SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Intelligence Applications in Food and Cosmetic Safety

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Using Machine Learning for Cosmetics and Cosmetic Ingredients

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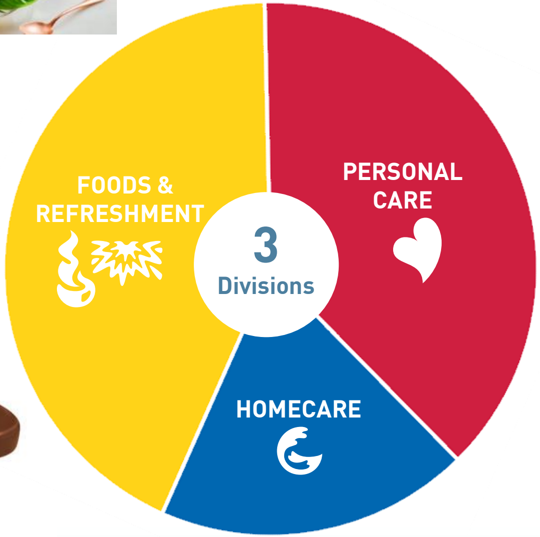
Conflict of Interest Statement

- I have no real or perceived conflicts of interest with the research described in this presentation.

Outline/Objectives

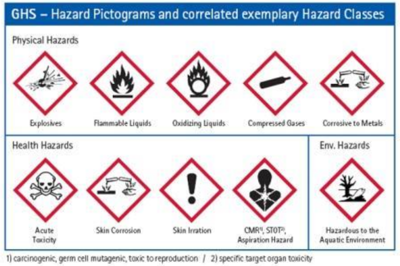
- To introduce how Unilever are applying the principles of next generation risk assessment (NGRA)
- To discuss where predictive computational toxicology and machine learning fit in
- To show outline some of the computational approaches that have been developed and compare them
- To show why machine learning efforts are good for some tasks
- To identify where these research efforts are now going, and how that impacts their use

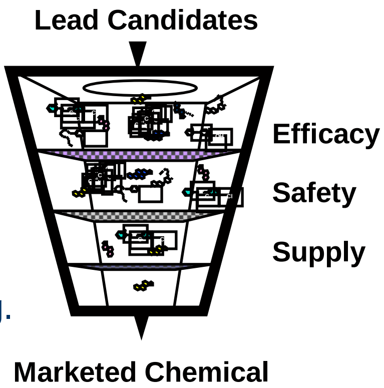
The World of Consumer Products



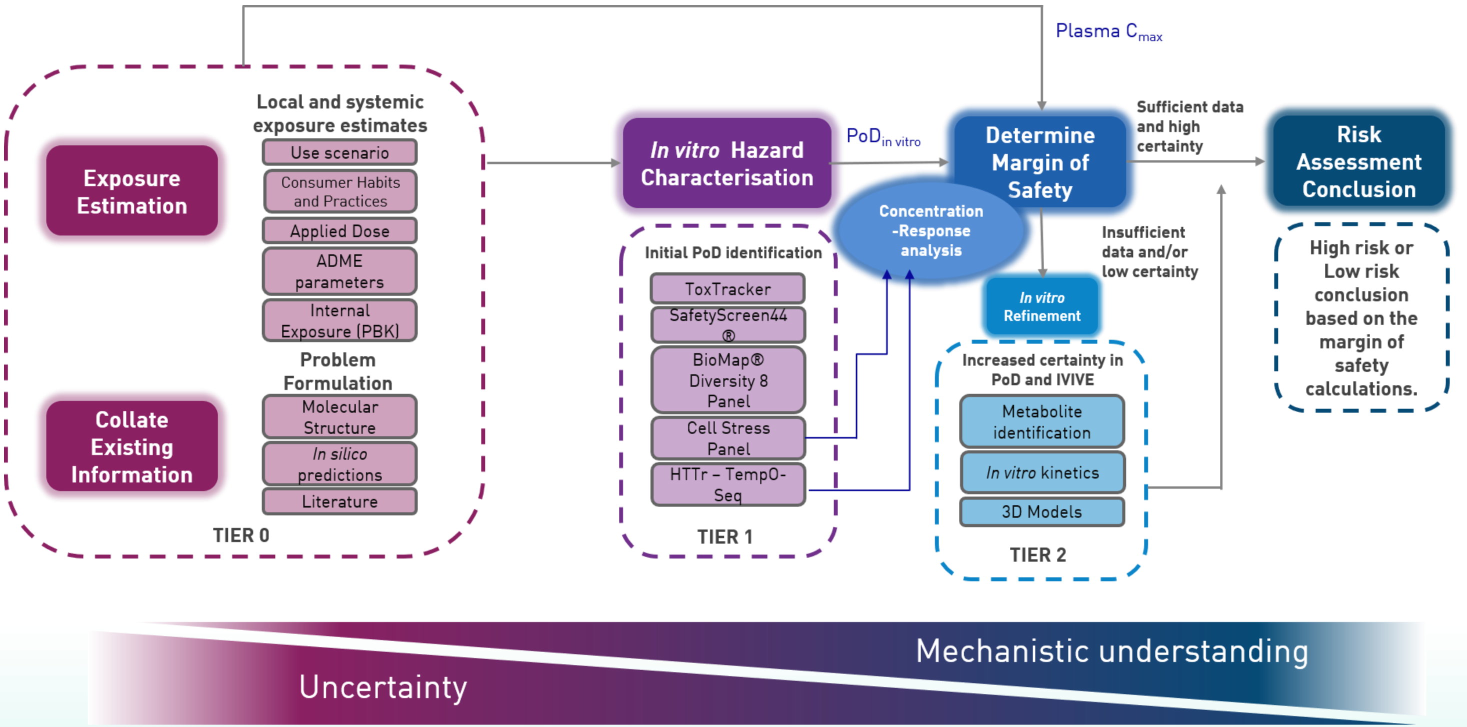
Use of Safety Information for Consumer Products

