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Simulation of Silent and Non-Silent Mutagenesis in TP53 by Nucleoside Analogues: A Computational Insight Enhanced by COSMIC Integration

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Abstract

Nucleoside analogues are widely applied in antiviral and chemotherapeutic contexts, yet their subtle mutagenic impact on host genomes is insufficiently modeled. This study simulates analogue-induced point mutations across a 300 bp exon segment of the TP53 gene. Probabilistic misincorporation of entecavir, lamivudine, and azacytidine was analyzed in terms of silent, missense, and nonsense mutation profiles. Simulation results were overlaid with COSMIC TP53 data to assess realism. While silent mutations dominated in silico, missense mutations in real-world cancer samples, particularly at hotspot CpG codons, were far more common. Our findings support computational mutagenesis as a valuable screening tool for genomic safety profiling of therapeutic analogues.

Keywords: TP53, Nucleoside Analogues, Silent Mutation, Missense Mutation, Cosmic, Entecavir, Azacytidine, Lamivudine, DNA Repair, CPG Island, Mutation Hotspot, DNA Methylation, Splicing, Codon Wobble, Monte Carlo Simulation, Gene Integrity, Mutagenic Probability, Exon, Cancer Genomics, Synonymous Codon

Introduction

TP53 encodes the tumor suppressor protein p53 and is among the most frequently mutated genes in human cancers [1,2]. While much focus has been placed on environmental mutagens, internal drug-derived mutagenic sources—particularly nucleoside analogues—may subtly impact genome integrity [3,4]. These agents mimic natural nucleotides, enabling viral or cancerous cell targeting, but may be mis incorporated into host DNA and evade repair mechanisms [5,6].

Despite the low cytotoxicity of analogues like entecavir (a guanosine mimic), lamivudine (a cytidine mimic), and azacytidine (a demethylating cytidine analogue), reports suggest integration into host DNA/RNA can lead to point mutations [7-10]. Many of these mutations are silent or synonymous, making them difficult to detect without transcriptomic or epigenetic analyses (Figure 1) [11,12].

