Judge John E. Jones, the *Kitzmiller v. Dover* Ruling, and Peer-Reviewed Pro-Intelligent Design Publications

~An illustrated Rebuttal~

"It [Intelligent Design] has not generated peer-reviewed publications"
(Judge John. E. Jones, *Kitzmiller v. Dover*, 400 F.Supp. 707, 735 (M.D. Pa. 2005)

"A final indicator of how ID has failed to demonstrate scientific warrant is the complete absence of peer-reviewed publications supporting the theory."
(*Id.* at 744)

"The evidence presented in this case demonstrates that ID is not supported by any peer-reviewed research, data or publications."
(*Id.* at 745)

"In addition to failing to produce papers in peer-reviewed journals..."
(*Id.* at 745)

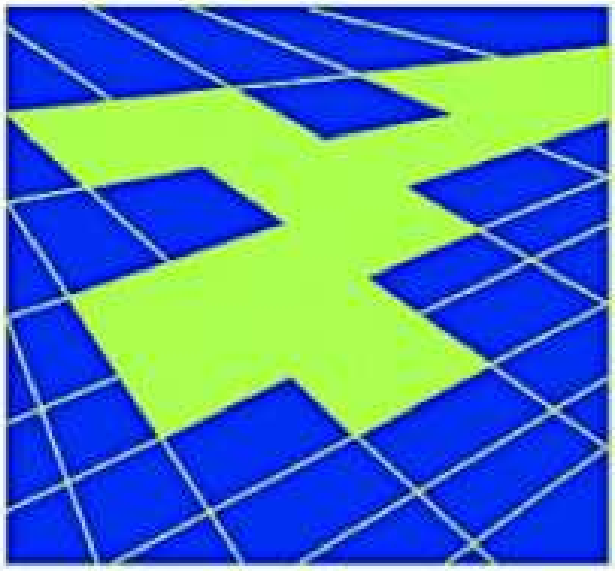
"It has failed to publish in peer-reviewed journals"
(*Id.* at 745)

According to Judge Jones, none of the following publications exist:

Cambridge Studies in Probability, Induction, and Decision Theory

THE DESIGN INFERENCE

ELIMINATING CHANCE THROUGH SMALL PROBABILITIES



WILLIAM A. DEMBSKI

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JMB

Extreme Functional Sensitivity to Conservative Amino Acid Changes on Enzyme Exteriors

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Mutagenesis studies and alignments of homologous sequences have demonstrated that protein function typically is compatible with a variety of amino-acid residues at most exterior non-active-site positions. These observations have led to the current view that functional constraints on sequence are minimal at these positions. Here, it is shown that this inference assumes that the set of acceptable residues at each position is independent of the overall sequence context. Two approaches are used to test this assumption. First, highly conservative replacements of exterior residues, none of which would cause significant functional disruption alone, are combined until roughly one in five have been changed. This is found to cause complete loss of function *in vivo* for two unrelated monomeric enzymes: barnase (a bacterial RNase) and TEM-1 β-lactamase. Second, a set of hybrid sequences is constructed from the 50 %-identical TEM-1 and *Proteus mirabilis* β-lactamases. These hybrids match the TEM-1 sequence except for a region at the C-terminal end, where they are random composites of the two parents. All of these hybrids are biologically inactive. In both experiments, complete loss of activity demonstrates the importance of sequence context in determining whether substitutions are functionally acceptable. Contrary to the prevalent view, then, enzyme function places severe constraints on residue identities at positions showing evolutionary variability, and at exterior non-active-site positions, in particular. Homologues sharing less than about two-thirds sequence identity should probably be viewed as distinct designs with their own sets of optimising features.

Keywords: exposed residues; protein homologues; molecular evolution; neutral theory; sequence space

Introduction

How amino acid sequences encode functional proteins has been a matter of intense interest for decades. Although many aspects of this problem remain unsolved, progress has been made in addressing the basic question of how tightly biological function constrains protein sequences. The currently accepted answer is that the constraints are quite loose, particularly at positions on the exterior of a protein that are not directly involved in binding or catalysis.