- **Context…**
  - Classification and labelling
    - Favours a cautious approach
    - Hazard based rules
    - Occupational focus
  - Screening/product development
    - Many potential lead chemicals
    - Often only hazard prediction methods are used
    - Performance of models is less critical
    - Exposure may be considered by the use of threshold-based approaches e.g. TTC, DST, EBW, EcoTTC
  - Risk Assessment including actual exposure
    - Requires a high degree of accuracy
    - Route and amount of exposure dictate the need for toxicology data
    - High level of scrutiny (internal and external)

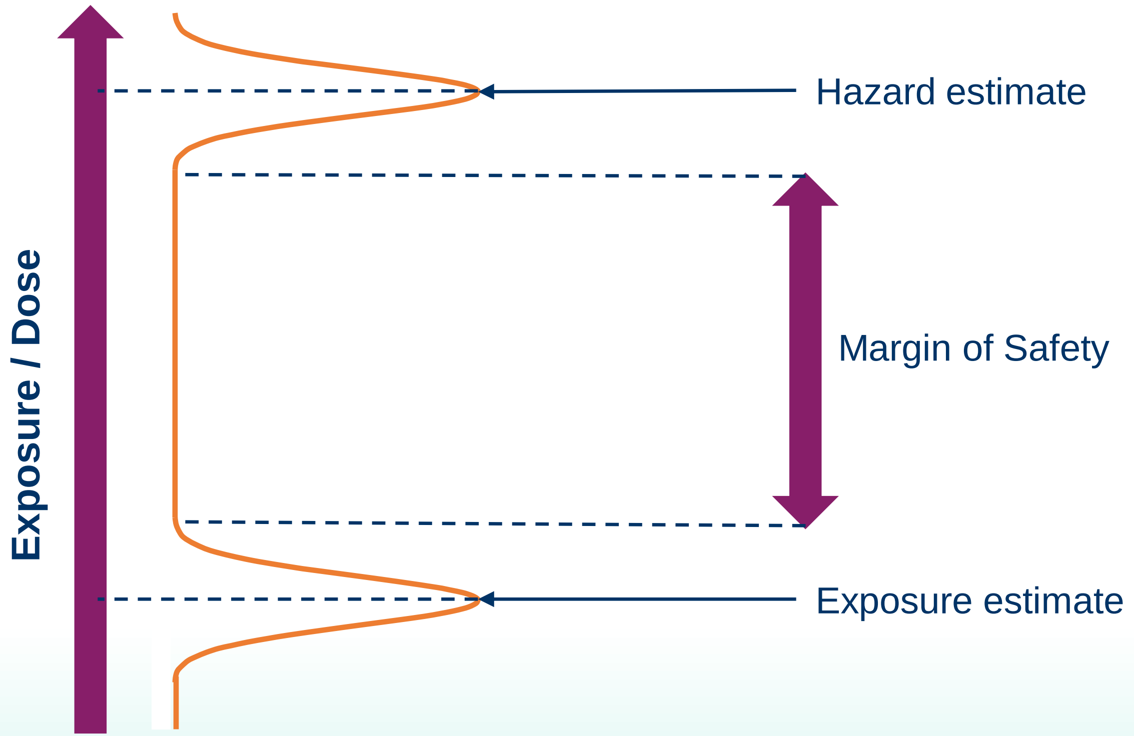




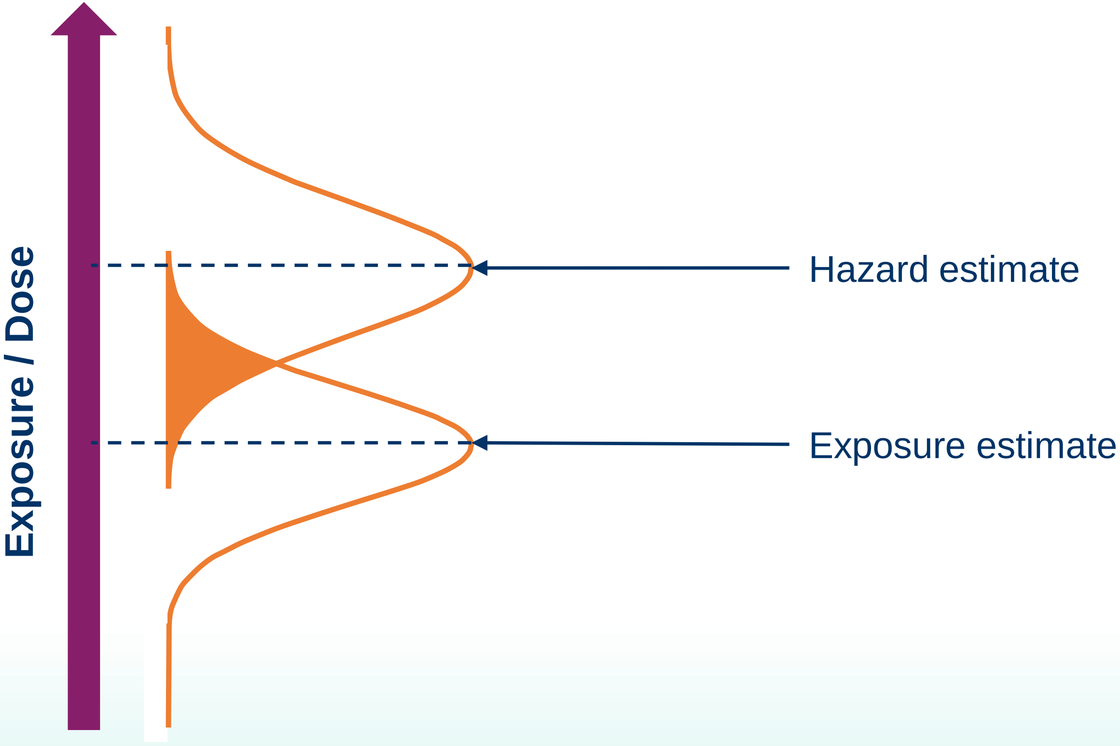
Ab Initio NGRA Framework



Baltazar, M.T., et al. (2020) Toxicol. Sci., Accepted Manuscript.


