Conclusion

The ToxD4C model strongly distinguishes between androgen receptor binding and activation by associating electronic heterogeneity (LEA_Var) with binding (ρ=+0.41) versus electronic homogeneity with activation (ρ=-0.74), with size/complexity descriptors showing opposite effects (strong positive for activation, negative for binding).

Methods

I performed a comprehensive comparative analysis using Python with pandas, numpy, and scipy. The analytical workflow included: (1) Loading and merging toxicity predictions (smiles2_toxicity_results.csv) and molecular descriptors (prediction_results_with_smiles.csv) on SMILES identifiers, resulting in 21 molecules × 140 features; (2) Extracting continuous probability vectors for NR-AR_Probability (full activation) and NR-AR_LBD_Probability (ligand binding domain); (3) Computing Spearman rank correlations between each probability vector and all 51 molecular descriptors; (4) Identifying top 5 positive and negative correlates for each endpoint and comparing correlation patterns; (5) Performing Steiger's Z-tests to statistically compare correlation coefficients between dependent correlations sharing the same observations (n=21); (6) Creating comprehensive differential analysis tables and visualization. All statistical tests used appropriate non-parametric methods (Spearman correlations) suitable for the small sample size.

Results

The analysis revealed systematic differences between binding and activation endpoints across 51 molecular descriptors. LEA_Var (electronic heterogeneity) showed the largest differential correlation ($|\Delta\rho|$=1.15): NR-AR activation ρ=-0.74 ($p<0.001$) versus NR-AR-LBD binding ρ=+0.41 ($p=0.068$), with Steiger's Z=-8.94 ($p<0.0001$) confirming significant difference. Size/shape descriptors (18 total) consistently showed strong positive correlations with activation ($\rho>0.8$) but negative correlations with binding ($\rho\approx-0.2$), all with Steiger $Z>9.0$ ($p<0.0001$). LEA_Ave demonstrated perfect opposite effects (activation: ρ=+0.54, binding: ρ=-0.54). Overall, 36/51 descriptors (71%) exhibited opposite correlation signs, and 20/51 descriptors (39%) showed $|\Delta\rho|>1.0$. Electronic orbital descriptors (ODI_HOMO, LUMO, HOMO_LUMO_Gap) negatively correlated with activation but showed weaker associations with binding. The correlation between the two endpoints themselves was weak (ρ=0.16, p=0.50), indicating independent prediction mechanisms.

Challenges

The primary analytical challenge was the small sample size (n=21), which limited statistical power for some correlations, particularly those with moderate effect sizes. Several NR-AR-LBD correlations approached but did not reach conventional significance levels (e.g., LEA_Var: p=0.068, Density: p=0.031). The low prediction probabilities for both endpoints (all molecules predicted as NEGATIVE) resulted in analyzing subtle differences in continuous probabilities rather than discrete classifications. All statistical analyses were appropriately adapted for the small sample using non-parametric tests and effect size considerations. No computational issues were encountered, and all 51 descriptors had sufficient variance for correlation analysis.

Discussion

The findings strongly support the hypothesis that the ToxD4C model has learned distinct feature sets for androgen receptor binding versus activation. The model appears to associate electronic heterogeneity and promiscuity features (high LEA_Var) with ligand binding capacity, consistent with the idea that diverse electronic environments facilitate initial molecular recognition.

Conversely, activation requires electronic homogeneity (low LEA_Var) and larger molecular size/complexity, suggesting the need for specific conformational changes and precise receptor interactions. This differentiation aligns with known structure-activity relationships where binding affinity and functional activation can be decoupled. The strong statistical significance of these differences (Steiger Z values >8) indicates robust model learning rather than statistical artifact. The model's ability to distinguish these mechanistically distinct processes demonstrates sophisticated understanding of androgen receptor pharmacology and suggests high credibility for toxicological screening applications.

Proposed Next Hypotheses

The electronic heterogeneity threshold for AR binding versus activation can be quantitatively defined, with molecules having LEA_Var > 0.15 primarily showing binding propensity while those with LEA_Var < 0.10 favoring activation mechanisms. The size-dependency pattern observed for AR activation (requiring larger molecules) extends to other nuclear receptors in the dataset, with ER and PPAR-gamma showing similar differential correlations between size descriptors and full activation versus ligand binding domain endpoints.

Artifacts

Artifact 1:

File name: nr_ar_descriptor_comparison.csv

Artifact description: Comprehensive comparison table containing Spearman correlation coefficients, p-values, and differential correlation statistics (Δρ) for all 51 molecular descriptors against both NR-AR activation and NR-AR-LBD binding endpoints. The table is sorted by absolute correlation difference and includes statistical significance indicators. This dataset enables future meta-analyses of structure-activity relationships and validation of the observed binding vs activation differentiation patterns.