The origins of this low-constraint view can be traced to three key developments in the latter half of the 1960s. During this period, the first systematic examination of a family of proteins, the globins, revealed both a high degree of sequence variation overall and a particularly high degree of variation at surface positions (Perutz *et al.*, 1965). A subsequent study of natural haemoglobin variants in humans (Perutz & Lehman, 1968) accounted for the earlier finding by showing that exterior positions readily tolerate substitution while interior ones do not. At about the same time, a hypothesis which became known as the neutral theory of molecular evolution emerged (Kimura, 1968, 1983). This theory proposes that the great majority of amino acid substitutions that become established over the course of evolution do so not as a result of selective benefit, but rather as a result of random drift. In order for this to be true, it must be the case that a sizeable proportion of new substitutions have no significant functional effect. Thus, the globin data

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Estimating the Prevalence of Protein Sequences Adopting Functional Enzyme Folds

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Proteins employ a wide variety of folds to perform their biological functions. How are these folds first acquired? An important step toward answering this is to obtain an estimate of the overall prevalence of sequences adopting functional folds. Since tertiary structure is needed for a typical enzyme active site to form, one way to obtain this estimate is to measure the prevalence of sequences supporting a working active site. Although the immense number of sequence combinations makes wholly random sampling unfeasible, two key simplifications may provide a solution. First, given the importance of hydrophobic interactions to protein folding, it seems likely that the sample space can be restricted to sequences carrying the hydropathic signature of a known fold. Second, because folds are stabilized by the cooperative action of many local interactions distributed throughout the structure, the overall problem of fold stabilization may be viewed reasonably as a collection of coupled local problems. This enables the difficulty of the whole problem to be assessed by assessing the difficulty of several smaller problems. Using these simplifications, the difficulty of specifying a working β-lactamase domain is assessed here. An alignment of homologous domain sequences is used to deduce the pattern of hydropathic constraints along chains that form the domain fold. Starting with a weakly functional sequence carrying this signature, clusters of ten side-chains within the fold are replaced randomly, within the boundaries of the signature, and tested for function. The prevalence of low-level function in four such experiments indicates that roughly one in 10^{64} signature-consistent sequences forms a working domain. Combined with the estimated prevalence of plausible hydropathic patterns (for any fold) and of relevant folds for particular functions, this implies the overall prevalence of sequences performing a specific function by any domain-sized fold may be as low as 1 in 10^{77}, adding to the body of evidence that functional folds require highly extraordinary sequences.

Keywords: functional constraints; sequence-function relationship; sequence-structure relationship; function landscape; sequence space

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Introduction

Every quantifiable function that can be performed by proteins has a definite mapping onto the conceptual space representing all protein sequences. What can be discovered about these functional maps? Although the immense size of sequence space greatly limits the utility of direct experimental exploration, the sparse sampling that is feasible ought to be of use in addressing the most basic question of the overall prevalence of function. Progress on this front will both enhance our understanding of how new functional proteins arise naturally and inform our approach to generating them artificially.

This is a difficult problem to approach experimentally, however, and no clear picture has yet emerged. A number of studies have suggested that functional sequences are not extraordinarily rare,[1–5] while others have suggested that they are.[6–9] One of two approaches is typically used in these studies. The first, which could be termed the forward approach, involves producing a large collection of

Abbreviations used: MIC, minimum inhibitory concentration; indels, insertions and deletions.

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Transposons: Eukaryotic

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Eukaryotic transposons are distinct mobile DNA sequences, many of which can autonomously 'jump' from their locations and insert into nonhomologous parts of the genome.

Advanced article

Article Contents

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Introduction

The first eukaryotic transposable elements were discovered by analysing mutations in the aleurone and endosperm of maize (*Zea mays*). The history of this discovery is a prime example of the length of time it sometimes takes for a new scientific idea to be accepted. Barbara McClintock published her first paper on the discovery of transposons in corn in 1948. Since the prevailing view of genes from about 1900 to well into the 1960s was that they were largely rather rigid autonomous units linked together like beads on a string, the critical attitude of the genetic community to the discovery of eukaryotic transposons was hardly surprising. McClintock's first three papers, addressed to a larger audience than her annual Rockefeller reports, had no impact on the scientific community at all (for details, see McClintock, 1987). However, in the 1960s the scientific climate changed, due to advances in molecular genetics (Jacob–Monod model, discovery of insertion sequences (IS) in bacteria, transposon-mediated resistance to antibiotics). After the first eukaryotic genes had been cloned and characterized in the mid-1970s, the reality of 'jumping genes' was soon established and the full recognition of McClintock's work finally resulted in the Nobel Prize for Physiology or Medicine in 1983.