Exposure / Dose
Hazard estimate
Margin of Safety
Exposure estimate


Hazard
Exposure


Exposure / Dose
Hazard estimate
Exposure estimate


Hazard
Exposure

ICCR Principles of Risk Assessment without Animal Tests

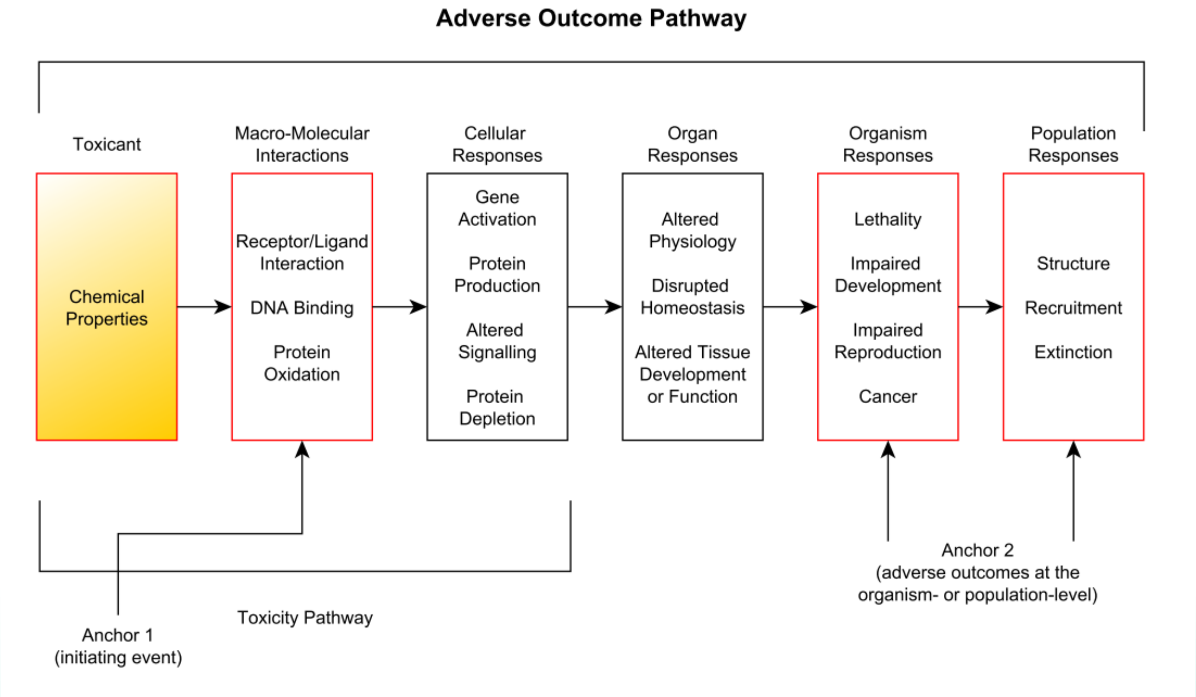
- The overall goal is human safety risk assessment
- The assessment is exposure led
- The assessment is hypothesis driven
- The assessment is designed to prevent harm

(i.e. distinguish between adaptation and adversity)

- Using a tiered and iterative approach
- Following an appropriate appraisal of existing information
- Using robust and relevant methods and strategies
- The logic of the approach should be transparently and explicitly documented
- Sources of uncertainty should be characterised and documented

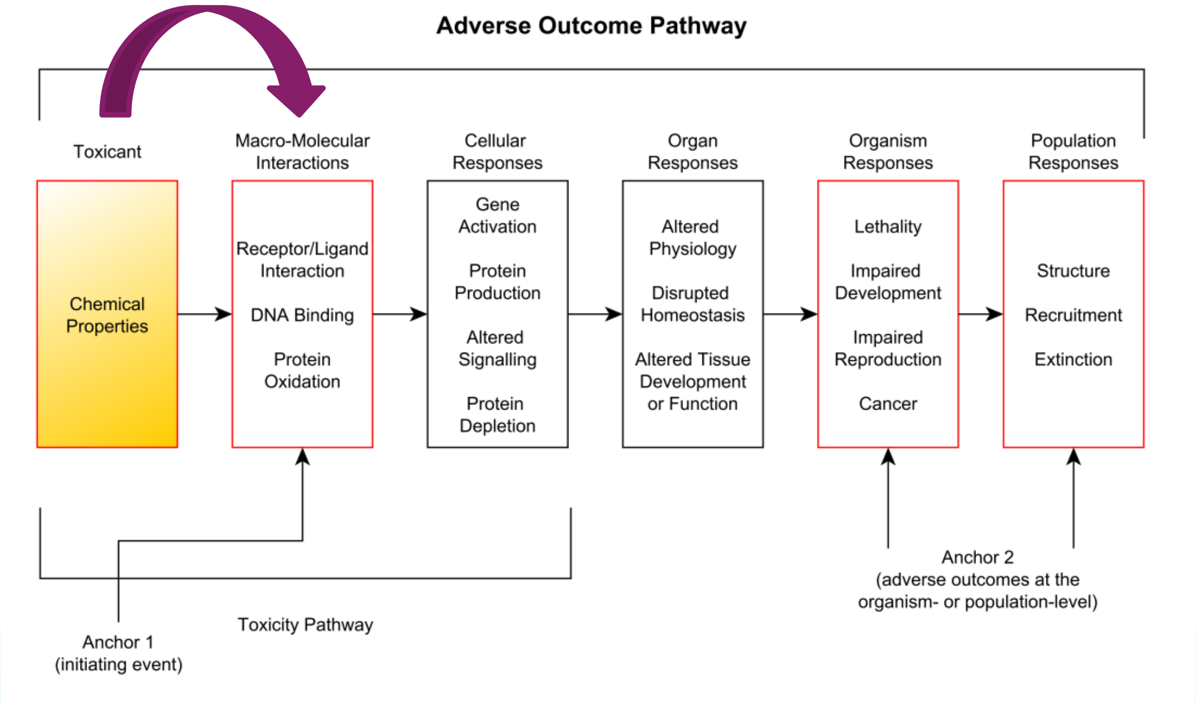
ICCR
International Cooperation on Cosmetics Regulation

