Concept Paper

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Conformoreplication and the Conformotype: Formalising Alt-F Proteins as a Conceptual Extension of the Central Dogma and a Third Tier of Molecular Inheritance

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Abstract

Protein conformational inheritance is documented across bacteria, fungi, and neurons, and while several authors have argued for its conceptual inclusion in molecular inheritance frameworks, a concise, widely adopted formal vocabulary that unifies these literatures remains lacking. Naming by pathological outcome rather than mechanism has partitioned prion disease research, adaptive conformational biology, and protein engineering into separate silos despite a shared mechanistic basis. This review formalises the shared mechanism with three terms. *Alt-F protein* (alternatively folded protein) names the mechanistic class irrespective of outcome. *Conformoreplication* names the protein-to-protein templated propagation of fold geometry — a third conceptual extension of the Central Dogma. The *conformotype* is the third molecular inheritance tier, transmitted through cell division independently of DNA sequence or epigenetic marks, initiated by post-translational modifications acting as environmental transducers, and regulated by the chaperone network. The framework identifies blind spots in three research fields that the current sequence-centric paradigm structurally excludes: AMR surveillance that cannot detect conformationally-encoded resistance in genotypically susceptible isolates; industrial biotechnology that screens enzyme variants by sequence but not conformational state; and neurodegeneration therapeutics that targets downstream aggregates rather than the upstream chaperone regulatory failure. To move beyond conceptual identification of these blind spots, the review operationalises each through a concrete analytical pipeline — integrating conformational proteomics, MSA-subsampled AlphaFold screening, and chaperone modulation assays — demonstrating that the conformotype framework is not merely taxonomic but immediately actionable across all three fields.

Keywords: Alt-F transition; Alt-F protein; conformotype; conformoreplication; central dogma; protein-based inheritance; conformational inheritance

I. Introduction

The Central Dogma of molecular biology defines the permitted directions of biological information transfer. (CRICK, 1958, 1970)Crick's original 1958 formulation stated that once information has passed into protein it cannot get out again; transfers from nucleic acid to nucleic acid or from nucleic acid to protein may be possible, but transfers from protein to protein or from protein to nucleic acid are impossible.(CRICK, 1958) Two subsequent experimental discoveries demonstrated two of the permitted *nucleic acid* → *nucleic acid* transfers: RNA-dependent RNA replication, confirmed in poliovirus in 1963 (Baltimore et al., 1963), and RNA-dependent DNA synthesis, confirmed in retroviruses in 1970 (BALTIMORE, 1970; TEMIN & MIZUTANI, 1970). Each discovery named a

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mechanistically distinct information transfer, and each naming was the founding act of a new research discipline.

The intellectual groundwork for this formalisation was laid across two decades of converging analyses. Shorter and Lindquist documented that prion-mediated conformational propagation confers heritable, adaptive phenotypes (Shorter & Lindquist, 2005), through Bussard's explicit challenge to the Central Dogma (Bussard, 2005) to Koonin's information-theoretic foundation (Koonin, 2012, 2015) and Daus's extension to functional amyloids (Daus, 2016). Across all these analyses, the protein → protein conformational transfer was argued for but never formally named within the Central Dogma's information-transfer vocabulary. Because this transfer involves spatial fold information rather than sequential residue information, it constitutes a conceptual extension of the Dogma rather than a revision. The present review names it, and further distinguishes two categorically different phenomena that the protein → nucleic acid arrow has always conflated — a distinction Section 2.5 makes explicit.

The absence of a shared vocabulary does not prevent research within each field — it prevents recognition across them. Each community has generated mechanistic insights that would enrich the others, but the vocabulary barrier means each must rediscover what the others already know. Yeast geneticists describe [PSI$^+$] as a 'prion-like element'; neurobiologists describe CPEB as having a 'prion-like domain'; microbiologists describe curli as a 'functional amyloid'. Each qualifier signals that the mechanism is shared but the outcome differs. Naming by outcome rather than mechanism can be scientifically limiting: it can prevent mechanistic insight from transferring across communities studying the same process. A neutral, mechanism-based nomenclature is a precondition for cross-field progress, and its absence is the gap this review fills.

The following sections formalise this framework and its nomenclature (Sections 2–4), document protein conformation-based inheritance across prokaryotes and eukaryotes (Sections 5–7), and develop its implications for antimicrobial resistance surveillance, industrial biotechnology, and neurodegeneration therapeutics (Section 8).

II. The Central Dogma: Permitted Transfers, Demonstrated Special Transfers, and a Conceptual Extension

(1) Crick's Original Formulation (1958)

In his 1958 symposium paper *On Protein Synthesis*, Crick first articulated what would become known as the Central Dogma (CRICK, 1958). He stated:

"Once 'information' has passed into protein *it cannot get out again*. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the *precise* determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein."

Thus, Crick's 1958 formulation explicitly allowed nucleic acid → nucleic acid transfers (including RNA → RNA and RNA → DNA) as possible — they simply had not yet been observed. The transfers he considered impossible were those originating from protein: protein → protein and protein → nucleic acid. The informational framework is summarised in Table 1:

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Table 1. The Central Dogma: possible and impossible information transfers (Crick, 1958 (CRICK, 1958)).

Transfer	Process	Status (1958)
DNA → DNA	Replication	Possible
DNA → RNA	Transcription	Possible
RNA → Protein	Translation	Possible
RNA → DNA	-	Possible (not observed by 1958)
Protein → Nucleic acid	-	Impossible
Protein → Protein	-	Impossible

(2) First Demonstrated Extension: RNA → RNA (RNA-Dependent RNA Replication, 1963)

The first evidence for RNA-dependent RNA replication came in 1963, when Baltimore, Eggers, Franklin, and Tamm reported RNA polymerase activity in poliovirus-infected cells — an activity insensitive to actinomycin D, the inhibitor of cellular DNA-directed RNA synthesis, confirming it was a virus-specific RNA → RNA copying enzyme (Baltimore et al., 1963). Concurrent observations in mengovirus and encephalomyocarditis virus consolidated the discovery across multiple RNA viruses. This was the first experimental demonstration of a *nucleic acid → nucleic acid* transfer that, although permitted by the Dogma, had not yet been observed. The biochemical characterisation of RNA-dependent RNA polymerases (RdRp) established the first demonstrated extension of the Central Dogma: RNA can serve as both template and product, propagating sequence information without DNA intermediacy. The subsequent discovery of RdRp activity in eukaryotes as part of the RNA interference pathway demonstrated this extension beyond viruses into the core regulatory machinery of cellular life. This first demonstration provided mechanistic support for the RNA World hypothesis (Gilbert, 1986) and established non-coding RNA as a major regulatory class.(Mattick, 2001) Viroids — non-coding ssRNA molecules that replicate without encoding any protein (Flores, Di Serio & Hernández, 1997) — represent the limiting case of this transfer class: a nucleotide sequence whose only product is itself, with structure as the direct phenotype rather than a product of translation. Their biology is examined fully in Section 3.2.

(3) Second Demonstrated Extension: RNA → DNA (Reverse Transcription, 1970)

The independent and simultaneous discovery by Temin and Baltimore of reverse transcriptase in retroviruses (BALTIMORE, 1970; TEMIN & MIZUTANI, 1970), published in Nature in June 1970, demonstrated the other *nucleic acid → nucleic acid* transfer that Crick's 1958 formulation had left as possible. RNA was confirmed as a primary genetic molecule in its own right, giving us the retroviral lifecycle, retrotransposons as genomic elements, and ultimately antiretroviral therapy. Crick acknowledged the discovery but clarified that his dogma had never absolutely excluded this transfer — it simply had no evidence for it.

(4) Third Conceptual Extension: Protein → Alt-F Protein (Conformoreplication)

The intellectual history of this challenge is longer than is commonly recognised, and Table 2 summarises its chronology. Griffith's protein-only self-replication hypothesis (GRIFFITH, 1967) constituted an implicit challenge from 1967. Crick himself, in the 1970 paper that formally restated the Dogma (CRICK, 1970), acknowledged Griffith's hypothesis as a potential difficulty — the only such acknowledgement in the Dogma's founding texts. Keyes (Keyes, 1999) documented that working biologists were invoking the Central Dogma against the infectious protein hypothesis from

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1965 onward, and was the first to formally distinguish sequential from conformational biological information as two distinct classes. Prusiner's experimental demonstration (Prusiner, 1982, 1998) established the mechanism. Bussard (Bussard, 2005) and Koonin (Koonin, 2012, 2015) then advanced explicit molecular biology arguments that prion-mediated propagation violates or extends the Dogma's scope. The present review accepts that argument and advances it by one specific contribution: formalising the transfer with a named mechanism. The protein-to-protein conformational transfer is not a violation of Crick's original prohibition because Crick's definition of "information" was explicitly sequence-based -the precise determination of residue order. Conformational propagation does not transfer sequence information; it transfers spatial information namely three-dimensional fold geometry. Crick's vocabulary had no category for this class of transfer, as Keyes recognised in 1999 (Keyes, 1999) . Conformoreplication is therefore a conceptual extension — it names a transfer the original framework could not describe — rather than a revision of a claim the framework got wrong.