Overview and Classification

The two major classes of eukaryotic transposable elements are distinguished by their mechanism of transposition. Class I elements are retrotransposons that transpose via an RNA intermediate. Here transcription is the first step in transposition, a mechanism of TEs (transposable elements) confined to eukaryotes. Class II elements transpose via a DNA intermediate, which has to be cut out from the host DNA prior to insertion (Figure 1). Both, class I and class II transposons comprise autonomous and nonautonomous elements. Only autonomous elements are equipped with all the sequences encoding the proteins essential for propagation in the host genome. In contrast, nonautonomous ones have to be mobilized by enzymatic activities which are supplied in *trans* by autonomous elements (Lewin, 2000). While resistances carried by some elements give a clear benefit in bacteria, eukaryotic elements do not show any comparable advantage for the host. They contribute significantly, however, to the amount of DNA in their host's genome.

During the last 20 years the structures and functions of eukaryotic transposons have been elucidated by a combination of classical genetics and molecular analysis. Transposable model systems representing different classes and mechanisms as well as their impact on the living organism are presented in the next paragraphs.

Class I: Retrotransposons

Ty1 – LTR retrotransposons

The element *Ty1* (transposon yeast) represents a class of elements that display characteristic properties of

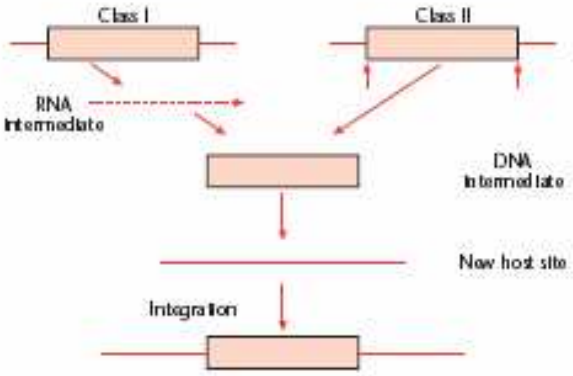

Figure 1 Transposition of class I and class II elements results in the integration of a DNA sequence into a new host acceptor site. Class I elements propagate via an RNA intermediate which is reverse transcribed into DNA. Class II elements transpose via a 'cut-and-paste' mechanism which is indicated by the two arrows at the borders of the elements.

Simulating evolution by gene duplication of protein features that require multiple amino acid residues

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(RECEIVED April 8, 2004; FINAL REVISION June 17, 2004; ACCEPTED June 17, 2004)

Abstract

Gene duplication is thought to be a major source of evolutionary innovation because it allows one copy of a gene to mutate and explore genetic space while the other copy continues to fulfill the original function. Models of the process often implicitly assume that a single mutation to the duplicated gene can confer a new selectable property. Yet some protein features, such as disulfide bonds or ligand binding sites, require the participation of two or more amino acid residues, which could require several mutations. Here we model the evolution of such protein features by what we consider to be the conceptually simplest route—point mutation in duplicated genes. We show that for very large population sizes N, where at steady state in the absence of selection the population would be expected to contain one or more duplicated alleles coding for the feature, the time to fixation in the population hovers near the inverse of the point mutation rate, and varies sluggishly with the λ^{th} root of $1/N$, where λ is the number of nucleotide positions that must be mutated to produce the feature. At smaller population sizes, the time to fixation varies linearly with $1/N$ and exceeds the inverse of the point mutation rate. We conclude that, in general, to be fixed in 10^9 generations, the production of novel protein features that require the participation of two or more amino acid residues simply by multiple point mutations in duplicated genes would entail population sizes of no less than 10^9.

Keywords: gene duplication; point mutation; multiresidue feature; disulfide bonds; ligand binding sites

Although many scientists assume that Darwinian processes account for the evolution of complex biochemical systems, we are skeptical. Thus, rather than simply assuming the general efficacy of random mutation and selection, we want to examine, to the extent possible, which changes are reasonable to expect from a Darwinian process and which are not. We think the most tractable place to begin is with questions of protein structure. Our approach is to examine pathways that are currently considered to be likely routes of evolutionary development and see what types of changes Darwinian processes may be expected to promote along a particular pathway.

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Abbreviation: MR, multiresidue

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A major route of evolutionary innovation is thought to pass through gene duplication (Ohno 1970; Lynch and Conery 2000; Wagner 2001; Chothia et al. 2003). Because one copy of the gene can continue to fulfill the original function, in this view a duplicate, redundant copy of a gene is substantially free from purifying selection, allowing it to freely accumulate mutations. Although the great majority of nonneutral mutations to duplicated genes are expected to result in a null allele (Walsh 1995; Lynch and Walsh 1998), that is, a gene that no longer codes for a functional protein, occasionally one might confer a novel function on the incipient paralog. If this occurs, then the duplicated gene can be refined by mutation and positive selection, independent of the parent gene.