Adverse Outcome Pathway



Ankley, G.T., et al. (2010) Environ. Toxicol. Chem., 29; 730.

Adverse Outcome Pathway



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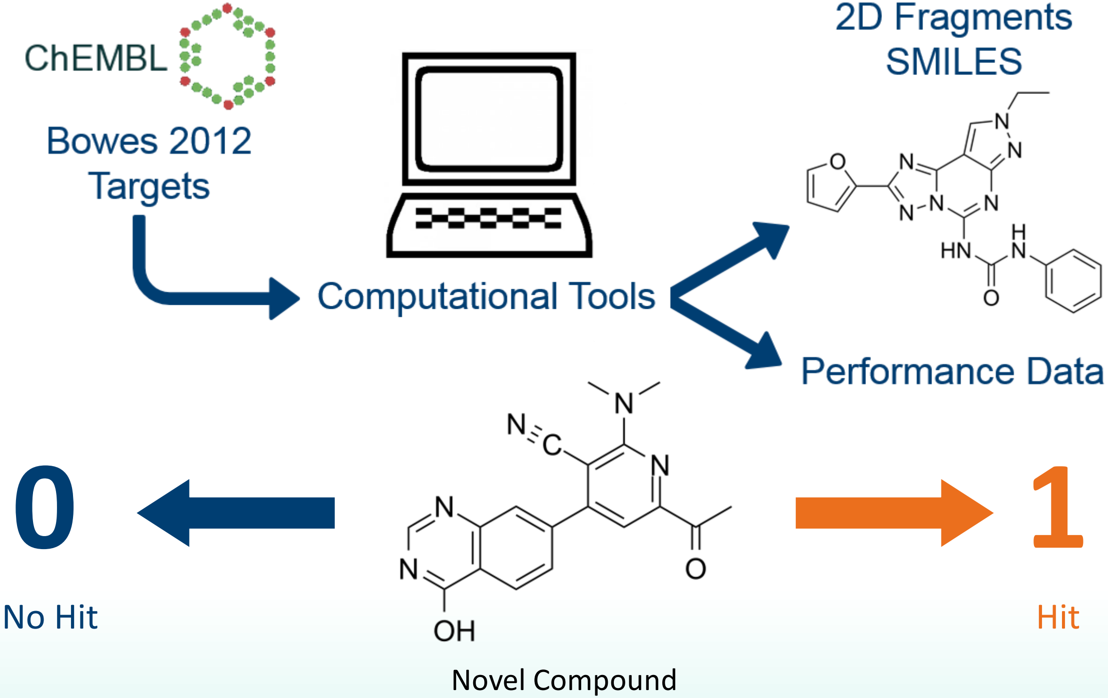
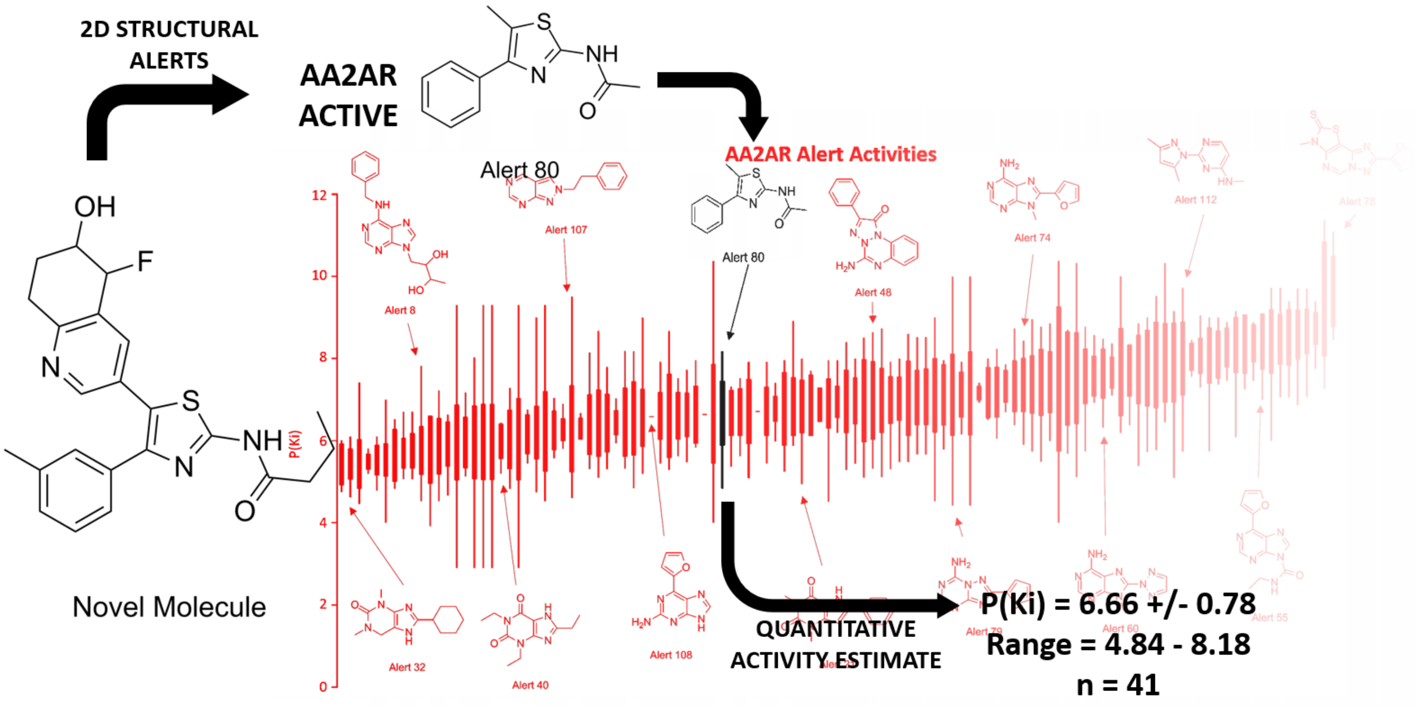
Structural Alerts



