples of forms which emerge' unspecified' from the intrinsic properties of their constituents

2. Doubts re: the genetic program concept. Man and chimp and post genomic *angst*.

Fig. 93 A.

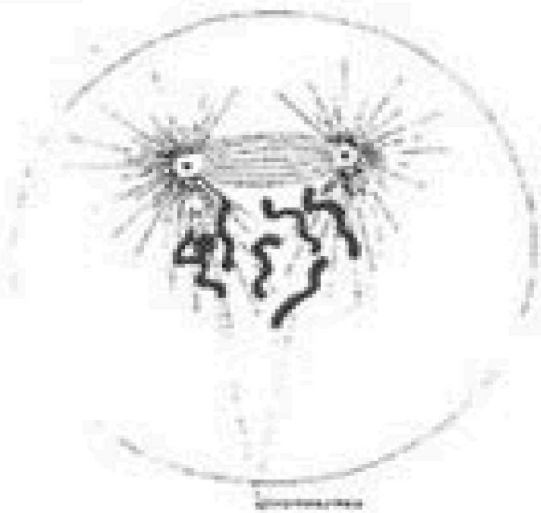


Fig. 93 A.

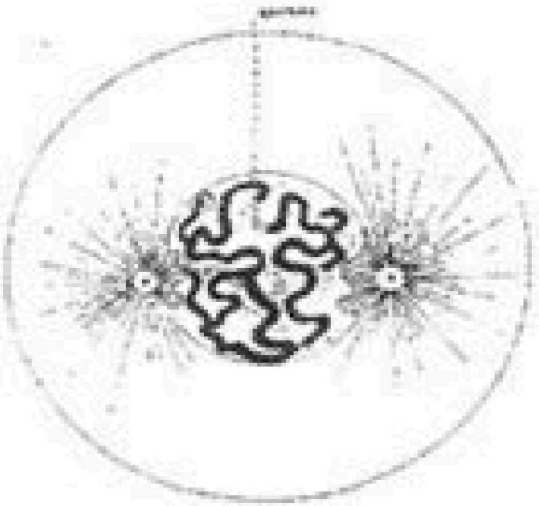


Fig. 93 B.

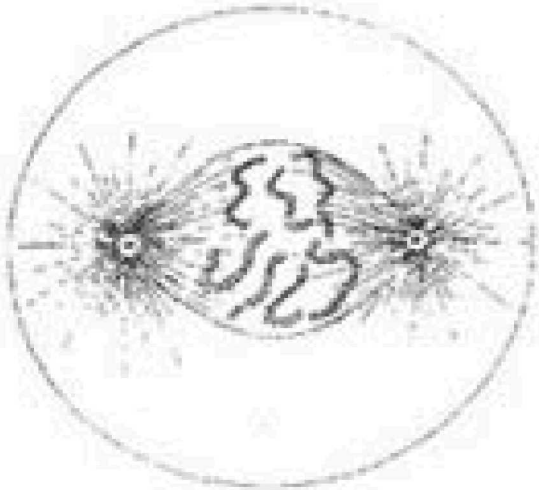


Fig. 94 A.

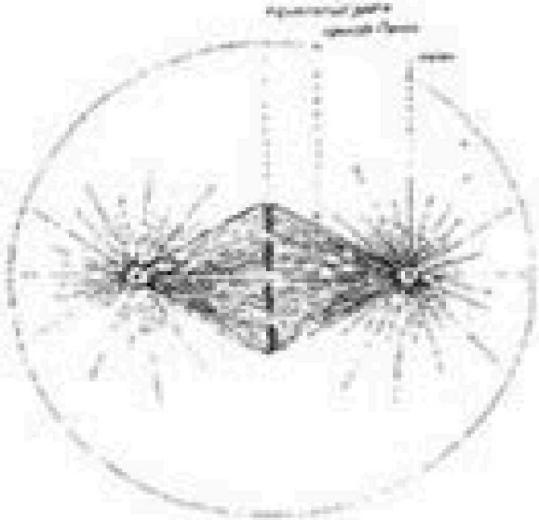


Fig. 94 B.

Modern biology is still mechanistic in essence.

1. Despite problems and obvious cases of emergent form biologists still view organic forms as 99% specified and contingent

2. Only simple organic forms are considered to be generated by physics eg round shape of cell or the flat shape of cell membrane - certain cell shapes - red cell diatoms, radiolarian shells etc.

3. ***All complex form is contingent and specified in the genes***

The Protein folds

The basic structural and functional building blocks of life

Immensely complex arrangements of matter

The first forms ‘reduced’ to atoms

The Protein Folds

What is their fundamental nature?

Are they a finite set of crystal like abstract Platonic *Form first* structures given by physics?

Or

Do they represent a potentially infinite set of contingent arrangements of matter cleverly contrived into complex forms to perform various functions?

Structural Classes of Protein Folds.

The folds can be classified into different basic structural classes. α, containing only α helices; α & β, containing α helices and β sheets; and β, containing only β sheets.

These classes can be further subclassified into different architectural subclasses.

In the α & β class - TIM barrel, Three Layer Sandwich and Roll.

Showing two different arrangements of the Three Layer Sandwich.

A finite number of folds

The total number of protein folds between 1000 - 4000 [Clothia, Finkelstein, Taylor]

Constructional rules limit the possible spatial arrangements of submotifs [Clothia, Finkelstein, Taylor]

Predicting the universe of fold forms from ‘laws of protein form’

Protein functions

- secondary modifications of primary forms a *Form first - function second* world

- the superfolds such as the TIM Barrel (triosephosphate isomerase, enolase and glycolate oxidase etc. - now more than 30 plus different enzymic functions)

- Myoglobin/hemoglobin

The protein folds

A set of natural crystal like forms which arise out of the intrinsic properties of a particular category of matter - amino acid polymers.

They represent the first set of complex biological forms which appear to conform to the 19th C pre Darwinian conception of nature.

The Protein folds

The axiom that all complex biological order represents contingent arrangements of matter is undermined

Immensely complex arrangements of matter can be ‘givens of physics’

Conclusion

The properties and forms of a set of organic forms have been shown to arise form the intrinsic properties of matter and not from clever contrivance. This represents the first major challenge to the mechanistic doctrine - that all complex form and function in the biological world arises from contingent contrivance.

This discovery raises the prospect that underlying the adaptive diversity of life at a cellular and organismic level there may be other sets of natural forms, that life may be as was believed in the 19th C 'an intrinsic property of matter' and an inevitable result of cosmic evolution.

The Nature of Organic Form

Contingent or lawful?

Complex contrivance or intrinsic property of matter?