In most models of the development of evolutionary novelty by gene duplication, it is implicitly assumed that a single, albeit rare, mutation to the duplicated gene can confer a new selectable property (Ohta 1987, 1988a,b; Walsh 1995). However, we are particularly interested in the ques-

Dynamic genomes, morphological stasis, and the origin of irreducible complexity

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Abstract

In spite of an enormous amount of genetic flux in plants and animals, the basic genetic processes and major molecular traits are believed to have persisted essentially unchanged for more than three-and-a-half billion years, and the molecular mechanisms of animal ontogenesis for more than one billion years. Moreover, systematics is based on virtually constant characters in space and time – otherwise this important branch of biology would not be possible. Additionally, the fossil record displays a regular pattern of abrupt appearances of new life forms (instead of their arrival by innumerable small steps in a Darwinian manner), followed by the constancy of higher systematic characters often from the genus level upwards, in many cases succeeded by an equally abrupt disappearance of the major life forms, which have died out after different periods of time. As the doyen of the synthetic theory, Ernst Mayr of Harvard, has just recently admitted, this constancy (stasis) of life forms in the face of tremendously dynamic genomes is one of the greatest problems of contemporary evolutionary biology and demands an explanation. In agreement with several researchers, I refer to arguments and facts supporting the view that irreducible complexity (Behe) in combination with specified complexity (Dembski) characterize basic biological systems and that these hypotheses might point to a non-gradualistic solution of the problem.

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Integrated Use of Multiple Interdependent Patterns for Biomolecular Sequence Analysis

David K. Y. Chiu, Thomas W. H. Lui

Abstract

Multiple interdependent patterns when consistently observed from analyzing biomolecular sequences can be a powerful indication in discovering underlying knowledge of the sequences. However, such network of interdependent patterns can be difficult to analyze or interpret. To simplify the complexity of the pattern analysis task while taking advantage of the richness from this representation, a characterization we refer to as *consigned interdependency* is proposed to describe the extracted complex patterns. Specifically, given a data sequence ensemble, suppose the interdependencies between all the units of the sequences can be extracted forming a network linking between the interdependent units of the sequences. By consigned interdependency, we refer to the detected interdependency when the network of statistical interdependencies among the ensemble are "transferred" to a subset of relations, variables or attribute values. We focus here on the third type of characterization pattern when multiple significant statistical interdependencies are transferred to a subset of values in the data ensemble. Three experiments are performed to evaluate the relevance of this characterization for pattern discovery. To evaluate some properties of the identified values, they are compared to those in high-order event patterns. To evaluate the usefulness of such consigned values as inputs for cluster analysis, a comparison using two architectures of self-organizing maps is performed. Finally, to evaluate the detected consigned values for pattern analysis, a comparison of the values to existing knowledge in the literature is performed on data of a cancer-related protein known as p53 protein. We found that interesting patterns are reflected from the proposed characterization.

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Keywords: Multiple Interdependent Patterns, Consigned Interdependency, Pattern Discovery, Self-organizing Map, Bioinformatics, p53 Protein, Cancer.

1. Introduction

Detection of complex specified information is introduced to infer unknown underlying causes for observed patterns [10]. By complex information, it refers to information obtained from observed pattern or patterns that are highly improbable by random chance alone. We evaluate here the complex pattern corresponding to multiple observations of statistical interdependency such that they all deviate significantly from the prior or null hypothesis [8]. Such multiple interdependent patterns when consistently observed can be a powerful indication of common underlying causes. That is, detection of significant multiple interdependent patterns in a consistent way can lead to the discovery of possible new or hidden knowledge.

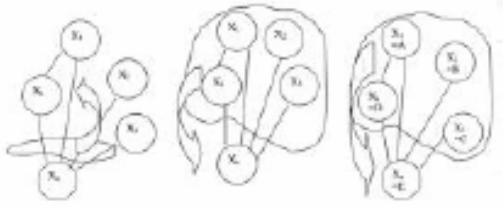

Figure 1. Three types of consigned interdependency: (a) type 1 (b) type 2 (c) type 3. Lines indicate statistical interdependency. Arrows indicate the interdependencies are ' consigned'

In this paper, we introduce a characterization we refer to as *consigned interdependency* and used as a means for knowledge discovery from analyzing a given biological sequence ensemble. By consigned interdependency, we refer to the detected patterns when the network of statistical interdependencies characterizing a data ensemble is "transferred" to a subset of relations, variables or attribute values (Figure 1). The motivation is that with the detection of significant interdependent patterns and the transferred characterization, an easier analysis can be performed for some pattern discovery tasks.