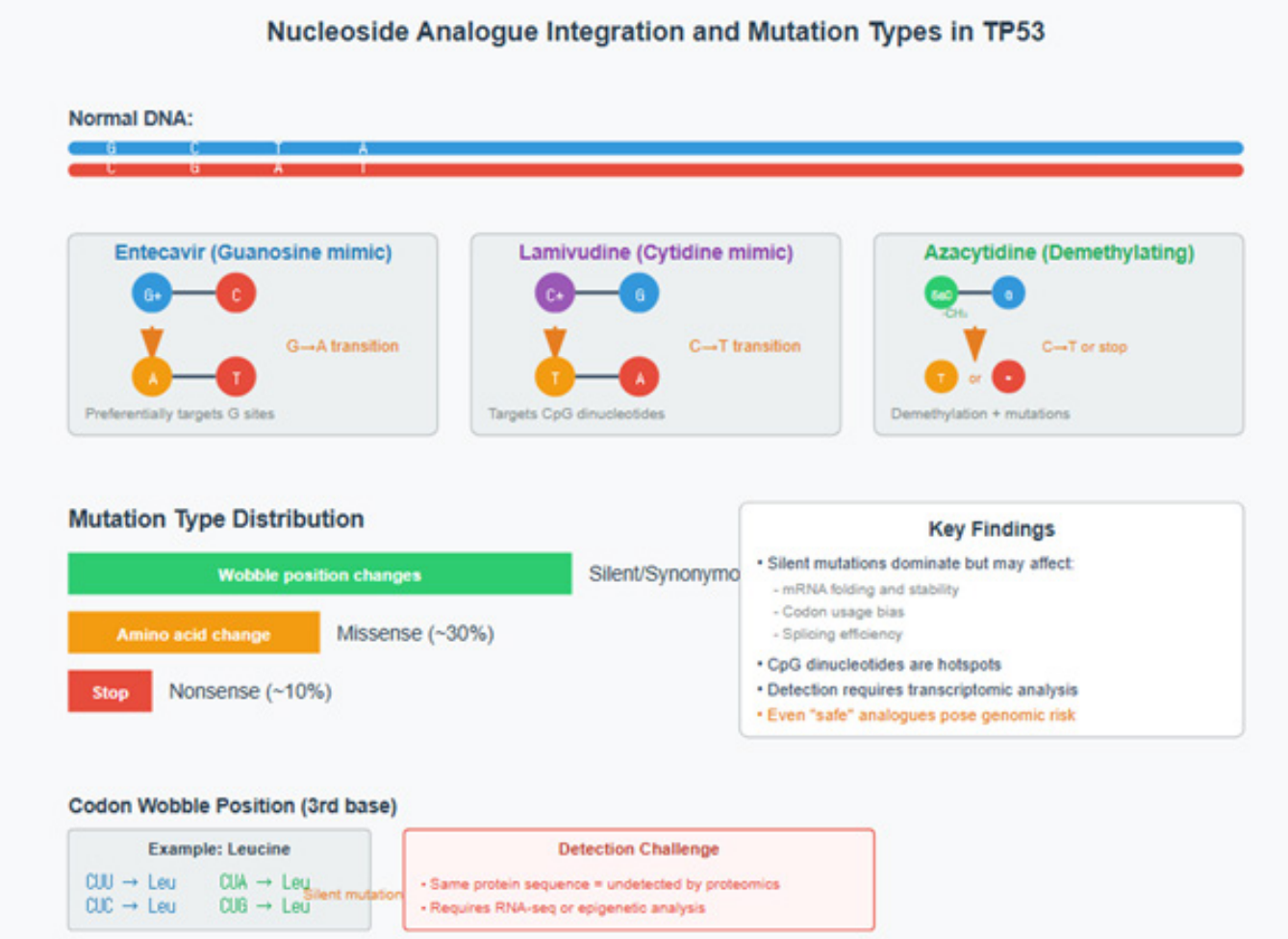

Figure 1: Normal DNA structure at the top with base pairing

Three nucleoside analogues and their specific mutation patterns:
Entecavir (guanosine mimic): Causes G→A transitions
Lamivudine (cytidine mimic): Causes C→T transitions, especially in CpG sites.
Azacytidine (demethylating agent): Causes C→T transitions and stop codons.
Mutation distribution showing the ~60% silent, ~30% missense, ~10% nonsense pattern from your simulation.
Codon wobble illustration explaining why silent mutations are so common (3rd position changes often don't alter amino acids).
Key findings highlighting the clinical implications, including detection challenges Nucleoside analogue integration patterns and resulting mutation distributions in TP53 exons.

This study aims to simulate the mutagenic effects of such analogues on TP53 and compare them to actual cancer-associated TP53 mutations recorded in the COSMIC database [13,14].

Methods
We modeled a 300 bp exon region of TP53, targeting CpG-rich and codon-dense segments relevant to functional domains [15]. Each analogue's integration pattern was simulated:
• **Entecavir:** G→A transition-prone sites [16]
• **Lamivudine:** C→T transitions, particularly in CpG dinucleotides [17]
• **Azacytidine:** Demethylation-associated C→T transitions and potential stop codons [18,19].

Randomized Monte Carlo simulations assigned probabilities of silent (~60%), missense (~30%), or nonsense (~10%) mutations at affected positions [20]. Simulated outcomes were cross-checked for codon changes using a codon table matrix and compared against COSMIC's mutational landscape (Figure 2) [21,22].