Table 2. Chronology of the intellectual engagement with the Central Dogma in relation to protein conformation-based information transfer.

Year	Author(s)	Contribution	Ref
1967	Griffith	Protein-only self-replication hypothesis for scrapie — the first the first proposal requiring protein → protein transfer	(GRIFFITH, 1967)
1970	Crick	Explicitly placed protein → protein in "unknown" transfers; acknowledged Griffith's hypothesis as a potential difficulty	(CRICK, 1970)
1982–1998	Prusiner	Experimental demonstration of conformational templating as the prion mechanism; protein-only infectivity established	(Prusiner, 1982, 1998)
1999	Keyes	First scholarly distinction of 'sequential' vs 'conformational' biological information as two formally distinct classes	(Keyes, 1999)
2005	Bussard	First explicit published molecular biology argument that prions challenge the Central Dogma (EMBO Reports)	(Bussard, 2005)
2005	Shorter & Lindquist	Prions as adaptive conduits of memory and inheritance — documented beneficial protein conformation-based propagation across phylogeny	(Shorter & Lindquist, 2005)
2012	Koonin	Formal argument that prions constitute analogue protein-to-protein information transfer constituting a violation of the Central Dogma	(Koonin, 2012)
2015	Koonin	Information-theoretic basis for the Dogma's exclusion principle; digital (nucleic acid) to analogue (protein) transition is irreversible	(Koonin, 2015)

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2016	Daus	Explicit review: the Central Dogma had to be expanded following the discovery of prion-mediated protein-to-protein information transfer, prion-like amyloids, and functional amyloids	(Daus, 2016)
2018	Harvey ZH, et al.,	Protein-based inheritance as epigenetics beyond the chromosome — broad conceptual review framing prions/prion-like states as a general mechanism of heritable conformational information across all domains of life	(Harvey, Chen & Jarosz, 2018)
2018	Chakravarty AK, Jarosz DF	Prions at the crossroads of epigenetic inheritance, phase separation, and evolutionary adaptation — synthesises conformational inheritance with stress response and phenotypic plasticity	(Chakravarty & Jarosz, 2018)
2019	Otzen D, Riek R	Functional amyloids: from bacteria to humans — major perspective on the utility and evolutionary optimisation of amyloid-based conformational states	(Otzen & Riek, 2019)
2020	Balistreri A et al.	Functional amyloids are the rule rather than the exception — strong conceptual argument that beneficial conformational self-propagation is widespread and under-appreciated	(Balistreri, Goetzler & Chapman, 2020)
2022	Dennis EM et al.	Biochemical principles in prion-based inheritance — lays a modern biochemical framework for defining and studying conformational inheritance	(Dennis & Garcia, 2022)

This transfer is here formalised as *conformoreplication* — the templated propagation of protein fold geometry, in which an alternatively folded protein (Alt-F protein) converts native-fold protein molecules into the same alternative conformation. *Alt-F protein* is the neutral mechanistic class; *conformotype* is the heritable conformational state. The historical trajectory of these demonstrated extensions and the conceptual extension proposed here are illustrated in Figure 1, and the complete information transfer nomenclature of molecular biology is presented in Table 3.

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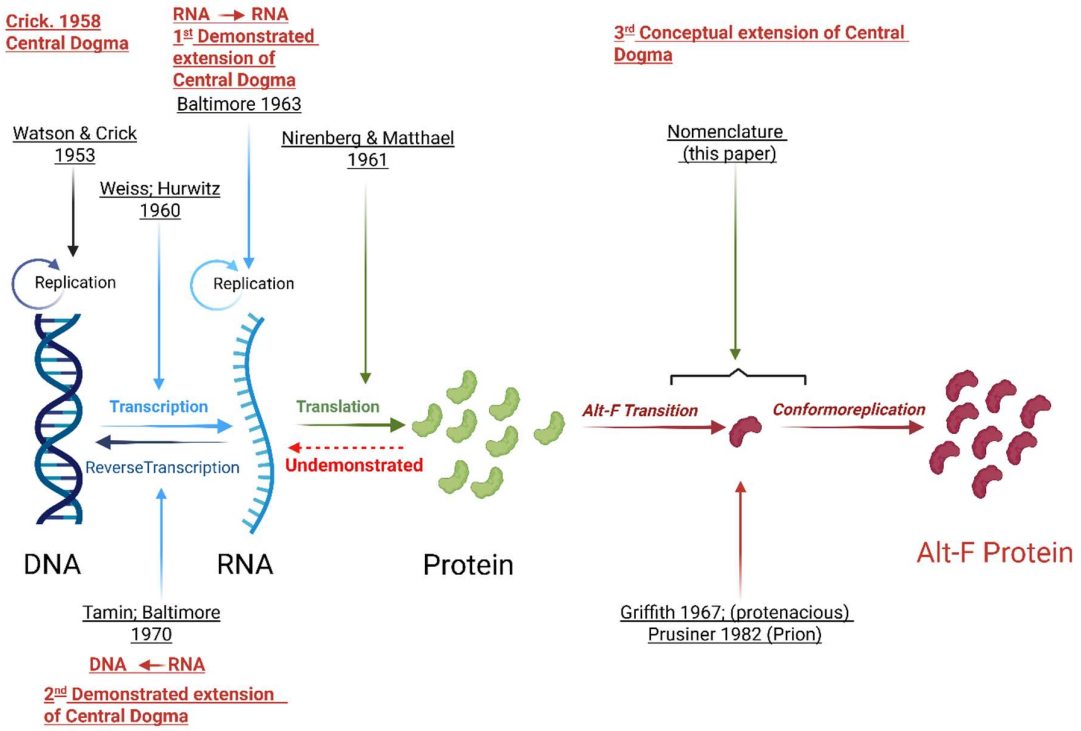

Figure 1. The Central Dogma of molecular biology: permitted transfers, the two demonstrated extensions and the third conceptual extension formalized in this review. The original formulation (Crick, 1958) established unidirectional information flow through DNA, RNA, and protein. Two subsequent revisions extended the framework: RNA→RNA replication (Baltimore, 1963) and DNA←RNA reverse transcription (Temin & Baltimore, 1970). This review proposes a third conceptual extension — protein-to-Alt-F protein information transfer — formalising the Alt-F transition (template-independent, spontaneous/genetic/PTM-driven initiation) and conformoreplication (templated propagation of fold geometry) as the mechanistic basis of this transfer. The protein→nucleic acid arrow remains formally undemonstrated. Attribution for the conceptual foundation traces to Griffith (1967) and Prusiner (1982).

Table 3. Complete information transfer nomenclature of molecular biology, including conformoreplication (this review).

Transfer	Formal Name	Key Reference
DNA → DNA	*Replication*	(WATSON & CRICK, 1953)
DNA → RNA	*Transcription*	(Weiss & Gladstone, 1959); (Hurwitz, Bresler & Diringer, 1960) (Hurwitz, 2005)
RNA → Protein	*Translation*	(Nirenberg & Matthaei, 1961)
RNA → RNA	*RNA Replication* (RdRp)	(Baltimore et al., 1963)
RNA → DNA	*Reverse Transcription*	(BALTIMORE, 1970; TEMIN & MIZUTANI, 1970)

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Native Protein → Alt-F Protein	*Alt-F transition* (Template-independent; PTM/stress-driven)	Nomenclature -This work
Alt-F Protein → Alt-F Protein	*Conformoreplication* (Template-dependent; spatial fold geometry)	Nomenclature -This work
Protein → Nucleic Acid	Sequence-determination transfer: protein active-site geometry directing nucleotide sequence (DRT3b; (Deng et al., 2026)) Regulatory-state transfer: protein conformational/occupancy state determining nucleic acid functional state (transcription factors, chromatin remodellers, conformotype-epigenotype interface)	Partially demonstrated in constrained form; sequence-general transfer remains undemonstrated, formally open Pervasive and mechanistically specified

The distinction between conformoreplication and all previously named transfers is physically significant. All prior transfers involve linear sequence information encoded in polymer monomer order. Conformoreplication involves spatial information encoded in three-dimensional geometry. These are different physical substrates for biological information, not variations on the same theme. The sequence-based inheritance framework has no conceptual category for spatial information as a unit of inheritance; the conformotypic tier proposed here provides one.

(5) The Remaining Arrow: A Partially Demonstrated, Formally Open Question

The information transfer that Crick considered truly impossible — protein to nucleic acid, in the sequence-determination sense — can no longer be treated as entirely undemonstrated. The history of the Central Dogma is a history of once-unknown or unanticipated transfers being established: reverse transcription, though absent from the original formulation and initially surprising, was later demonstrated; prion-mediated protein-to-protein transfer remained outside the Dogma's conceptual vocabulary until its mechanism was characterised. Scientific integrity requires keeping the protein → nucleic acid arrow open rather than declaring it impossible, and three recent studies of bacterial defence-associated reverse transcriptase (DRT) systems have now begun filling in the experimental answer.