John A. Davison

A Prescribed Evolutionary Hypothesis

Abstract. *I propose that phylogeny took place in a manner similar to that of ontogeny by the derepression of preformed genomic information which was expressed through release from latency (derepression) by the restructuring of existing chromosomal information (position effects). Both indirect and direct evidence is presented in support of the Prescribed Evolutionary Hypothesis.*

1. INTRODUCTION

Historically there have been two major hypotheses to explain organic change, that of Lamarck, based on the transmission of characters acquired during the life of the individual and that of Darwin, which placed Nature in the role of selecting and thereby preserving those genetic changes which proved to be of advantage to the organism. These changes were presumed to be the means by which evolution proceeded. Each of these hypotheses has been thoroughly tested. The Lamarckian hypothesis was tested by August Weismann in Darwin's own day with negative results. The

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The origin of biological information and the higher taxonomic categories

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Introduction

In a recent volume of the Vienna Series in Theoretical Biology (2003), Gerd B. Müller and Stuart Newman argue that what they call the "origination of organismal form" remains an unsolved problem. In making this claim, Müller and Newman (2003:3–10) distinguish two distinct issues, namely, (1) the causes of form generation in the individual organism during embryological development and (2) the causes responsible for the production of novel organismal forms in the first place during the history of life. To distinguish the latter case (phylogeny) from the former (ontogeny), Müller and Newman use the term "origination" to designate the causal processes by which biological form first arose during the evolution of life. They insist that "the molecular mechanisms that bring about biological form in modern day embryos should not be confused" with the causes responsible for the origin (or "origination") of novel biological forms during the history of life (p. 3). They further argue that we know more about the causes of ontogenesis, due to advances in molecular biology, molecular genetics and developmental biology, than we do about the causes of phylogenesis—the ultimate origination of new biological forms during the remote past.

In making this claim, Müller and Newman are careful to affirm that evolutionary biology has succeeded in explaining how pre-existing forms diversify under the twin influences of natural selection and variation of genetic traits. Sophisticated mathematically-based models of population genetics have proven adequate for mapping and understanding quantitative variability and populational changes in organisms. Yet Müller and Newman insist that population genetics, and thus evolutionary biology, has not identified a specifically causal explanation for the origin of true morphological novelty during the history of life. Central to their concern is what they see as the inadequacy of the variation of genetic traits as a source of new form and structure. They note, following Darwin himself, that the sources of new form and structure must precede the action of natural selection (2003: 3)—that selection must act on what already exists. Yet, in their view, the "genocentricity" and "incrementalism" of the neo-Darwinian mechanism has meant that an adequate source of new form and structure has yet to be identified by theoretical biologists. Instead, Müller and Newman see the need to identify epigenetic sources of morphological innovation during the evolution of life. In the meantime, however, they insist neo-Darwinism lacks any "theory of the generative" (p. 7).

As it happens, Müller and Newman are not alone in this judgment. In the last decade or so a host of scientific essays and books have questioned the efficacy of selection and mutation as a mechanism for generating morphological novelty, as even a brief literature survey will establish. Thomson (1992:107) expressed doubt that large-scale morphological changes could accumulate via minor phenotypic changes at the population genetic level. Miklos (1993:29) argued that neo-Darwinism fails to provide a mechanism that can produce

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Computational universes

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Accepted 25 November 2004

Dedicated to the 60th Birthday of Mohammed El Naschie

Abstract

Suspicions that the world might be some sort of a machine or algorithm existing "in the mind" of some symbolic number cruncher have lingered from antiquity. Although popular at times, the most radical forms of this idea never reached mainstream. Modern developments in physics and computer science have lent support to the thesis, but empirical evidence is needed before it can begin to replace our contemporary world view.