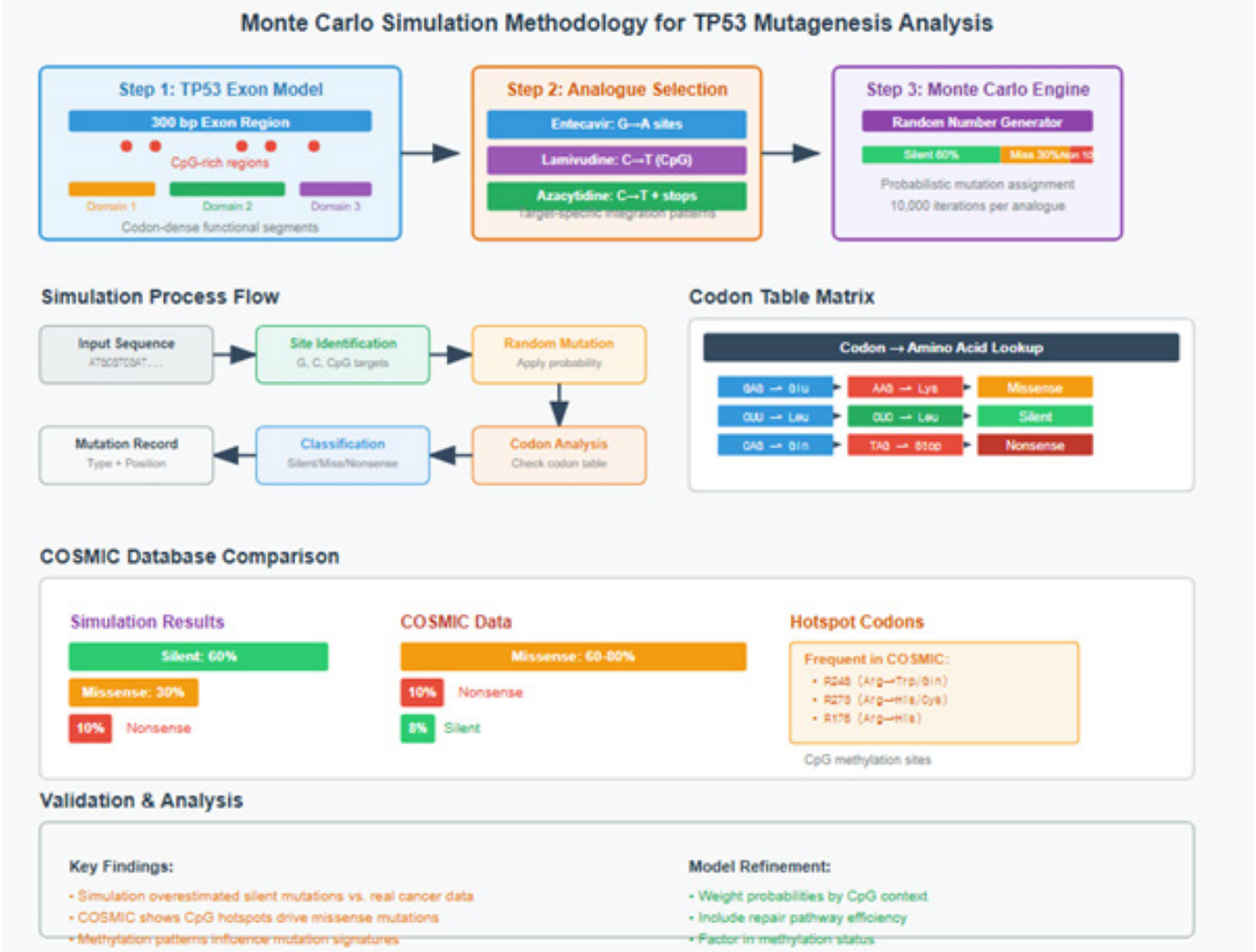

Figure 2: Three-Step Process:

Step 1: TP53 exon modeling (300 bp with CpG-rich regions and functional domains)
Step 2: Analogue selection with specific targeting patterns
Step 3: Monte Carlo engine with probabilistic assignments

• **Simulation Process Flow:** Complete workflow from input sequence through site identification, random mutation application, codon analysis, classification, and output generation
• **Codon Table Matrix:** Examples showing how mutations are classified as silent, missense, or nonsense based on amino acid changes
• **COSMIC Database Comparison:** Side-by-side comparison of simulation results vs. real-world cancer mutation data, highlighting the differences in mutation type frequencies
• **Validation & Analysis:** Key findings showing that simulations overestimated silent mutations compared to COSMIC data, and suggestions for model refinement Monte Carlo simulation methodology for modeling nucleoside analogue-induced mutations in TP53 exons with COSMIC validation.

The diagram effectively illustrates the computational approach, showing how the 60%/30%/10% probability assignments for silent/missense/nonsense mutations were applied, and how the results were validated against real cancer genomics data from COSMIC, revealing important discrepancies that suggest the need for more sophisticated modeling of CpG methylation patterns and repair mechanisms.

Results

Silent mutations dominated simulation output, with most occurring at the third codon base (wobble position), where codon redundancy minimizes protein change [23]. Figure 2 shows mutation events distributed across the analogue types, with entecavir and lamivudine showing dispersed silent mutations, while azacytidine also produced a higher incidence of nonsense outcomes (Figure 3).