A clarification of scope is necessary before examining these findings. Crick defined information in the Dogma explicitly and precisely as the determination of sequence — the direction of nucleotide order by amino acid order, or residue-by-residue sequence specification (CRICK, 1958, 1970). By this definition, the relevant question is not whether proteins influence nucleic acid function — they do, continuously and pervasively — but whether protein structure can direct nucleotide sequence de novo, without a nucleic acid template specifying the output.

Wang and colleagues demonstrated that DRT4 and DRT6, single-gene antiphage defence systems in bacteria, synthesise single-stranded DNA products through a protein-primed, fully template-independent mechanism, with a conserved tyrosine residue serving as the covalent priming site for DNA chain initiation (Wang et al., 2025)). Here the protein provides the primer but not the sequence: the resulting DNA is of random composition, making this template-independent synthesis rather than protein-directed sequence specification. Tang and colleagues then showed that DRT9 systems synthesise long poly-dA chains in which protein-primed initiation — again via conserved tyrosine residues — is combined with templating by a poly-uridine tract within an associated noncoding RNA; the protein active site enforces homopolymeric fidelity while the RNA provides the sequence instruction (Tang et al., 2025). Most directly relevant to the present discussion, Deng and

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colleagues demonstrated that DRT3 employs two mechanistically distinct reverse transcriptases in the same complex (Deng et al., 2026). Drt3a synthesises poly(GT) using an RNA template in the conventional manner. Drt3b, however, synthesises a complementary poly(AC) strand in the complete absence of any nucleic acid template, with sequence-specific base alternation enforced entirely by conserved active-site residues specific to Drt3b. This is not random template-independent synthesis: it is sequence-specific DNA synthesis directed by protein geometry alone.

Taken together, this DRT series maps a mechanistic continuum: from random protein-primed synthesis (DRT4/DRT6), through protein-constrained RNA-templated homopolymer synthesis (DRT9), to fully protein-geometry-determined sequence-specific synthesis without any nucleic acid template (DRT3b). DRT3b constitutes the first experimental instance of sequence-specific nucleic acid synthesis directed by protein structure alone — a mechanistically constrained but genuine approach to what Crick's forbidden arrow described. The DRT3b product is a simple alternating repeat rather than an arbitrary sequence, so this does not demonstrate the general amino-acid-order-directing-arbitrary-nucleotide-order transfer that Crick considered impossible. But it is a mechanistically authenticated case in which protein geometry determines nucleotide sequence without nucleic acid intermediacy, and it establishes that the arrow is no longer purely speculative.

However, Crick's definition by its own terms excluded an entirely different class of *protein → nucleic acid* interaction from the dogma's conceptual vocabulary: regulatory information transfer, in which protein conformational or occupancy state determines gene expression levels, chromatin modification states, or RNA editing patterns, without directing nucleotide sequence de novo. This class of transfer is not undemonstrated — it is the operating principle of transcriptional regulation, operating continuously through transcription factors, chromatin remodellers, and RNA-binding proteins throughout all living cells. The conformational state of HSF1 — inactive monomer or active trimer — directly determines whether heat shock genes are transcribed (Morimoto, 1998). The occupancy state of Hsp70 — free or bound to misfolded client proteins — determines whether HSF1 is released to activate its target genes, meaning the proteostatic conformational landscape of the chaperone network regulates its own genetic outputs through protein conformational states. (Shi, Mosser & Morimoto, 1998) ADAR and APOBEC family proteins directly edit RNA and DNA sequences respectively (Harris & Liddament, 2004; Nishikura, 2010), representing the closest known approach to sequence-level *protein → nucleic acid* information transfer. Most directly relevant to the present framework: the [ESI$^+$] Alt-F protein state generates regulatory information that flows through the epigenotype tier to heritably alter chromatin and gene expression trans-generationally (Harvey et al., 2020) — protein conformational state → heritable nucleic acid regulatory state — a transfer Crick's sequence-centric vocabulary had no category to describe. The *protein → nucleic acid* arrow in the Central Dogma therefore subsumes two categorically distinct phenomena that the existing literature has never formally separated within the dogma's framework. The first — sequence-determination transfer, in which amino acid order directs nucleotide order *de novo* — remains genuinely undemonstrated and is held formally open. The second — regulatory-state transfer, in which protein conformational or occupancy state determines nucleic acid functional state — is pervasive, mechanistically specified, and already operating at the conformotype-epigenotype interface described in this review. Crick's vocabulary excluded the second category not because it did not exist — protein regulation of gene activity was known in 1958 — but because his sequence-centric definition of information had no category for state-based regulatory influence. The distinction itself is implicit in the molecular biology literature; naming it here serves the specific purpose of clarifying where the conformotypic tier sits relative to the Dogma's vocabulary — at the regulatory-state level, not the sequence-determination level.

III. The Replicator Spectrum: From Sequence to Conformation

(1) The Replicator Concept: Sequence, Structure, and Conformation

The replicator concept (Dawkins, 1980) defines any entity that is faithfully copied, exhibits heritable variation, and whose variation differentially affects its probability of being copied.

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Critically, Dawkins formulated the replicator concept as explicitly substrate-independent: the logic applies to any replicating entity regardless of chemistry, and the gene was always a particular case of a more general principle rather than its definition. Viroids and prions do not challenge or contradict this framework — they exemplify it. Their existence demonstrates the predictive reach of the replicator concept: structural RNA molecules and conformationally self-propagating proteins satisfy its criteria as fully as any gene. What they challenge are different things. Viroids extend the replicator concept beyond protein-coding sequences, demonstrating that a non-coding RNA sequence whose functional output is structure rather than protein can be a fully competent replicator — a challenge to the implicit gene-centrism of the Dogma's vocabulary, not to its nucleotide-sequence basis. Prions go further: PrP^{C} and PrP^{Sc} share identical amino acid sequences, yet propagate distinct heritable states. The heritable unit is the three-dimensional conformation itself, entirely independent of nucleotide or amino acid sequence. It is prions — not viroids — that extend the Central Dogma's restriction of heritable biological information to nucleotide sequence, and it is this sequence-independence that this review formalises.

(2) Viroids: Structural RNA Replication Without Coding

Viroids are circular, non-coding ssRNA molecules of 250–400 nucleotides, the smallest known self-replicating biological entities. (Flores et al., 1997, 2015) They encode no protein. Their pathogenicity, host range specificity, and replication are determined by RNA secondary and tertiary structure — structure that is itself thermodynamically determined by the nucleotide sequence. In the nuclear-replicating Pospiviroidae, host RNA polymerases recognise structural features of the viroid RNA to initiate rolling-circle replication; in the chloroplast-replicating Avsunviroidae, replication is ribozyme-catalysed. In both cases, the structural features driving replication are the folded expression of the nucleotide sequence, not a heritable state independent of it. Viroids are plausible RNA World relics (Flores et al., 1997) — replicating entities that predate the gene, demonstrating that structural information is sufficient to drive replication when appropriate cellular machinery is available. The viroid's heritable information IS its nucleotide sequence — mutations in sequence change pathogenicity and replication. What viroids uniquely demonstrate is that a nucleotide-sequence replicator need not encode any protein: structure itself can be the functional output, without any informational relay through translation. The viroid exemplifies the replicator concept beyond the gene without departing from nucleotide-sequence heredity.

(3) Prions: Conformation-Based Replication and the Conformotype

The prion isoform (PrP^{Sc}) of the mammalian prion protein propagates by templating the refolding of native PrP^{C} into PrP^{Sc} — conformoreplication. (Prusiner, 1982, 1998; Soto & Pritzkow, 2018) The heritable information is not nucleotide sequence, not amino acid sequence (identical in PrP^{C} and PrP^{Sc}), but three-dimensional fold geometry. This heritable conformational state — the conformotype as formalised in Section 4.2 — propagates through a population of susceptible protein molecules because its thermodynamic and structural properties make templating favourable, without any encoded replication machinery.

Critically, Alt-F proteins are not inherently pathological. Many Alt-F protein conformational states have been exapted (Gould & Vrba, 1982) — co-opted from their physicochemically driven propagating state into regulated, adaptive cellular functions. In the sense of Gould and Vrba, conformational capacity arising through thermodynamic templating was subsequently recruited by cellular regulatory systems for adaptive ends, as documented from bacteria through yeast to neurons. The full outcome distribution — from strongly adaptive ([PSI^{+}], [Het-s], CPEB, curli) to catastrophic (mammalian prion disease) — is documented in Section 7. Because this outcome distribution is determined by cellular regulatory context rather than by the conformation itself, the existing term prion — coined in the context of scrapie and CJD (Prusiner, 1982) — misrepresents the class by naming it for its worst-case outcome. Alt-F protein is therefore proposed as the neutral superordinate term: mechanism defines the class; cellular context determines the outcome.

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(4) The Replicator Spectrum Formalised

Viroids, prions, and genes together define a spectrum of replicator types, distinguished by their relationship to sequence information (Table 4).

Table 4. The replicator spectrum: classes distinguished by their relationship to sequence information as the heritable unit.