1. Historical notes

In a broad context, the development of rationalism, the enlightenment and science can be perceived as an awakening from the illusory world of the senses (*Maya* in Sanskrit); as a growing awareness that "facts" which once were perceived as self-evident turned out to be utterly wrong. Humanity once took it for granted that it was located at the epicentre of the Universe. A closer inspection revealed that there is no ground to claims of any preference in location: Earth is conveniently situated in a solar system of a remote part of our galaxy, which in turn is part of a group of galaxies and of the physical Universe as we perceive it today. People also trusted that their bodies are made-up of solid stuff. Later on they learned that, as their bodies consist of atomic and subatomic "point" particles, things only appear to be solidly filled, but in another perspective, space is "almost empty." Time turned out to be relative to the motion of observers, and single "particles" such as photons and neutrons, seemed to be at two or more spatial positions at once. On another issue, people previously thought that they have been created in a different way than other species. As it turned out, from a biological point of view, mankind evolved and spread just like locusts and everyone else around. This is corroborated not only by phylogenetic evidence, but by analysis of the very DNA code that constitutes the genetic heritage and blueprint of our ancestors and of all living beings. Indeed, the DNA itself turns out to be a biochemical code running on cellular computers to the effect of creating, maintaining and reproducing the organism of which it is a part.

Further disillusionments may lie ahead. Consciousness is still an "undiscover'd country," and may be it is just a manifestation of neuronal brain functions. Or, consciousness may be just the opposite: transcendental. Despite the achievements of Freud, certain dream phases are barely understood. Artists have speculated that we are "fleshware"

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Biological function and the genetic code are interdependent

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Accepted 30 August 2005

Abstract

Life never ceases to astonish scientists as its secrets are more and more revealed. In particular the origin of life remains a mystery. One wonders how the scientific community could unravel a one-time past-tense event with such low probability. This paper shows that there are logical reasons for this problem. Life expresses both function and sign systems. This parallels the logically necessary symbolic self-referring structure in self-reproducing systems. Due to the abstract realm of function and sign systems, life is not a subsystem of natural laws. This suggests that our reason is limited in respect to solve the problem of the origin of life and that we are left taking life as an axiom.

1. Gödel formulas are subsystems of the mind

Logic (ancient Greek logice = sense/think) is in ordinary language the reasoning used to reach a conclusion from a set of assumptions. More formally, logic is the study of inference. Inference is the process whereby new assertions are produced from already established ones [1]. Logic is based on assumptions about the real world that seem obvious or unquestionable like "it should not be possible to exist and not exist at the same time". If something turns out to be logically impossible we automatically loose faith in it. In 1933, Kurt Gödel [2] proved that it was logically impossible to prove all mathematics within mathematics. This theorem has been named Gödel's first incompleteness theorem. Somewhat simplified, the theorem states: *In any consistent formalization of mathematics that is sufficiently strong to axiomatize the natural numbers—that is, sufficiently strong to define the operations that collectively define the natural numbers—one can construct a true (!) statement that can be neither proved nor disproved within that system itself* [1].

Gödel's statement says: "I am unprovable in this formal system". This turns out to be a difficult statement for a formal system to deal with since whether the statement is true or not the formal system will end up contradicting itself. However, we then know something that the formal system does not: that the statement is really true. The trick utilized by Gödel is to make the statement refer to itself (self-reference). Later it has been developed related theorems such as Turing's "Halting problem" [3] and Chaitin's constant Ω, which is the halting probability [4]. Turing's halting problem parallels essential incompleteness as formulated by Nagel and Newman [5] "*Gödel showed that Principia, or any other system within which arithmetic can be developed, is essentially incomplete. In other words, given any consistent set of arithmetical axioms, there are true mathematical statements that cannot be derived from the set . . .*".

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CHROMOSOME REARRANGEMENTS AND TRANSPOSABLE ELEMENTS

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Key Words Barbara McClintock, chromosome rearrangements, synteny, living fossils, stasis

■ **Abstract** There has been limited corroboration to date for McClintock's vision of gene regulation by transposable elements (TEs), although her proposition on the origin of species by TE-induced complex chromosome reorganizations in combination with gene mutations, i.e., the involvement of both factors in relatively sudden formations of species in many plant and animal genera, has been more promising. Moreover, resolution is in sight for several seemingly contradictory phenomena such as the endless reshuffling of chromosome structures and gene sequences versus synteny and the constancy of living fossils (or stasis in general). Recent wide-ranging investigations have confirmed and enlarged the number of earlier cases of TE target site selection (hot spots for TE integration), implying preestablished rather than accidental chromosome rearrangements for nonhomologous recombination of host DNA. The possibility of a partly predetermined generation of biodiversity and new species is discussed. The views of several leading transposon experts on the rather abrupt origin of new species have not been synthesized into the macroevolutionary theory of the punctuated equilibrium school of paleontology inferred from thoroughly consistent features of the fossil record.

CONTENTS