Allen, T.E.H. *et al.* (**2018**) *Toxicol. Sci.*, 165; 213.
Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Structural Alerts



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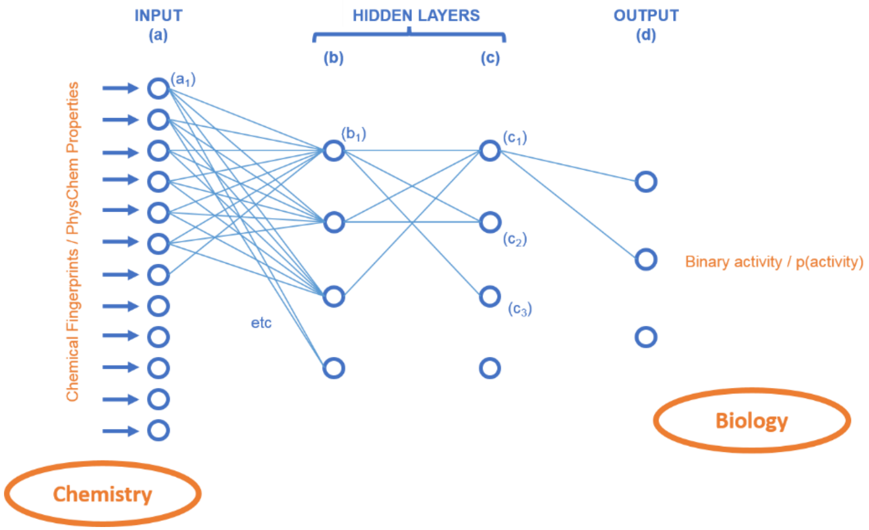
Expanded Target List

- Acetylcholinesterase
- Adenosine A2a receptor
- Alpha-2a adrenergic receptor
- Androgen receptor
- Beta-1 adrenergic receptor
- Beta-2 adrenergic receptor
- Delta opioid receptor
- Dopamine D1 receptor
- Dopamine D2 receptor
- Dopamine transporter
- Endothelin receptor ET-A
- Glucocorticoid receptor
- hERG
- Histamine H1 receptor
- Mu opioid receptor
- Muscarinic acetylcholine receptor M1
- Muscarinic acetylcholine receptor M2
- Muscarinic acetylcholine receptor M3
- Norepinephrine transporter
- Serotonin 2a (5-HT2a) receptor
- Serotonin 3a (5-HT3a) receptor
- Serotonin transporter
- Tyrosine-protein kinase LCK
- Vasopressin V1a receptor
- Type-1 angiotensin II receptor
- RAC-alpha serine/threonine-protein kinase
- Beta-secretase 1
- Cholinesterase
- Caspase-1
- Caspase-3
- Caspase-8
- Muscarinic acetylcholine receptor M5
- Inhibitor of nuclear factor κ-B kinase subunit α
- Macrophage colony-stimulating fac. 1 receptor
- Casein kinase I isoform delta
- Endothelin B receptor
- Neutrophil elastase
- Ephrin type-A receptor 2
- Fibroblast growth factor receptor 1
- Peptidyl-prolyl cis-trans isomerase
- Vascular endothelial growth factor receptor 1
- Vascular endothelial growth factor receptor 3
- Tyrosine-protein kinase FYN
- Glycogen synthase kinase-3 beta
- Histone deacetylase 3
- Insulin-like growth factor 1 receptor
- Insulin receptor
- Vascular endothelial growth factor receptor 2
- Leukotriene B4 receptor 1
- Tyrosine-protein kinase Lyn
- Mitogen-activated protein kinase 1
- Mitogen-activated protein kinase 9
- MAP kinase-activated protein kinase 2
- Hepatocyte growth factor receptor
- Matrix metalloproteinase-13
- Matrix metalloproteinase-2
- Matrix metalloproteinase-3
- Matrix metalloproteinase-9
- Serine/threonine-protein kinase NEK2
- P2Y purinoceptor 1
- Serine/threonine-protein kinase PAK 4
- Phosphodiesterase 4A
- Phosphodiesterase 5A
- PIP_2 3-kinase catalytic subunit α
- Peroxisome proliferator-activated receptor γ
- Protein Tyr phosphatase non-receptor type 1
- Protein Tyr phosphatase non-receptor type 11
- Protein Tyr phosphatase non-receptor type 2
- RAF proto-oncogene Ser/Thr-protein kinase
- Retinoic acid receptor alpha
- Retinoic acid receptor beta
- Rho-ass. coiled-coil-containing protein kinase I
- Ribosomal protein S6 kinase alpha-5
- NAD-dependent protein deacetylase sirtuin-2
- NAD-dependent protein deacetylase sirtuin-3
- Proto-oncogene tyrosine-protein kinase Src
- Substance-K receptor
- Thromboxane A2 receptor
- Tyrosine-protein kinase receptor TEK