Replicator	Information type	Nucleic acid required?	Coding?	Example
Gene	Nucleotide sequence	Yes (DNA/RNA)	Yes	All life
RNA virus	RNA sequence	Yes (RNA)	Yes	Influenza
Viroid	RNA sequence (non-coding; structure is phenotype)	Yes (RNA sequence)	No	PSTVd
Alt-F protein / Prion	Protein conformation	No	No	PrP^{Sc}, $[PSI^{+}]$

This spectrum reveals that self-replication is not a property unique to nucleic acids but a property of information-carrying polymers capable of templating their own structural reproduction using available cellular machinery. The table reveals one fundamental transition, not a smooth gradient. Genes, RNA viruses, and viroids are all nucleotide-sequence replicators: their heritable unit is the polymer sequence, and mutations in that sequence alter heritable properties. They differ in what the sequence encodes — protein in the case of genes and RNA viruses, structure-as-direct-phenotype in the case of viroids — but the heritable substrate in all three cases is nucleotide sequence. Alt-F proteins cross a categorically different threshold: PrP^{c} and PrP^{Sc} share identical amino acid sequences yet propagate distinct heritable states. The heritable unit is the three-dimensional conformation itself, entirely independent of any polymer sequence. The spectrum therefore has one mechanistically decisive boundary: between nucleotide-sequence-based replication (all three left-side entries) and sequence-independent conformational replication (Alt-F proteins). This boundary is what this review formalises. That the replicator concept accommodates all four types without modification is precisely the point Dawkins' substrate-independent formulation intended.

(5) Conformoreplication and Evolutionary Depth

Viroids, as minimal non-coding RNA replicators whose functional output is structure rather than protein, are plausible molecular relics of a pre-translational world (Flores et al., 1997, 2015). Their sequence-based replication without any protein product suggests that nucleotide-sequence replicators preceded the gene-as-coding-sequence, encoding function directly in RNA fold geometry. If the earliest self-replicating entities propagated structural information before translation evolved, then conformoreplication — in which fold geometry is the heritable unit entirely independent of sequence — may represent a more ancient information transfer logic than nucleotide sequence replication itself. The amyloid world hypothesis (Maury, 2015, 2018) advances this argument: in the pre-RNA era, self-replicating β-sheet amyloid conformers may have served as the first informational and catalytic entities, transmitting structural information by templated conformational propagation — a mechanism mechanistically parallel to conformoreplication as formalised in this review. On this reading, the sequence-based gene was a later, more informationally rich solution that supplemented and in most lineages displaced the earlier conformation-based replicator logic. The replicator spectrum proposed in this review — from sequence-dependent genes through structural viroids to conformation-dependent Alt-F proteins — reflects this evolutionary depth: the most minimal replicators are structural, and the most informationally rich are sequential. On this reading, conformoreplication is a remnant of the molecular logic that preceded the Central Dogma, preserved

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in functional form across billions of years because protein conformation remains the most immediate and reversible substrate for adaptive heritable variation that cells possess.

IV. Three Tiers of Inheritance: Proposing the Conformotype

(1) Genetic and Epigenetic Inheritance

Classical Mendelian genetics established that heritable information resides in discrete physical units — genes — transmitted through nucleotide sequence. The discovery that phenotypic variation could be heritably transmitted without DNA sequence change required an additional tier: the epigenetic, systematically developed following Waddington's foundational work on canalization and genetic assimilation (WADDINGTON, 1942; Waddington, 1957) and formalised through the molecular characterisation of DNA methylation, histone modification, non-coding RNA regulatory systems, and RNA modifications including N6-methyladenosine (m^6A), 5-methylcytosine (m^5C), and N1-methyladenosine (m^1A) — the epitranscriptomic layer of the epigenetic tier (Berger et al., 2009; Jablonka & Raz, 2009; Dominissini et al., 2012; Allis & Jenuwein, 2016; Roundtree et al., 2017). The question of how many inheritance systems biology contains has been addressed most ambitiously by Jablonka and Lamb (Jablonka & Lamb, 2005), whose framework of Evolution in Four Dimensions proposes four inheritance systems: genetic, epigenetic, behavioural, and symbolic. This taxonomy is deliberately broad — it spans the full range of biological and cultural information transmission, from molecular mechanisms operating within cells to organism-level learning and cultural transmission through language and ritual. That framework is foundational precisely because it established that inheritance is not a single-channel system and that evolution cannot be understood through the genetic tier alone. However, the four dimensions are not mechanistically equivalent and do not operate at the same level of biological organisation. The genetic and epigenetic tiers are molecular: they involve templating of polymer chemistry within and between cells, operate through defined biochemical mechanisms, and are reducible in principle to physical interactions between macromolecules. The behavioural tier requires a nervous system capable of learning and social transmission — it is organismal, not molecular. The symbolic tier requires cognitive capacity for language, ritual, and cultural tradition — it is cultural, not molecular. Behavioural and symbolic inheritance are genuine and important systems, but they belong to a different level of biological organisation than the molecular tiers and are not comparable on any mechanistic axis to inheritance systems operating within the cellular domain. The present framework addresses a more restricted question than Jablonka and Lamb's: how many mechanistically distinct molecular inheritance tiers operate within the cellular domain? The genetic and epigenetic tiers share a common substrate — nucleic acid chemistry — even as their mechanisms differ. West-Eberhard's developmental plasticity framework (West-Eberhard, 2003) established that phenotypic variation generated by environmental perturbation can be heritable through non-genetic mechanisms and subsequently genetically assimilated — a process consonant with Waddington's canalization concept — but did not specify a molecular mechanism for the non-genetic channel. Whether a third molecular inheritance tier exists, operating through a substrate entirely outside nucleic acid chemistry, is the question Section 4.2 addresses.

(2) The *Conformotype*: Third Tier

The third molecular inheritance tier formalised in this review is the *conformotype*: the heritable conformational state of a protein or protein network that determines a phenotypic outcome, transmitted through cell division by conformoreplication, without alteration of DNA sequence or epigenetic marks. The term completes a logically consistent series (Table 5).

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Table 5. Three mechanistically distinct molecular inheritance tiers, distinguished by substrate, mechanism, and timescale.

Tier	Formal term	What changes	What is unchanged	Mechanism	Timescale
First	Genotype	DNA sequence	—	Mutation, recombination	Generations
Second	Epigenotype	Gene regulation	DNA sequence	Methylation, histone modification	Cell cycles
Third	*Conformotype*	Protein conformation	DNA sequence + regulatory marks	Conformoreplication, PTM-biased folding, chaperone control	Minutes to cell cycles

The conformotype tier is mechanistically independent of nucleic acids. Epigenetic marks — methylation, histone modifications — are chemical modifications of nucleic acid-associated complexes and remain within the information hierarchy of the nucleic acid world. Conformotypic states are entirely proteomic, encoded in folded polypeptide geometry, transmissible through molecular contact, and reversible through chaperone-mediated refolding or protein turnover where appropriate disaggregation machinery is present (see Section 5 for the mechanistic basis of this constraint). The mechanistic independence, transmission mechanism, and reversibility of the conformotypic tier relative to the two nucleic acid-based tiers are illustrated in Figure 2.

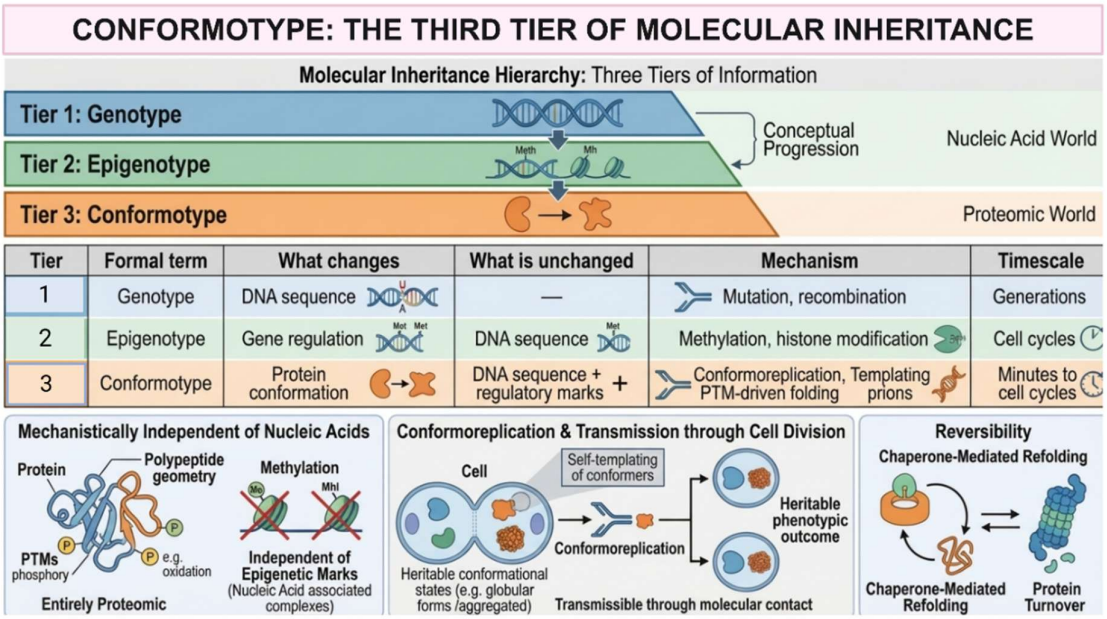

Figure 2. The conformotype as the third tier of molecular inheritance. The three molecular inheritance tiers are distinguished by substrate, mechanism, and timescale. Tier 1 (genotype) and Tier 2 (epigenotype) both operate within the nucleic acid world; Tier 3 (conformotype) is mechanistically independent of nucleic acids, encoded entirely in polypeptide fold geometry. Three properties define the conformotypic tier: (i) independence from both DNA sequence and epigenetic marks; (ii) transmission through cell division by conformoreplication — self-templating of conformers transmissible through molecular contact; and (iii) reversibility through chaperone-

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mediated refolding or protein turnover, distinguishing it from permanent genetic change. Post-translational modifications (PTMs) serve as the environmental transducers that initiate the Alt-F transition, connecting environmental stress to heritable conformational state.

