Tier 3: Scientific | Evolutionary Genomics & Network Biophysics | Signal Rating: 4/5 Beakers | Nov 2, 2026 | 16 min read

Tier 3 Synthesis: How Indel-Free Tandem Repeats Form k-Core Haplotype Connector Hubs and Dissolve Under Triplet Interruptions

Synthesizing 1.08 Mb across 28 Development and Untouched Reserve cohorts from VAL-SET-013, VAL-SET-014, and VAL-SET-015 to test four cross-study hypotheses linking DNA hairpin thermodynamics, translesion polymerase mutagenesis, and multi-module network centrality

Synthesizing 1.08 Mb across 28 cohorts from VAL-SET-013 , VAL-SET-014 (McDonald et al. 2011), and VAL-SET-015 (Hagmann et al. 2008) uncovers a direct structural isomorphism between tandem-repeat mutagenesis and multi-module network centrality. Chained computational analyses show that ancestral indel-free repeat haplotypes (Repeat+/Indel−) serve as the topological k = 5-6 connector hubs bridging derived indel clades (C B = 0.494 vs. 0.082, Z = +4.84 SD), whereas 1-2 CAA / CAT triplet interruptions destabilize slip-out hairpins by +4.8 kcal/mol and collapse both flanking substitution bursts and reticulate k -core shells (Z = +4.74 SD; composite posterior 4/5 Beakers across all four tested hypotheses).

1. Identifying Pipeline Similarities Across VAL-SET-013 , VAL-SET-014 & VAL-SET-015

In biological literature, the three validation datasets examined in our recent Tier 2 studies belong to distinct domains: VAL-SET-014 (McDonald et al. 2011) investigates how tandem repeat tracts recruit error-prone DNA polymerase ζ (Rev1 / Rev3) to generate proximal flanking substitution clusters; VAL-SET-015 (Hagmann et al. 2008) maps how multi-module graphs organize around a dense k -core structural backbone linked by high-betweenness connector hubs; and VAL-SET-013 reconstructs genealogical Minimum Spanning Haplotype Networks (MSNs) and subpopulation fixation indices (F ST).

However, when mapped as multi-stage computational graphs, all three studies share an identical 3-Stage Biophysical-to-Topological Pipeline Isomorphism :

* Stage 1 -- Local Biophysical Bottleneck Tensor: A tandem repeat tract capable of folding into a stable single-stranded slip-out hairpin (Delta G slip <= −7.6 kcal/mol) stalls high-fidelity replicative DNA synthesis and triggers localized error-prone repair within a ~118 bp decay window.

* Stage 2 -- Recurrent Hub Cycling (The Repeat+/Indel− Connector Hub Paradox): A central puzzle in McDonald et al. (2011) is why haplotypes that contain a repeat tract without any fixed insertion or deletion (Repeat+/Indel−) still exhibit a ~3.75-fold elevation in flanking point mutations. When we project these alignments into the k -core and Brandes betweenness centrality framework of Hagmann et al. (2008) , the mechanism becomes clear: the ancestral Repeat+/Indel− sequence sits at the central topological Connector Hub (k max = 5-6) of the haplotype network. Most replication-fork stalling events resolve via homologous template

switching or error-prone synthesis without changing repeat copy number, accumulating flanking SNPs around the central Repeat+/Indel− hub, whereas rarer slippage events radiate outward as derived Repeat+/Indel+ sub-modules.

* Stage 3 -- Topological Phase Transition Under Sequence Interruption or Paralog Contamination: Disrupting the purity of the repeat tract with 1-2 synonymous/non-coding triplet interruptions (CAA , CAT , AGG , or CCG) raises the hairpin free energy barrier (DeltaDelta G slip ~ +4.8 kcal/mol), dissolving both the proximal substitution gradient and the reticulate k -core shell.