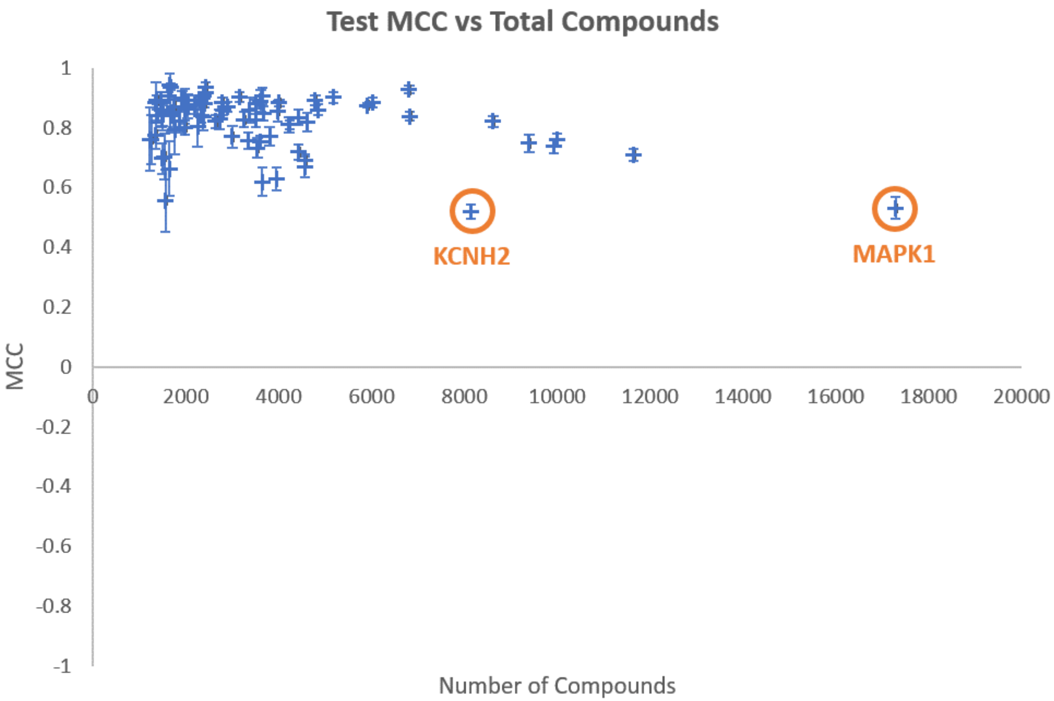
Neural Networks



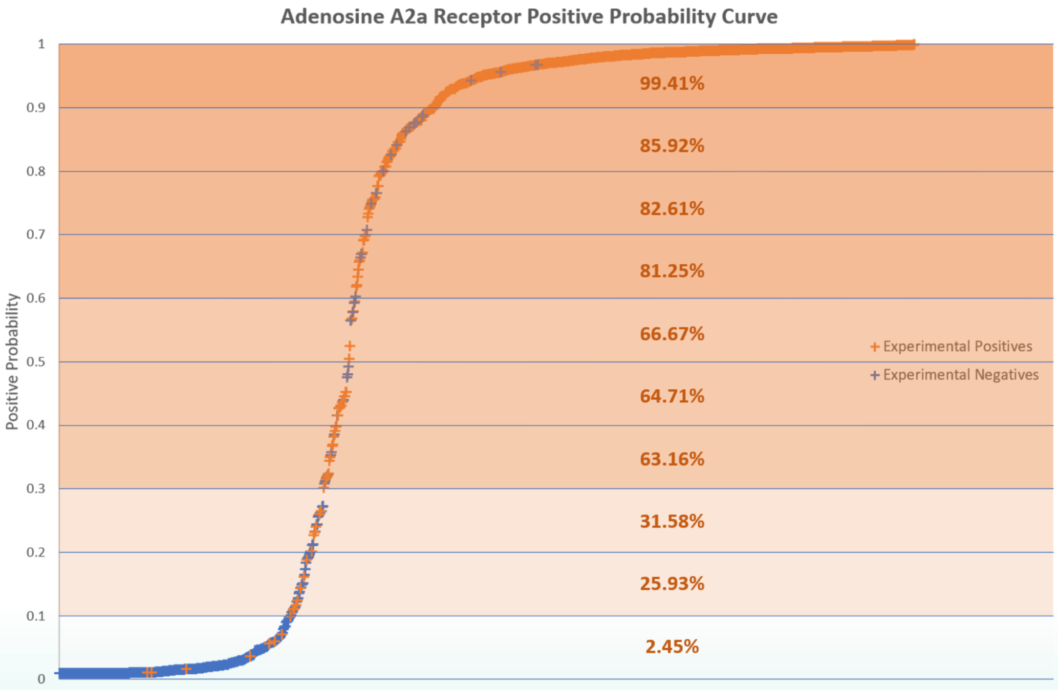
Average Model Performance

	Training Data					Validation Data					Test Data				
	SE	**SP**	**ACC**	**MCC**	**ROC-AUC**	**SE**	**SP**	**ACC**	**MCC**	**ROC-AUC**	**SE**	**SP**	**ACC**	**MCC**	**ROC-AUC**
AVERAGE	92.1	96.5	95.8	0.901	0.99	86.9	93.2	92.5	0.822	0.96	86.2	92.9	92.2	0.814	0.96
SD	8.8	4.2	3.1	0.069	0.02	11.7	5.9	4.1	0.091	0.04	12.1	6.5	4.2	0.093	0.04