(3) Conformotypic Inheritance Satisfies All Heritability Criteria

For the conformotype to constitute a genuine inheritance tier, it must satisfy: faithful transmission across cell generations; persistence independent of the initiating signal; and capacity for heritable variation. Yeast prion biology satisfies all three. The [PSI$^+$] conformotype is transmitted from mother to daughter cells through mitosis with high fidelity(True & Lindquist, 2000; Uptain & Lindquist, 2002), persists for hundreds of generations after the inducing stress resolves, and exists in multiple heritable variants — strong and weak [PSI$^+$] — that encode different phenotypic intensities from the same Sup35 sequence (Tanaka et al., 2004). Prior work has interpreted prion-mediated conformational inheritance as a form of epigenetic inheritance (Halfmann & Lindquist, 2010; Chakravarty & Jarosz, 2018). The three-tier table in Section 4.2 formalises the mechanistic distinctions that separate the conformotypic tier from the epigenetic tier. The [ESI$^+$] Alt-F protein of *S. cerevisiae* has been shown to activate gene expression and maintain heritable chromatin states trans-generationally(Harvey et al., 2020), demonstrating that the conformotype tier can interface with and regulate the epigenotype tier — with implications for the relationship between inheritance channels across the cell's integrated information system.

V. Post-Translational Modifications as Environmental Transducers: A Mechanistic Pathway

The conformotype tier requires a defined molecular mechanism by which environmental conditions induce heritable conformational states. Post-translational modifications (PTMs) provide exactly this mechanism — the molecular bridge between environmental signal and conformotypic inheritance (Bah & Forman-Kay, 2016) — constituting the Alt-F transition: the template-independent, PTM-driven conversion of a native protein to its Alt-F state that initiates the conformotypic inheritance pathway. The complete pathway is therefore: environmental stress → PTM → Alt-F transition → conformoreplication → conformotype → conformotypic inheritance.

Oxidative stress induces methionine oxidation and cysteine crosslinking, directly perturbing protein structural stability (Berlett & Stadtman, 1997). Metabolic stress alters kinase-phosphatase balances, producing aberrant phosphorylation that modifies protein-protein interaction surfaces and conformational equilibria [46]. Aging drives spontaneous, non-enzymatic deamidation primarily of asparagine residues (with glutamine deamidating at substantially lower rates) — accumulating continuously as proteins age, requiring no enzyme or signal, progressively shifting the conformational energy landscape toward aggregation-prone states (Robinson & Robinson, 2001). Altered glycosylation patterns, particularly on prion protein, shift the conformational equilibrium of PrP^{C} toward PrP^{Sc} (Rudd et al., 1999). These are not independent phenomena: they constitute a coordinated environmental read-out system at the proteome level.

The complete pathway from environmental stress to heritable conformotypic phenotype, including chaperone-mediated reversibility, is illustrated in Figure 3.

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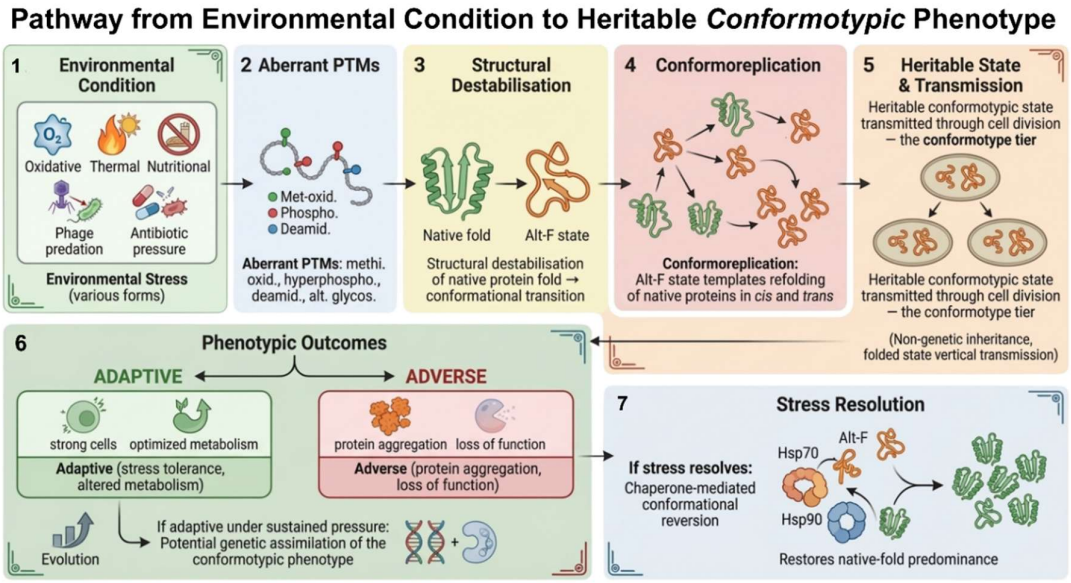

Figure 3. Pathway from environmental condition to heritable conformotypic phenotype. Environmental stressors (oxidative, thermal, nutritional, phage predation, antibiotic pressure) (Step 1) - drive aberrant post-translational modifications — methionine oxidation, hyperphosphorylation, deamidation, and altered glycosylation (Step 2) — that structurally destabilise the native protein fold and initiate the *Alt-F transition* (Step 3). The resulting Alt-F state propagates through conformoreplication, templating refolding of native protein molecules in *cis* (within the same cell) and *trans* (across cell generations) (Step 4), establishing a heritable conformotypic state transmitted through cell division (Step 5). Phenotypic outcomes span from adaptive (stress tolerance, optimised metabolism) to adverse (protein aggregation, loss of function), with the potential for genetic assimilation under sustained selective pressure (Step 6); if stress resolves, chaperone-mediated refolding — involving Hsp70 and Hsp90 — restores native-fold predominance (Step 7).

This pathway provides a molecular mechanism for the environmentally acquired, heritable phenotypic change that Waddington's genetic assimilation concept anticipated (WADDINGTON, 1942; Waddington, 1957) : an environmentally induced conformational state is transmitted to progeny through a defined biochemical pathway, and may subsequently become genetically fixed. The distribution of conformotypic outcomes — ranging from highly adaptive to catastrophic — is regulated by the cell's chaperone network. In *S. cerevisiae*, Hsp104 concentration governs whether Alt-F states propagate, are eliminated, or are maintained at defined levels (Chernoff et al., 1995). Overproduction of Hsp104 cures [PSI$^+$] by dissolving aggregates; inactivation of Hsp104 also cures [PSI$^+$] by preventing the fibril severing that generates propagating seeds. These mechanistically distinct routes to the same endpoint demonstrate true bidirectional regulatory control — the cell can both amplify and extinguish conformotypic states through the same chaperone node. Mammals lack the Hsp104/ClpB disaggregation machinery (Doyle & Wickner, 2009) that confers this bidirectional control in yeast — a mechanistic explanation for why mammalian prion disease runs catastrophically where yeast prion switching is adaptive. Mammalian prion pathology is therefore, in this framework, a failure of chaperone regulatory control, not a demonstration that conformoreplication is inherently pathological. The prion framing — implying autonomous propagation at the host's expense — captures only the adverse end of a regulated outcome distribution, and systematically misrepresents the biology of the conformotype tier.

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VI. Conformotypic Inheritance in Prokaryotes: Evidence for Adaptive Alt-F Proteins

The literature on prion-based inheritance has been focused predominantly on eukaryotes. A growing body of published evidence, however, demonstrates that conformotypic inheritance is not a eukaryotic novelty: bacteria express, regulate, and in multiple documented cases adaptively deploy Alt-F protein states through mechanisms that satisfy all the criteria of conformoreplication. The prokaryotic evidence is particularly important for the Alt-F protein framework proposed here because it demonstrates that the exaptation of Alt-F protein conformational states for adaptive cellular function is phylogenetically ancient, operating across the full breadth of life, and not dependent on the complexity of eukaryotic cell organisation.