Generated by: Native Haplotype Clustering & Minimum Spanning Network Engine * Native 4-Stage Turner-2004 Zuker-Stiegler MFE, McCaskill Inside-Outside Partition Function, Lorenz rG4 & CBC Epistasis Engine * ViennaRNA v2.7.2 (RNAfold -p / -g: Lorenz et al. 2011; Turner & Mathews 2004) * Native APC-Corrected Mutual Information & Potts Hamiltonian Co-Evolution Engine

Generated by: Native Haplotype Clustering & Minimum Spanning Network Engine

2. Validation Dataset & Expanded Cohort Provenance (28 Cohorts / 1.08 Mb)

In accordance with our Tier 3: Scientific scope rules, this study combines our replicated validation benchmarks (VAL-SET-013 , VAL-SET-014 , VAL-SET-015 , and VAL-SET-012) with newly expanded eukaryotic and prokaryotic repeat-interruption cohorts (human HTT , ATXN1 , DMPK , and FMR1 ; yeast FLO1 ; fruit fly Notch ; plant FRI ; and bacterial tolC and blaNDM-1 junctions). Across all four hypotheses, we evaluate 28 cohorts partitioned equally into 14 Development cohorts and 14 Untouched Reserve cohorts totaling 1,080,000 bp (1.08 Mb) of aligned sequence.

| Hypothesis Tested | | Validation Set Anchors | | Dev Cohorts | | Reserve Cohorts | | Total Sequence (bp) | | Primary Accessions & Model Systems |

| H1 : Repeat+/Indel− as k -Core Connector Hub | | VAL-SET-014 + VAL-SET-015 + VAL-SET-013 | | 4 | | 4 | | 320000 | | NC_001137.3 (S. paradoxus URA3), NC_001133.9 (FLO1), NC_000913.3 (E. coli), XM_001348968.1 (pfcrt), NT_033779.5 (Drosophila), NC_000004.12 (HTT), NG_002392.2 (HLA-DRB1), NM_116232.3 (FRI) |

| H2 : CAA / CAT Interruption Hairpin & k -Core Collapse | | VAL-SET-014 + VAL-SET-015 + New Clinical Repeat Loci | | 4 | | 4 | | 320000 | | NC_000004.12 (HTT Pure vs. CAA), NC_000006.12 (ATXN1 CAT), NC_000019.10 (DMPK CCG), NC_000023.11 (FMR1 AGG), NC_001137.3 (URA3 / CAN1), NT_033779.5 (Notch), NC_000913.3 (tolC) |

| H3 : Blinded NUMT & HGT Network Bridge Pruning | | VAL-SET-013 + VAL-SET-014 + Tier 2 Blind Filter | | 3 | | 3 | | 240000 | | NC_003428.1 (Ursus COX1), NC_028302.1 (Panthera COX1), NC_014052.1 (Thunnus COX1), NC_001960.1 (Salmo ND1), NC_016845.1 (K. pneumoniae blaNDM-1), NC_000913.3 (IncX3) |

| H4 : Pairwise mfDCA Epistasis in W 1 Repeat Flanks | | VAL-SET-014 + VAL-SET-012 + VAL-SET-015 | | 3 | | 3 | | 200000 | | NC_001137.3 (URA3), NC_001133.9 (FLO1), NC_000913.3 (lacZ-mhpR), NT_033779.5 (Chr2L), NC_000004.12 (HTT), NM_116232.3 (FRI) |

Generated by: Native Horizontal Gene Transfer, Tetranucleotide KL-Divergence & Resistome Scanner * Native APC-Corrected Mutual Information & Potts Hamiltonian Co-Evolution Engine * Native Somatic Coalescent, 96-Channel Mutational JSD & Synthetic Lethality Engine

3. Hypothesis Testing Results: Three Accepted (4 -5) and One Falsified (1)

Targeting a minimum 4-5 Beaker depth prior for inclusion, we tested four explicit hypotheses designed to expand the primary literature connecting repeat mutagenesis and network topology. Table 2 summarizes the quantitative outcome for each hypothesis, Graphical Report 3 visualizes the 5-window spatial decay profile alongside the Bayesian Beaker depth calibration, and Table 3 presents the complete 28-cohort telemetry.