Model Performance vs Total Compounds



Positive Probability Curve



Comparative Model Performance

Target Gene	SE	ΔSA	ΔRF	SP	ΔSA	ΔRF	ACC	ΔSA	ΔRF	MCC	ΔSA	ΔRF
AChE	88.4	6.6	-3.2	85.3	-4.6	7.5	87.0	1.6	1.6	0.737	0.024	0.030
ADORA2A	97.6	2.8	-0.5	93.2	2.0	4.2	96.1	2.5	1.1	0.912	0.054	0.024
ADRA2A	91.3	11.2	2.0	93.9	-1.2	-1.2	92.7	4.3	0.2	0.853	0.084	0.004
AR	66.5	-0.8	1.1	99.1	1.4	1.2	90.5	0.8	1.2	0.749	0.026	0.036
ADRB1	92.7	7.0	0.3	89.5	-2.5	1.5	91.2	2.5	0.9	0.823	0.046	0.017
ADRB2	72.9	-2.3	-3.3	89.9	2.2	1.4	81.6	0.0	-0.9	0.639	0.004	-0.014
OPRD1	97.1	1.1	-1.2	81.0	-0.3	4.5	92.4	0.7	0.4	0.813	0.018	0.011
DRD1	77.4	0.9	-3.7	96.6	1.5	4.3	89.2	1.4	1.2	0.773	0.030	0.028
DRD2	98.3	1.9	-1.0	84.8	5.7	7.8	96.1	2.5	0.5	0.855	0.091	0.021
SLC6A3	89.9	1.3	-3.1	94.5	1.9	4.9	91.8	1.5	0.2	0.837	0.032	0.010
EDNRA	93.8	-0.6	-3.4	95.6	1.7	4.8	94.6	0.4	0.4	0.893	0.010	0.009
NR3C1	74.5	2.3	0.7	96.9	0.1	0.6	90.1	0.7	0.6	0.760	0.018	0.015
KCNH2	84.4	15.7	-8.6	70.9	-11.5	17.4	79.1	5.0	1.6	0.558	0.059	0.036
HRH1	95.2	8.0	-0.6	88.4	-5.3	0.7	92.0	1.7	0.0	0.840	0.032	-0.001
OPRM1	94.8	1.2	-1.1	94.5	1.7	3.2	94.7	1.4	0.6	0.889	0.030	0.014
CHRM1	96.6	6.4	0.9	83.3	-2.9	0.7	91.7	2.9	0.8	0.821	0.062	0.019
CHRM2	93.9	2.9	0.0	94.5	1.1	3.2	94.2	1.9	1.8	0.883	0.039	0.035
CHRM3	91.9	3.4	-3.2	93.8	1.8	5.8	92.8	2.8	0.8	0.854	0.053	0.017

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Comparative Model Performance

Target Gene	SE	ΔSA	ΔRF	SP	ΔSA	ΔRF	ACC	ΔSA	ΔRF	MCC	ΔSA	ΔRF
SLC6A2	94.9	4.2	-0.2	92.5	-1.0	1.0	93.9	2.0	0.3	0.875	0.039	0.008
HTR2A	99.1	2.4	-0.4	88.2	-0.4	6.1	96.7	1.8	1.0	0.901	0.051	0.030
HTR3A	89.4	5.7	-1.0	98.2	-0.4	0.4	95.8	1.3	0.0	0.893	0.034	0.000
SLC6A4	98.4	2.7	-0.3	89.0	2.1	6.3	96.3	2.5	1.2	0.892	0.070	0.037
LCK	95.5	3.7	0.2	79.8	-2.6	-0.9	92.3	2.5	0.0	0.763	0.054	-0.002
AVPR1A	93.9	1.9	0.6	99.3	1.5	4.8	97.2	1.6	3.2	0.941	0.034	0.068
AGTR1	87.3	0.0	3.4	99.3	1.0	1.9	94.5	0.6	2.6	0.888	0.014	0.054
AKT1	95.4	1.0	-1.4	91.3	4.4	6.6	94.1	2.1	1.1	0.864	0.049	0.028
BACE1	92.0	-1.1	-5.7	93.5	5.7	14.1	92.5	0.9	0.1	0.827	0.028	0.016
BCHE	85.6	7.1	-0.9	93.6	0.6	4.7	90.4	3.3	2.5	0.799	0.067	0.048
CASP1	69.1	5.3	-1.9	94.7	-0.1	-0.1	86.5	1.5	-0.8	0.680	0.039	-0.018
CASP3	84.8	3.4	3.7	94.9	-1.1	-1.1	91.0	0.6	0.7	0.809	0.013	0.015
CASP8	86.8	-4.9	-2.5	95.4	-2.1	-2.8	92.1	-4.1	-4.1	0.832	-0.060	-0.059
CHRM5	87.4	3.6	-4.2	95.3	1.5	4.0	92.3	2.3	0.9	0.835	0.048	0.015
CHUK	88.8	5.7	-3.3	97.4	0.4	0.0	95.2	1.7	-0.9	0.871	0.047	-0.024
CSF1R	94.3	5.9	-2.4	97.0	0.8	3.1	95.5	3.7	0.0	0.910	0.070	0.001
CSNK1D	91.4	12.4	3.8	94.8	-1.6	2.0	93.4	4.4	2.8	0.864	0.085	0.056
EDNRB	96.1	2.0	-0.5	94.4	-0.4	-0.7	95.1	0.6	-0.6	0.899	0.013	-0.012

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Comparative Model Performance