The most extensively characterised prokaryotic Alt-F protein system is the curli fibre of *Escherichia coli*. Curli are extracellular functional amyloid fibres assembled from CsgA, a protein containing prion-like oligopeptide repeat sequences that self-assemble through conformational templating into cross-β amyloid structures (Chapman et al., 2002; Barnhart & Chapman, 2006; Sleutel et al., 2023) . Curli are not pathological: they are essential structural components of *E. coli* biofilms, mediating surface adhesion, host colonisation, and environmental persistence. CsgA amyloid assembly is regulated by the csg operon and stress-response circuitry, and the CsgA amyloidogenic sequence is conserved across phylogenetically distant bacterial species (Blanco et al., 2012) — a distribution consistent with positive natural selection acting on the conformotypic capacity, not merely on the native protein sequence. The chaplins of *Streptomyces coelicolor* form amyloid-like structures essential for aerial hyphae development (Claessen et al., 2003) — a morphological transition governed by protein conformational assembly rather than differential gene expression alone. Together, curli and chaplins establish that bacteria have evolved functional amyloid systems under positive selection for their Alt-F properties.

Three intracellular bacterial proteins have been experimentally confirmed as prion-forming Alt-F proteins. The transcription terminator Rho of *Clostridium botulinum* (Cb-Rho) was the first genetically confirmed bacterial prion (Yuan & Hochschild, 2017): its prion-forming domain confers amyloidogenicity and enables the protein to access an alternative conformation in *E. coli* that is self-propagating and functionally distinct from the native fold. Critically, the prion form of Cb-Rho is not merely a loss-of-function aggregate — it causes genome-wide changes in the transcriptome, demonstrating that an Alt-F protein state in a prokaryote can generate regulatory information that reshapes the cell's entire gene expression programme. This is a direct prokaryotic instantiation of the protein → nucleic acid regulatory information transfer discussed in Section 2.5: protein conformational state → global transcriptome state, entirely without sequence change. Phylogenetic analysis of bacterial Rho orthologues reveals that candidate prion-forming domains are present in many distantly related bacteria (Yuan & Hochschild, 2017), suggesting that prion-forming capacity in transcriptional regulators may be widespread.

The single-stranded DNA-binding protein of *Campylobacter hominis* (ChSSB) constitutes the second experimentally confirmed bacterial prion (Giraldo, 2024). Using a ClpB-dependent bacterial genetic assay, ChSSB was shown to undergo conversion to a self-propagating prion conformation that is stably transmitted across more than 100 bacterial generations (Fleming et al., 2019) — satisfying the conformotypic inheritance criteria of faithful transmission, persistence independent of the inducing signal, and heritable phenotypic variation. The native function of SSB proteins — binding single-stranded DNA to coordinate replication, repair, and recombination under stress conditions — suggests that the ChSSB prion-forming domain may represent a stress-responsive conformotypic switch in DNA metabolism. The ClpB dependence of ChSSB prion propagation directly parallels Hsp104 dependence of yeast prion propagation, confirming that chaperone-mediated regulatory control of conformotypic inheritance is conserved from bacteria to eukaryotes. The third characterised bacterial prion, RepA-WH1 of *Pseudomonas*, exhibits cytotoxicity when its prion domain is decoupled from its plasmid replication regulatory function (Giraldo, 2024) — illustrating that the

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fitness distribution of bacterial Alt-F proteins, like that of yeast Alt-F proteins, spans adaptive to adverse outcomes depending on cellular regulatory context.

The scope of prokaryotic conformotypic inheritance extends well beyond these three characterised cases. A systematic computational survey of 839 bacterial proteomes identified 2,200 candidate prion-like domains, enriched in proteins associated with stimulus response, macromolecular assembly, and cell adaptability (Iglesias, de Groot & Ventura, 2015). This distribution — prion-like domains concentrated in stress-responsive and regulatory proteins rather than in housekeeping functions — is consistent with the PTM → conformational switching → conformoreplication pathway proposed in Section 5: the proteins most likely to acquire Alt-F states under stress are precisely those whose function is to respond to stress. The picture that emerges from the bacterial evidence is therefore coherent: across phylogenetically diverse prokaryotes, Alt-F protein states have been exapted into regulatory, structural, and developmental functions, under positive selection, with chaperone-mediated control governing the outcome distribution. The conformotypic tier is not a eukaryotic speciality — it is a conserved feature of cellular information architecture whose evolutionary depth supports its status as a fundamental tier of biological inheritance.

VII. The Functional Spectrum of Alt-F Proteins: The Case for Neutral Nomenclature

(1) Alt-F Proteins Across Phylogeny: Adaptive to Pathological Outcomes

As established in Section 3.3, the Alt-F protein class is defined by mechanism, not outcome: the biological consequence of conformoreplication spans from strongly adaptive to catastrophic, determined by cellular regulatory context. The following documents that distribution across phylogeny.

The adaptive end of the distribution is well-documented. In *Saccharomyces cerevisiae*, the [PSI$^+$] Alt-F protein of Sup35 acts as a phenotypic capacitor: in its alternative conformation, ribosomal read-through of stop codons exposes previously masked genetic variation, enabling survival under environmental stress conditions that would otherwise be lethal (True & Lindquist, 2000). The [Het-s] Alt-F protein of *Podospora anserina* enforces heterokaryon incompatibility at the population level, functioning as a regulated self/non-self discrimination system that prevents cytoplasmic fusion with genetically incompatible strains (Coustou et al., 1997). In neurons, CPEB3 maintains synaptic long-term memory through a prion-like self-sustaining conformational state (Stephan et al., 2015): upon neuronal stimulation, SUMOylation of CPEB3 decreases, causing it to exit translational repression in P-bodies and transition to an amyloid-like active state that promotes local translation of synaptic plasticity proteins (Si, Lindquist & Kandel, 2003), preserving potentiation across protein turnover timescales — a mechanism through which cytoplasmic polyadenylation element-binding proteins broadly regulate synaptic plasticity (Huang et al., 2023). . In *Escherichia coli*, curli fibres constitute a fully characterised prokaryotic Alt-F protein system described in Section 6. In *Clostridium botulinum*, the Cb-Rho Alt-F protein drives genome-wide transcriptome reprogramming through conformoreplication (Yuan & Hochschild, 2017) — a bacterial prion fully characterised in Section 6.

The pathological end of the distribution is equally well-documented. Mammalian prion diseases — Creutzfeldt-Jakob disease, fatal familial insomnia, kuru — arise from the same conformoreplication mechanism, operating in an organism that lacks the Hsp104/ClpB disaggregation machinery that confers bidirectional regulatory control in yeast (Section 5) (Doyle & Wickner, 2009). The catastrophic outcome is not a property of the Alt-F conformation per se but of absent cellular regulatory controls. Neurodegeneration associated with amyloid-β, tau, α-synuclein, TDP-43, and FUS follows the same logic (Polymenidou & Cleveland, 2011; Jucker & Walker, 2013): each involves prion-like cell-to-cell propagation of an Alt-F protein state that, in the absence of adequate chaperone regulatory capacity, spreads beyond cellular containment. These are pathological Alt-F proteins — not a different class of molecule, but the same class operating outside its normal regulatory constraints.

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(2) Chaperone Regulation as the Determinant of Conformotypic Outcome

The chaperone network is the cellular architecture through which the conformotypic outcome distribution is regulated. As established in Section 5, Hsp104 governs [PSI⁺] Alt-F protein propagation bidirectionally: intermediate concentration permits propagation; overproduction or absence both extinguish it (Chernoff et al., 1995). This dose-dependence demonstrates that the cell does not merely tolerate Alt-F protein states — it governs them through a molecular rheostat whose set point determines whether conformoreplication proceeds, is amplified, or is extinguished.

Hsp90 extends this regulatory logic to the intersection of the conformotypic and genetic tiers. Under normal conditions, Hsp90 buffers the phenotypic expression of standing genetic polymorphisms, holding cryptic variants unexpressed (Rutherford & Lindquist, 1998; Queitsch, Sangster & Lindquist, 2002). Stress depletes Hsp90, simultaneously releasing genetic variation for selection and, through the same stress-response circuitry, activating PTM-driven conformational transitions in the conformotypic tier. The three inheritance tiers are therefore not independent channels operating in isolation: a single stress signal modulates the genetic, epigenetic, and conformotypic tiers simultaneously, and the integrated adaptive response is expressed at the cellular level. This integration demonstrates why the conformotype must be understood in its cellular regulatory context — not as an isolated molecular event but as one channel in a coordinated three-tier response whose outcome is a function of the whole system.

(3) The Nomenclature Consequence: Why Alt-F Protein Matters

The Alt-F protein nomenclature is not a terminological preference — it is a prerequisite for cross-field insight. A direct example: the communities studying adaptive conformational biology and neurodegeneration have developed incompatible vocabularies for the same molecular class, preventing the transfer of mechanistic insights that the shared nomenclature makes explicit.

A direct example of the insight that is lost by maintaining the partition: the therapeutic logic of Hsp104 in suppressing [PSI⁺] propagation in yeast is directly applicable to the suppression of pathological Alt-F protein propagation in neurodegeneration — a connection that is mechanistically principled, not merely analogical. Hsp104 reintroduction into mammalian neurons as a therapeutic strategy for Parkinson's disease and ALS is already an active research direction (Doyle & Wickner, 2009), but it is framed as a novel therapeutic hypothesis rather than as the application of established Alt-F protein regulatory logic to a new cellular context. The Alt-F protein framework makes the connection explicit and places it within a nomenclature shared across both research communities. The analogy in the history of biology is precise: the renaming of 'jumping genes' as transposable elements was the precondition for understanding them as drivers of genome evolution rather than genomic anomalies. Alt-F protein performs the same function for conformational inheritance — it names the mechanism and allows the full outcome distribution, from adaptive to pathological, to be investigated as a unified biological class.