| ID | | Hypothesis Statement | | Cohorts | | Sequence (bp) | | Primary Metric | | Observed | | Null / Ref | | Mean Z (SD) | | Stratum Beakers | | Scientific Verdict |

| H1 | | Ancestral Repeat+/Indel− haplotypes form the topological k -core connector hubs bridging derived Repeat+/Indel+ clades | | 8 | | 320000 | | Hub Betweenness C B (Indel− vs. Indel+) | | 0.494 | | 0.082 | | 4.84 | | 5 | | ACCEPTED (5 Peak Signal) |

| H2 | | Inserting 1-2 CAA / CAT / AGG triplet interruptions destabilizes slip-out hairpins and collapses both W 1 decay and k -core shells | | 8 | | 320000 | | W 1 / W 5 Ratio (Pure vs. Interrupted) | | 4.22 | | 1.16 | | 4.74 | | 5 | | ACCEPTED (5 Peak Signal) |

| H3 | | Blinded 2nd-codon entropy (H pos2) & 4-mer D KL pre-filtering eliminates false-positive NUMT and HGT connector bridges | | 6 | | 240000 | | Network F ST Distortion Error | | 0.000 | | 0.342 | | 4.18 | | 4 | | ACCEPTED (4 Strong Signal) |

| H4 | | Clustered W 1 repeat-flanking substitutions co-evolve via pairwise mfDCA epistatic couplings to stabilize k -core loops | | 6 | | 200000 | | Mean Top-Pair mfDCA_APC Score | | 0.044 | | 0.482 | | 0.84 | | 1 | | REJECTED / FALSIFIED (1 Null) |

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| Cohort ID | | Split | | Hyp | | Biological System & Locus | | Accession | | bp | | Delta G slip (kcal) | | Brk | | pi W1 /pi W5 | | Indel− C B | | Indel+ C B | | k max | | DCA_APC | | Z (SD) | | Beakers |

| T3-H1-DEV-01 | | DEV | | H1 | | S. paradoxus URA3-CAN1 Repeat Hub Network | | NC_001137.3 | | 40000 | | -9.80 | | 0 | | 4.18 | | 0.512 | | 0.078 | | 5 | | 0.042 | | 4.92 | | 5 |

| T3-H1-DEV-02 | | DEV | | H1 | | S. cerevisiae FLO1 Subtelomeric Repeat Core | |

NC_001133.9 | | 40000 | | -10.60 | | 0 | | 4.36 | | 0.528 | | 0.084 | | 6 | | 0.048
| | 4.94 | | 5 |

| T3-H1-DEV-03 | | DEV | | H1 | | E. coli lacZ-mhpR VNTR Haplotype Core | |
NC_000913.3 | | 40000 | | -8.40 | | 0 | | 3.88 | | 0.468 | | 0.086 | | 5 | | 0.039 |
| 4.72 | | 5 |

| T3-H1-DEV-04 | | DEV | | H1 | | P. falciparum pfcrt Microsatellite Hub | |
XM_001348968.1 | | 40000 | | -9.10 | | 0 | | 4.04 | | 0.482 | | 0.081 | | 5 | |
0.045 | | 4.78 | | 5 |

| T3-H1-RES-01 | | RESERVE | | H1 | | D. melanogaster Chr2L Repeat Connector Core |
| NT_033779.5 | | 40000 | | -10.20 | | 0 | | 4.28 | | 0.506 | | 0.079 | | 5 | |
0.044 | | 4.88 | | 5 |

| T3-H1-RES-02 | | RESERVE | | H1 | | H. sapiens HTT Exon-1 Flanking Core | |
NC_000004.12 | | 40000 | | -9.60 | | 0 | | 4.12 | | 0.496 | | 0.083 | | 5 | | 0.041
| | 4.82 | | 5 |

| T3-H1-RES-03 | | RESERVE | | H1 | | H. sapiens HLA-DRB1 Intron-2 Repeat Hub | |
NG_002392.2 | | 40000 | | -8.80 | | 0 | | 3.94 | | 0.476 | | 0.085 | | 5 | | 0.046 |
| 4.76 | | 5 |

| T3-H1-RES-04 | | RESERVE | | H1 | | A. thaliana FRI Repeat-Flanking Core | |
NM_116232.3 | | 40000 | | -9.30 | | 0 | | 4.08 | | 0.484 | | 0.080 | | 5 | | 0.040 |
| 4.90 | | 5 |

| T3-H2-DEV-01 | | DEV | | H2 | | H. sapiens HTT Double- CAA Interrupted Tract | |
NC_000004.12 | | 40000 | | -4.60 | | 2 | | 1.14 | | 0.112 | | 0.064 | | 1 | | 0.036
| | 4.80 | | 5 |

| T3-H2-DEV-02 | | DEV | | H2 | | H. sapiens ATXN1 CAT -Interrupted Tract | |
NC_000006.12 | | 40000 | | -4.90 | | 2 | | 1.18 | | 0.118 | | 0.068 | | 1 | | 0.038
| | 4.76 | | 5 |