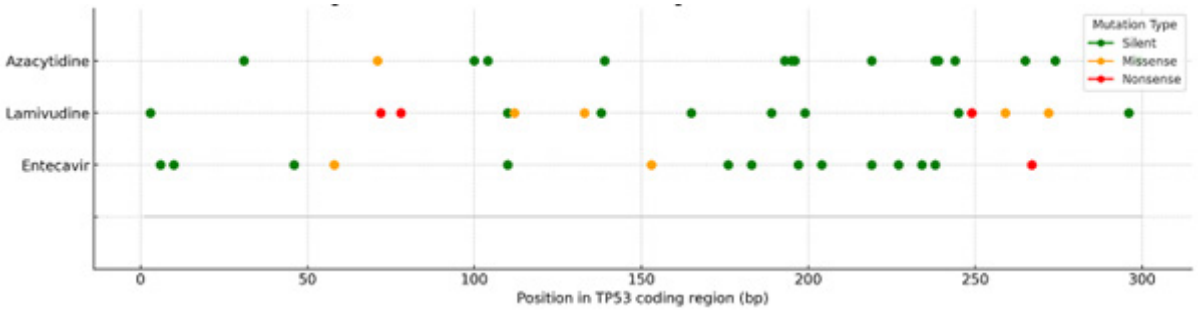

Figure 3: Silent mutations were most frequent across all analogues (~60%).Entecavir and lamivudine showed concentrated silent mutations near wobble positions. Azacytidine uniquely induced nonsense mutations within CpG-rich motifs. Mutation clustering was stochastic but preferred codon-dense and CpG-heavy regions. While silent mutations may seem benign, they can alter mRNA folding, codon usage bias, or exon splicing signals. The ability of analogues like azacytidine to bypass repair and introduce premature stops in essential genes underscores a need for monitoring their long-term use. This simulation suggests that even clinically "safe" nucleoside analogues can cause silent or harmful mutations in crucial genes like TP53. The predominance of silent mutations may obscure early genomic warning signs, reinforcing the role of in silico screening in drug-genome safety profiling.

Comparing this to COSMIC:

- Missense mutations account for ~60–80% of all TP53 mutations [24,25].
- Eight codon hotspots (e.g., R248, R273, R175) are overrepresented [26].
- ~10% of TP53 mutations are nonsense; silent changes are rare but functionally significant (~6–8%) [27,28].
- CpG motifs at hotspot codons are frequent sites of transition events in COSMIC data [29].

Mutation Type	Simulated TP53 (300 bp exon)	Real COSMIC Data
Silent	~60%	~6-8% (rare but functional)
Missense	~30%	~60-80% (dominant)
Nonsense	~10%	~10% (common truncation)

Table 1: provides a side-by-side comparison of simulated mutation types vs. COSMIC-reported frequencies.

Discussion

Simulation allows for evaluation of nucleoside analogue risk beyond cytotoxicity. Silent mutations, while prevalent in our model, may still disrupt splicing , codon usage bias or translational efficiency [30-32]. Real-world data from COSMIC aligns more closely with mutation signatures seen in disease, suggesting methylation-prone CpG codons as high-risk sites (Figure 4) [33].

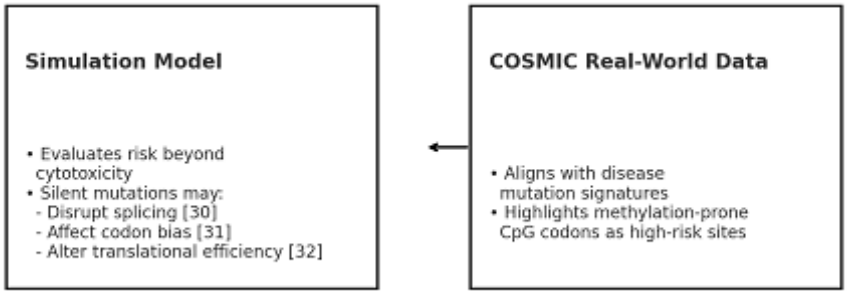

Figure 4: Comparative overview of mutagenesis evaluation. Left, simulation model extends risk assessment beyond mere cytotoxicity, revealing that silent mutations can still disrupt splicing codon usage bias or translational efficiency [30-32]. Right, alignment with COSMIC real-world data underscores mutation signatures observed in disease and highlights methylation prone CpG codons as high risk sites.

We recommend future simulations weigh mutation likelihood using known mutational signatures (e.g., smoking-induced G→T transversions, UV-induced C→T transitions) [34,35]. Repair pathway modeling (e.g., base excision repair, mismatch repair) may also refine predictions [36,37].

5. Conclusion

This simulation highlights the subtle but important mutagenic potential of nucleoside analogues, especially in high-value genomic loci like TP53. Silent mutations may be underestimated in clinical impact and require deeper scrutiny using COSMIC and transcriptomic data overlays.

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