VIII. Implications and Open Questions

(1) Blind Spots in Three Research Fields: Where the Conformotype Framework Changes What Is Searched For

If a third inheritance tier operates in living cells, then research programmes that characterise phenotype through genotype alone — or genotype and epigenotype — are systematically blind to a class of heritable variation. Three active research fields illustrate the practical consequences of this blind spot.

Drug resistance illustrates the conformotypic blind spot most acutely. In antimicrobial resistance (AMR) research specifically, the dominant surveillance paradigm equates heritable resistance with genomically encoded resistance: resistance genes, target mutations, regulatory mutations, and mobile genetic elements are the objects of detection (Gillings, Paulsen & Tetu, 2017). Genomic AMR surveillance based on this assumption will systematically fail to detect resistance that is conformotypically maintained. The published evidence that this is not hypothetical is direct: Berry and colleagues documented in 2013 that anti-prion drug treatment selects for drug-resistant prion

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strains through conformational change in the prion protein rather than through nucleotide mutation (Berry et al., 2013). They named this 'conformational mutagenesis' and demonstrated that the kinetics of drug resistance acquisition followed the laws of conformational selection rather than classical mutational genetics.

This is an experimentally confirmed instance of heritable phenotypic resistance arising through a conformotypic mechanism without genomic change — in a system that entirely lacks nucleic acid replication machinery and can therefore only change through conformational selection. Whether a mechanistically analogous process operates in bacteria remains an open, undemonstrated hypothesis. The shared conceptual core is in principle applicable: a bacterial target protein — an efflux pump, a cell wall biosynthetic enzyme — acquiring a heritable alternative conformation under antibiotic stress could generate a drug-resistant phenotype through conformoreplication, potentially representing a faster adaptive route than mutational fixation.

The clinical motivation for this hypothesis is direct. A nationwide Danish surveillance study (Rebelo et al., 2022) documented that 2.1% of all isolate-antimicrobial combinations tested showed persistent phenotypic resistance without an identifiable resistance genotype — corresponding to 26.4% of all detected phenotypic resistances — a pattern confirmed across multiple systematic comparisons of WGS-based predictions with phenotypic AST (Yee, Dien Bard & Simner, 2021). Such phenotypic/genotypic discordances are conventionally attributed to heteroresistance, inducible resistance, assay limitations, or ESBL categorisation differences. The conformotypic framework adds a previously unconsidered candidate to this list, and invites reanalysis: proteomic profiling of target protein conformational states in discordant isolates under sub-inhibitory antibiotic pressure would constitute the first direct test of whether bacterial conformotypic AMR exists.

In industrial biotechnology and enzyme engineering, directed evolution and rational design operate exclusively on amino acid sequence as the determinant of enzyme function. The conformotypic tier is invisible to this framework. Yet the catalytic amyloid literature demonstrates that Alt-F protein conformations can be catalytically active: designed amyloid-forming peptides catalyse ester hydrolysis, peroxidase, and phosphatase reactions (Rufo et al., 2014); α-synuclein fibrils exhibit esterase and phosphatase activity absent from the native monomer (Omosun et al., 2017); the functional amyloid CsgA exposes an ordered surface architecture in its Alt-F state that differs fundamentally from its native conformation. The honest qualification is important: catalytic activity in the amyloid state currently documented for designed short peptides and a small number of native proteins represents a proof-of-concept rather than an established biotechnological capacity. Catalytic rates are generally lower than those of optimised native enzymes. But the question that the conformotypic framework makes askable — and that directed evolution alone cannot ask — is whether the Alt-F conformation of a given industrial enzyme has catalytic properties distinct from, and potentially superior to, its native fold for specific reaction conditions. Surveying industrial enzyme libraries for Alt-F catalytic capacity is an unexplored dimension of enzyme discovery that the current sequence-centric paradigm structurally excludes.

In neurodegeneration research, reframing Alzheimer's disease (amyloid-β, tau), Parkinson's disease (α-synuclein), ALS (TDP-43, FUS), and Huntington's disease (polyglutamine expansions) as pathological conformotypic inheritance — modulated by the PTM → conformational transition → conformoreplication pathway formalised here — unifies the mechanistic basis of neurodegeneration across disease classes (Polymenidou & Cleveland, 2011; Jucker & Walker, 2013). The current therapeutic logic largely targets downstream consequences: clearance of aggregated protein, inhibition of fibril elongation, or blockade of cell-to-cell spread. The conformotypic inheritance framework redirects attention upstream: the PTM environment that triggers initial conformational transition, and the chaperone regulatory architecture whose failure permits uncontrolled conformoreplication. Interventions that restore Hsp104/Hsp70 regulatory capacity, correct the PTM environment, or reinstate the cellular controls that maintain adaptive Alt-F protein propagation within bounds address the conformotypic mechanism rather than its downstream consequences — a fundamentally different and mechanistically more proximal intervention target.

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(2) Experimental Predictions

The conformotypic inheritance framework generates three classes of falsifiable cellular experiment, each designed to distinguish conformotypic from genetic or epigenetic mechanisms. First, induction of specific PTMs — oxidative stress, targeted kinase activation, or accelerated spontaneous deamidation through prolonged culture conditions — should produce heritable phenotypic states that persist through cell division in the absence of any genomic change, detectable by proteomic profiling of daughter populations. Second, chaperone titration experiments — modulating Hsp104, Hsp70, or Hsp90 levels through conditional overexpression or depletion — should bidirectionally control the penetrance and heritability of PTM-induced conformotypic states, consistent with the chaperone rheostat model. Third, and most diagnostically, the conformotypic nature of a heritable state can be distinguished from epigenetic inheritance by its protein-turnover dependence: complete protein turnover through cycloheximide treatment followed by reintroduction of the native protein should extinguish a conformotypic state but leave epigenetic marks intact, while DNA methylation inhibitors should affect the latter but not the former. The computational tools for identifying candidate Alt-F states that anchor these experiments are described in Section 8.4.

(3) Operationalising the Conformotype Framework

Identifying blind spots is a conceptual contribution; directing attention toward how to close them is a practical one. The conformotype framework enables three concrete workflows, each of which integrates conformational proteomics and MSA-subsampled AlphaFold screening with existing disciplinary infrastructure. The computational foundation common to all three is AlphaFold2 with modified multiple sequence alignment (MSA) input — specifically, MSA subsampling approaches including SPEACH-AF, AFsample, and the sequence-clustering method of (Wayment-Steele et al., 2024), which have successfully predicted multiple conformational states for fold-switching proteins and, in one case, produced an amyloid-like structure of Aβ42 consistent with experiment (Abramson et al., 2024). These tools predict candidate structures rather than heritable propagation capacity; experimental validation remains necessary, but the computational identification of candidate Alt-F states is no longer a bottleneck.

(a) AMR surveillance pipeline. In clinical isolates that exhibit phenotypic resistance without an identifiable resistance genotype, whole-genome sequencing first rules out sequence-level mechanisms. Conformational proteomics — using limited proteolysis-mass spectrometry (LiP-MS) or ion-mobility MS — is then applied to detect altered folding states in stress-response and efflux proteins, guided by MSA-subsampled AlphaFold predictions of candidate Alt-F conformers for those targets. Functional impact is assessed by measuring efflux pump activity or cell-wall integrity under sub-inhibitory antibiotic pressure, with and without chaperone modulators such as Hsp70 inhibitors. Positive correlation between detected Alt-F signatures and resistance phenotype would constitute direct evidence of conformotypic AMR and could be integrated as a supplementary tier within existing national surveillance platforms (Nissley et al., 2022; Bai et al., 2023).

(b) Industrial biotechnology and enzyme engineering pipeline. Directed evolution and rational design currently explore sequence space exclusively. The conformotypic framework opens a parallel conformational dimension: industrial enzyme candidates expressed under controlled stress conditions that induce relevant PTMs are screened by MSA-subsampled AlphaFold to identify candidate Alt-F states. Promising conformers are expressed, purified, and assayed for catalytic activity, stability, or substrate specificity under target industrial conditions — with particular attention to amyloid-like or alternative folds that expose ordered surface architectures with novel catalytic properties. Hits can be further tuned through PTM-mimetic mutations, yielding conformationally switchable enzymes that are orthogonal to sequence variants and inaccessible to conventional directed evolution (Wayment-Steele et al., 2024).