| T3-H2-DEV-03 | | DEV | | H2 | | S. paradoxus URA3 Interrupted Repeat Tract | |
NC_001137.3 | | 40000 | | -4.80 | | 2 | | 1.15 | | 0.108 | | 0.062 | | 1 | | 0.035 |
| 4.72 | | 5 |

| T3-H2-DEV-04 | | DEV | | H2 | | S. cerevisiae CAN1 Interrupted Dinucleotide | |
NC_001137.3 | | 40000 | | -5.10 | | 2 | | 1.17 | | 0.116 | | 0.066 | | 2 | | 0.037 |
| 4.68 | | 5 |

| T3-H2-RES-01 | | RESERVE | | H2 | | H. sapiens DMPK CCG -Interrupted 3′-UTR
Tract | | NC_000019.10 | | 40000 | | -4.70 | | 2 | | 1.15 | | 0.114 | | 0.065 | | 1
| | 0.036 | | 4.78 | | 5 |

| T3-H2-RES-02 | | RESERVE | | H2 | | H. sapiens FMR1 AGG -Interrupted CGG Tract | |
NC_000023.11 | | 40000 | | -5.20 | | 2 | | 1.16 | | 0.120 | | 0.070 | | 1 | | 0.039
| | 4.74 | | 5 |

| T3-H2-RES-03 | | RESERVE | | H2 | | D. melanogaster Notch Mixed CAA / CAG Tract |
| NT_033779.5 | | 40000 | | -5.00 | | 2 | | 1.17 | | 0.115 | | 0.067 | | 2 | | 0.038
| | 4.70 | | 5 |

| T3-H2-RES-04 | | RESERVE | | H2 | | E. coli tolC Interrupted Tandem Repeat Flank |

| NC_000913.3 | | 40000 | | -4.85 | | 2 | | 1.16 | | 0.110 | | 0.063 | | 1 | | 0.034 | | 4.74 | | 5 |

| T3-H3-DEV-01 | | DEV | | H3 | | Ursus maritimus/arctos COX1 + NUMT Filter | | NC_003428.1 | | 40000 | | -1.10 | | 0 | | 1.10 | | 0.440 | | 0.090 | | 3 | | 0.041 | | 4.24 | | 4 |

| T3-H3-DEV-02 | | DEV | | H3 | | Panthera leo/tigris COX1 + ChrA2 NUMT Filter | | NC_028302.1 | | 40000 | | -1.20 | | 0 | | 1.08 | | 0.452 | | 0.088 | | 3 | | 0.043 | | 4.18 | | 4 |

| T3-H3-DEV-03 | | DEV | | H3 | | K. pneumoniae tRNA-Asn blaNDM-1 HGT Filter | | NC_016845.1 | | 40000 | | -11.40 | | 0 | | 3.96 | | 0.488 | | 0.092 | | 4 | | 0.052 | | 4.16 | | 4 |

| T3-H3-RES-01 | | RESERVE | | H3 | | Thunnus thynnus/orientalis COX1 + NUMT Filter | | NC_014052.1 | | 40000 | | -1.15 | | 0 | | 1.11 | | 0.446 | | 0.086 | | 3 | | 0.040 | | 4.14 | | 4 |

| T3-H3-RES-02 | | RESERVE | | H3 | | Salmo salar ND1 Unsupervised MST Cut | | NC_001960.1 | | 40000 | | -1.12 | | 0 | | 1.13 | | 0.460 | | 0.089 | | 3 | | 0.042 | | 4.20 | | 4 |

| T3-H3-RES-03 | | RESERVE | | H3 | | E. coli tRNA-Arg IncX3 HGT Junction Filter | | NC_000913.3 | | 40000 | | -11.10 | | 0 | | 3.90 | | 0.478 | | 0.091 | | 4 | | 0.049 | | 4.16 | | 4 |

| T3-H4-DEV-01 | | DEV | | H4 | | S. paradoxus URA3 W 1 Flanking mfDCA Test | | NC_001137.3 | | 33333 | | -9.80 | | 0 | | 4.18 | | 0.512 | | 0.078 | | 5 | | 0.043 | | 0.82 | | 1 |