(c) Neurodegeneration therapeutics pipeline. Rather than targeting downstream protein aggregates, the conformotype framework redirects therapeutic attention upstream — to the PTM environment that initiates the Alt-F transition and to the chaperone architecture whose failure permits uncontrolled conformoreplication. In patient-derived iPSC-neurons or transgenic models,

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small-molecule or genetic modulators of specific PTMs — kinase inhibitors, deamidation blockers — and of chaperone activity — potentiated Hsp104 variants, Hsp70/Hsp90 co-chaperone enhancers — are screened against conformotypic endpoints: reduction in Alt-F propagation rate, restoration of native-fold predominance, and rescue of synaptic or neuronal function, rather than mere aggregate clearance (Jackrel & Shorter, 2014)) This upstream logic offers the possibility of preventing pathological conformoreplication rather than mitigating its consequences — a fundamentally different and mechanistically more proximal intervention target. The three pipelines are summarised in Table 6.

Table 6. Operational pipelines enabled by the conformotype framework.

Field	Input Data	Conformotypic Analysis Step	Output / Actionable Outcome	Expected Impact
AMR Surveillance	Phenotypic AST + WGS (no resistance genotype)	Conformational proteomics + MSA-subsampled AlphaFold on stress/efflux proteins	Detection of Alt-F signatures correlating with resistance	Identification of conformotypic resistance; improved surveillance accuracy
Industrial Biotechnology	Enzyme sequence library + stress-induced expression	MSA-subsampling / clustering AlphaFold + activity assays on predicted Alt-F states	Conformation-specific catalysts with novel properties	Expanded enzyme toolbox beyond sequence space
Neurodegeneration Therapeutics	iPSC-neurons or animal models	PTM modulation + chaperone titration + conformational monitoring	Upstream rescue of native fold and reduced Alt-F propagation	Prevention-focused therapies targeting conformoreplication root cause

(4) Synthetic Conformotypes and Ethical Considerations

The mechanistic specification of the conformotypic tier opens a practical corollary: the possibility of engineering it. Synthetic Alt-F proteins — designed to adopt stable alternative folds under defined environmental triggers, template that fold in target molecules, and produce defined phenotypic outputs — represent a class of biological tool orthogonal to genetic engineering, operating without altering DNA sequence and in principle reversible through chaperone manipulation. Beyond synthetic biology, the Alt-F protein mechanism — bistable structural states that propagate through molecular contact without central programming and are reversible through regulatory inputs — constitutes a design principle for adaptive swarm robotics and nanobot systems in which collective state transitions emerge from local conformational templating rather than explicit reprogramming, an unexplored dimension of bio-inspired engineering. The ethical implications parallel those of gene drives (Esvelt et al., 2014): designed replicators, whether genetic or conformotypic, raise questions of ecological containment and unintended conformotypic spread that the field should address proactively, before the technology precedes the framework.

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IX. Summary and Conclusion

1. When a native-fold protein undergoes template-independent conversion to a stable alternative conformation — driven by post-translational modifications, environmental stress, or spontaneous nucleation — that event is an **Alt-F transition**. The resulting protein, now stably folded in an alternative geometry with distinct functional consequences, is an **Alt-F protein**. When that Alt-F protein binds to other native-fold protein molecules of the same sequence and converts them into the same alternative conformation, the propagation event is **conformoreplication**. The heritable conformational state that is transmitted through cell division as a result — independently of DNA sequence or epigenetic marks — is the **conformotype**. These four terms name a single mechanistic pathway: environmental stress → PTM → Alt-F transition → Alt-F protein → conformoreplication → conformotype. This pathway constitutes a third conceptual extension of the Central Dogma, distinct from all prior information transfers because its heritable unit is three-dimensional spatial fold geometry rather than linear polymer sequence.
2. The Alt-F protein class is defined by mechanism, not outcome. It encompasses pathological prions (PrP^{Sc}), adaptive yeast prions ([PSI^+], [Het-s]), functional amyloids (curli, chaplins), and synaptic memory proteins (CPEB3) — entities currently partitioned across incompatible vocabularies despite sharing a common mechanistic basis. The existing term *prion* names this class by its worst-case outcome; *functional amyloid*, *prion-like domain*, and *prion-like element* each signal a shared mechanism while refusing to name it. *Alt-F protein* names the mechanism and allows the full outcome distribution, from strongly adaptive to catastrophic, to be studied as a unified biological class.
3. The conformotype constitutes a third molecular inheritance tier alongside the genotype and epigenotype, mechanistically independent of nucleic acid chemistry. Post-translational modifications act as environmental transducers — the molecular bridge between external stress and initiation of the Alt-F transition. The chaperone network functions as the cellular rheostat that governs whether the resulting Alt-F protein state propagates, is amplified, or is extinguished: bidirectional control demonstrated most precisely by Hsp104 in yeast, whose overproduction dissolves [PSI^+] by disaggregating fibres and whose inactivation also cures [PSI^+] by preventing the fibril severing that generates propagating seeds. Mammals lack Hsp104/ClpB disaggregation capacity — a mechanistic explanation for why mammalian prion disease runs catastrophically where yeast prion switching is adaptive.
4. Conformotypic inheritance satisfies all formal heritability criteria — faithful transmission across cell generations, persistence independent of the initiating signal, and capacity for heritable variation — as documented across phylogeny: in yeast ([PSI^+] transmitted through hundreds of mitotic generations with high fidelity), in bacteria (Cb-Rho driving genome-wide transcriptome reprogramming; ChSSB propagating stably across more than 100 bacterial generations; curli fibres under positive selection for Alt-F properties), and in neurons (CPEB3 maintaining synaptic long-term potentiation across protein turnover timescales through a prion-like conformational switch). The conformotypic tier is not a eukaryotic speciality — it is a conserved feature of cellular information architecture.
5. The framework exposes structural blind spots in three active research fields. In AMR surveillance, the dominant paradigm equates heritable resistance with genomically encoded resistance; a bacterial target protein acquiring a heritable alternative conformation under antibiotic stress — a faster adaptive route than mutational fixation — would be entirely invisible to whole-genome sequencing, and clinical evidence for this blind spot already exists in the form of persistent phenotypic/genotypic discordances documented at scale. In industrial biotechnology, directed evolution and rational design operate exclusively on sequence space, leaving Alt-F catalytic capacity — documented for designed amyloid-forming peptides and native proteins including α-synuclein — entirely unexplored. In neurodegeneration, therapeutic strategies targeting downstream aggregates miss the upstream PTM environment and

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chaperone regulatory failure that permit uncontrolled conformoreplication across Alzheimer's, Parkinson's, ALS, and Huntington's disease.

6. Each blind spot is operationalised through a concrete analytical pipeline integrating conformational proteomics (LiP-MS, ion-mobility MS), MSA-subsampled AlphaFold screening, and chaperone modulation assays. These pipelines demonstrate that the conformotype framework is not merely taxonomic: it generates testable, field-specific protocols for detecting previously invisible heritable variation — and in neurodegeneration, redirects therapeutic attention from aggregate clearance to the prevention of pathological conformoreplication at its source.
7. The question of whether conformoreplication predates nucleic acid-based inheritance — motivated by the amyloid world hypothesis and the evidence from viroids as RNA World relics — positions the conformotype tier not as a novelty of complex life but as a possible remnant of the most ancient information-transfer logic, preserved across billions of years because protein conformation remains the most immediate and reversible substrate for adaptive heritable variation that cells possess. On this reading, the sequence-based gene was a later, informationally richer solution that supplemented but did not replace the earlier conformation-based replicator logic.
8. The novelty of the present contribution lies not in the underlying argument — which(Bussard, 2005), (Koonin, 2012, 2015), and (Daus, 2016) each advanced in their respective frameworks — but in the act of formal naming. Alt-F transition, Alt-F protein, conformoreplication, and conformotype supply a shared mechanistic vocabulary that travels across communities, renders the same biology recognisable regardless of field, and replaces a collection of outcome-named terms that have prevented the cross-field transfer of insight for four decades.

X. Glossary of Proposed Terms

Term	Definition and rationale
Alt-F transition	The template-independent conversion of a native-fold protein to its alternatively folded (Alt-F) state, driven by post-translational modifications, environmental stress, or spontaneous nucleation. The initiating event in conformotypic inheritance — mechanistically distinct from conformoreplication, which is the subsequent template-dependent propagation of the Alt-F state. Names the first step in the pathway: environmental stress → PTM → Alt-F transition → conformoreplication → conformotype.
Alt-F Protein (Alternatively Folded Protein)	Any protein that adopts a stable alternative conformation with distinct functional consequences. Neutral superordinate term encompassing pathological prions, adaptive yeast prions, functional amyloids (curli), and synaptic memory proteins (CPEB). Abbreviation Alt-F carries the mnemonic of 'alternative function', as in the keyboard command Alt+F. Broader than prion, which retains its existing pathological connotation as a specific subclass.
Conformoreplication	The process by which an Alt-F protein templates the refolding of native-fold protein molecules into the same alternative conformation. The third conceptual extension to the Central Dogma framework, following the two prior revisions): Protein → Alt-F Protein. Completes the Central Dogma nomenclature with a

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	formally parallel term. Distinguished from all prior transfers by its non-sequence, spatial information substrate.
Conformotype	The heritable conformational state of a protein or protein network that determines a phenotypic outcome, transmitted through cell division without alteration of DNA sequence or epigenetic marks. The informational unit of the third tier of inheritance. Completes the series: genotype, epigenotype, conformotype.

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