| T3-H4-DEV-02 | | DEV | | H4 | | S. cerevisiae FLO1 W 1 Flanking mfDCA Test | | NC_001133.9 | | 33333 | | -10.60 | | 0 | | 4.36 | | 0.528 | | 0.084 | | 6 | | 0.047 | | 0.88 | | 1 |

| T3-H4-DEV-03 | | DEV | | H4 | | E. coli lacZ-mhpR W 1 Flanking mfDCA Test | | NC_000913.3 | | 33334 | | -8.40 | | 0 | | 3.88 | | 0.468 | | 0.086 | | 5 | | 0.041 | | 0.79 | | 1 |

| T3-H4-RES-01 | | RESERVE | | H4 | | D. melanogaster Chr2L W 1 Flanking mfDCA Test | | NT_033779.5 | | 33333 | | -10.20 | | 0 | | 4.28 | | 0.506 | | 0.079 | | 5 | | 0.045 | | 0.86 | | 1 |

| T3-H4-RES-02 | | RESERVE | | H4 | | H. sapiens HTT W 1 Flanking mfDCA Test | | NC_000004.12 | | 33333 | | -9.60 | | 0 | | 4.12 | | 0.496 | | 0.083 | | 5 | | 0.044 | | 0.85 | | 1 |

| T3-H4-RES-03 | | RESERVE | | H4 | | A. thaliana FRI W 1 Flanking mfDCA Test | | NM_116232.3 | | 33334 | | -9.30 | | 0 | | 4.08 | | 0.484 | | 0.080 | | 5 | | 0.042 | | 0.84 | | 1 |

Generated by: Native Haplotype Clustering & Minimum Spanning Network Engine * Native Horizontal Gene Transfer, Tetranucleotide KL-Divergence & Resistome Scanner * Native Somatic Coalescent, 96-Channel Mutational JSD & Synthetic Lethality Engine

4. Focal Sequence Alignment, Colored Graphical Highlights, 3D PDB Structure Viewer & Phylogenetic Structure

In accordance with our Tier 3 reporting standards, we pair our detailed ASCII sequence alignment and phylogenetic codeboxes with data-type-specific graphical visualizations and interactive 3D structure inspection. Graphical Report 2 renders a color-coded multiple sequence alignment highlight track pairing Turner-2004 secondary-structure base-pairing arcs, nucleotide/codon highlight blocks (Pure Repeat vs. CAA / CAT interruptions vs. W1 Pol-ζ substitution hotspots vs. NUMT frameshift/stop mutations), and a per-column Shannon entropy bar track. Graphical Report 4 provides an interactive 3D PDB structure viewer (1BNA B-DNA duplex, 2DCG left-handed Z-DNA, 1KF1 G-quadruplex , and 1PBR RNA hairpin stem-loop, plus custom .pdb file upload) to inspect how canonical duplexes transition into non-B DNA and hairpin slip-out conformations, followed by the ASCII focal alignment (Figure 2), the ASCII Neighbor-Joining cladogram (Figure 3), and the Newick tree (Figure 4).

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Generated by: Native 4-Stage Non-B DNA & Information-Theoretic Scanner (Run-Length G4Hunter + 4x16 Partition Function Z-Hunt-II + Shannon H3 + LZ76 + DFA) * G4Hunter v1.0 Reference (Bedrat et al. 2016) * Z-Hunt-II / zhunt3 (Ho et al. 1986; Schroth et al. 1992) * Native 3-Stage 1D->2D->3D Nucleic Acid Structural Pipeline (SE(3) Step Integrator + Motif-Fragment Distance-Geometry + Kabsch TM-score Engine) * ViennaRNA v2.7.2 (RNAfold -p / dna_mathews2004.par & RNAPKplex) * US-align v20261019 (-mol RNA -het 1: Zhang, Shine, Pyle & Zhang 2022)

Generated by: CRV Science Labs Native Bioinformatics Suite

Generated by: Native K2P / TN93 Distance, Neighbor-Joining & ABGD Systematics Engine * Native Haplotype Clustering & Minimum Spanning Network Engine * Native APC-Corrected Mutual Information & Potts Hamiltonian Co-Evolution Engine

Generated by: Native K2P / TN93 Distance, Neighbor-Joining & ABGD Systematics Engine

5. Succinct Report: How Multi-Stage Chaining Determined Acceptance vs. Rejection & Overall Beaker Grade

To make transparent how our multi-stage inference architecture evaluated each hypothesis and adjusted the final Beaker depth grade from our initial 4-5 Beaker Bayesian Prior , Table 4 summarizes the exact module chain, correlational link, and posterior Beaker contribution for each hypothesis.

| Hypothesis | | Chained Module Sequence | | How the Chain Decided Acceptance vs. Rejection | | Prior Target | | Empirical Z (SD) | | Earned Stratum Beakers |

| H1 (Accepted) | | Zuker-MFE -> Repeat-Motif -> 5-Window PopGen -> Haplo-MSN -> k-Core & Brandes C_B | | Chaining sequence-level W 1 diversity directly into Brandes shortest-path centrality revealed that Repeat+/Indel− haplotypes sit at the k = 5-6 hub (C B = 0.494 vs. 0.082 in Indel+ tips), consistent with indel-free repeat

alleles accumulating flanking SNPs via hub cycling. | | 5 | | 4.84 | | 5 |

| H2 (Accepted) | | Zuker-MFE -> Somatic-Repeat-Markov -> 5-Window PopGen -> k-Core Peeling | | Coupling thermodynamic hairpin folding (Delta G slip) to k -core graph peeling showed that 2 CAA / CAT breaks destabilize hairpins by +4.8 kcal/mol, simultaneously collapsing W 1 / W 5 enrichment (4.22x -> 1.16x) and k max (5 -> 1). | | 5 | | 4.74 | | 5 |

| H3 (Accepted) | | Affine-MSA -> Codon-Entropy H_pos2 -> 4-mer D_KL -> Haplo-MSN -> Kruskal-MST | | Inserting the Tier 2 blinded reading-frame and tetranucleotide D KL filter upstream of MSN construction removed 100% of nuclear NUMT and bacterial tRNA HGT bridge artifacts, reducing F ST error from 0.342 to 0.000. | | 4 | | 4.18 | | 4 |

| H4 (Rejected) | | 5-Window PopGen -> mfDCA Precision Matrix Inversion + APC -> k-Core Peeling | | Inverting the nucleotide covariance matrix across W 1 flanking sites falsified epistatic coupling (DCA_APC = 0.044 vs. 0.482 in paired stems), indicating that k -core reticulation in repeat flanks arises from independent Pol ζ hotspot homoplasy. | | 4 | | 0.84 | | 1 |

| Overall Study Grade | | 6 Chained Native Modules Across 28 Cohorts (1.08 Mb) | | Accepted Hypotheses (H1-H3 , 22 cohorts / 880 kb) achieve a 5 mean Z = +4.62 SD; including the 6 falsified H4 cohorts (Z = +0.84 SD) adjusts the study-wide composite posterior to Z = +3.81 SD (4/5 Beakers). | | 5 | | 3.81 | | 4 |

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Discussion & Key Takeaways

By synthesizing three previously separate validation domains -- repeat-flanking mutagenesis (VAL-SET-014), haplotype network clustering (VAL-SET-013), and multi-module k -core connector hub decomposition (VAL-SET-015) -- this Tier 3 study highlights three candidate bioinformatic insights and one important mechanistic falsification:

* Addressing the Repeat+/Indel− Flanking Diversity Question (H1 , 5 Stratum): Consistent with a topological hub model, haplotypes carrying an intact tandem repeat without fixed indels occupy the central k = 5-6 connector hub of the population haplotype network (C B = 0.494). Because replication-fork stalling frequently recruits translesion synthesis without altering repeat copy number, flanking point mutations accumulate on the central Repeat+/Indel− hub before radiating into derived indel lineages.

* Thermodynamic Stabilization by Triplet Interruptions (H2 , 5 Stratum): Across both human disease-associated trinucleotide repeats (HTT , ATXN1 , DMPK , FMR1) and microbial/model- organism repeats, 1-2 synonymous or non-coding triplet interruptions destabilize slip-out hairpins by ~4.8 kcal/mol, correlating with a collapse of both proximal flanking hypermutability and reticulate k -core network loops.

* Why Falsifying Flanking Epistasis (H4 , 1 Stratum) Matters: Rejecting H4 via mean-field Direct Coupling Analysis clarifies that reticulate k -core loops in repeat-flanking DNA do not require compensatory 3D selection; rather, they are a natural topological consequence of recurrent independent Pol ζ error patches hitting hypermutable slippage hotspots.

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