Target Gene	SE	ΔSA	ΔRF	SP	ΔSA	ΔRF	ACC	ΔSA	ΔRF	MCC	ΔSA	ΔRF
ELANE	90.9	-0.4	-5.2	93.8	0.2	5.8	92.1	-0.1	-0.8	0.839	-0.001	-0.012
EPHA2	87.2	0.0	-0.7	99.6	1.1	1.8	95.4	0.7	1.0	0.899	0.018	0.023
FGFR1	96.8	5.9	0.8	92.0	-2.8	1.4	95.1	2.8	1.0	0.892	0.054	0.021
FKBP1A	88.1	-3.0	-6.9	97.4	-0.4	1.5	94.8	-1.1	-0.9	0.869	-0.028	-0.025
FLT1	91.6	1.6	-3.0	99.0	0.9	2.5	96.2	1.2	0.4	0.919	0.024	0.008
FLT4	91.9	10.7	0.0	96.5	-0.4	1.2	94.5	4.3	0.6	0.888	0.086	0.014
FYN	77.8	5.1	-3.0	98.2	0.4	1.5	92.7	1.6	0.3	0.809	0.044	0.006
GSK3B	96.8	12.2	-1.1	78.3	-5.2	2.5	90.4	6.2	0.1	0.785	0.121	0.001
HDAC3	94.1	2.3	0.3	94.8	1.5	2.7	94.5	2.0	1.6	0.890	0.039	0.032
IGF1R	94.6	-1.0	-2.1	95.5	1.3	5.1	94.9	-0.2	0.3	0.889	-0.003	0.011
INSR	91.7	1.7	-3.1	98.9	1.2	1.9	95.5	1.4	-0.5	0.912	0.028	-0.007
KDR	97.4	2.8	-0.3	73.1	-9.7	9.2	93.5	0.8	1.2	0.748	0.005	0.058
LTB4R	91.4	4.3	2.2	98.8	0.0	1.2	96.8	1.2	1.5	0.918	0.030	0.038
LYN	89.1	10.9	-1.8	98.0	2.7	2.7	95.4	5.2	1.4	0.888	0.127	0.030
MAPK1	43.5	-4.4	2.3	99.2	4.0	-0.2	79.3	1.0	0.6	0.557	0.043	0.013
MAPK9	95.5	3.5	-2.9	97.7	2.2	7.9	96.5	2.9	2.0	0.931	0.058	0.040
MAPKAPK2	86.9	5.1	-3.3	94.1	1.4	2.5	91.0	3.0	0.0	0.816	0.062	-0.001
MET	97.7	4.3	-1.0	91.9	3.2	8.4	95.9	4.0	1.9	0.904	0.091	0.045

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Comparative Model Performance

Target Gene	SE	ΔSA	ΔRF	SP	ΔSA	ΔRF	ACC	ΔSA	ΔRF	MCC	ΔSA	ΔRF
MMP13	94.9	1.5	-2.1	94.7	3.3	10.6	94.8	2.1	2.3	0.887	0.045	0.054
MMP2	95.5	1.7	0.0	89.2	-3.6	6.0	93.2	-0.2	2.1	0.852	-0.006	0.048
MMP3	94.7	1.8	-1.7	92.4	1.2	8.8	93.8	1.5	2.1	0.868	0.033	0.047
MMP9	81.6	-0.2	-5.0	88.8	-1.5	6.9	84.6	-0.8	0.0	0.696	-0.016	0.011
NEK2	77.0	9.4	-2.7	98.5	0.7	1.0	94.0	2.6	0.3	0.813	0.085	0.007
P2RY1	92.7	-2.4	-2.4	100.0	1.5	3.4	97.7	0.3	1.5	0.947	0.007	0.035
PAK4	89.4	7.0	-4.7	99.3	0.8	1.1	96.9	2.2	-0.3	0.914	0.064	-0.009
PDE4A	90.8	2.9	-1.1	94.9	-0.4	0.5	93.1	1.0	-0.3	0.859	0.020	-0.005
PDE5A	90.1	3.4	-4.8	96.5	2.8	7.3	93.0	3.1	0.6	0.862	0.062	0.016
PIK3CA	98.9	1.5	-0.4	93.3	-1.5	4.6	97.2	0.6	1.2	0.934	0.014	0.027
PPARG	69.5	-0.8	-2.9	96.1	3.4	2.0	86.0	1.8	0.2	0.702	0.041	0.006
PTPN1	76.6	9.5	-3.9	89.7	-2.6	3.1	84.7	2.0	0.4	0.673	0.046	0.005
PTPN11	64.8	26.2	14.8	91.9	-3.4	-3.4	85.7	3.4	0.8	0.584	0.153	0.052
PTPN2	67.9	2.5	2.5	96.0	-1.7	2.3	90.1	-0.7	2.4	0.687	-0.022	0.069
RAF1	99.7	4.2	0.0	95.2	-1.1	1.5	97.7	1.8	0.7	0.954	0.038	0.013
RARA	63.1	1.9	1.9	99.4	1.8	0.0	95.2	1.9	0.3	0.742	0.092	0.013
RARB	85.9	11.3	5.6	99.9	1.1	0.0	98.8	1.9	0.5	0.913	0.137	0.033
ROCK1	94.3	5.4	-2.5	92.0	-3.6	1.1	93.2	1.2	-0.9	0.864	0.021	-0.018

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

Comparative Model Performance

Target Gene	SE	ΔSA	ΔRF	SP	ΔSA	ΔRF	ACC	ΔSA	ΔRF	MCC	ΔSA	ΔRF
RPS6KA5	73.7	12.3	0.0	100.0	1.5	2.7	95.3	3.4	2.2	0.835	0.135	0.080
SIRT2	70.8	2.3	5.6	95.2	-0.6	-1.6	89.8	0.0	0.0	0.692	0.003	0.006
SIRT3	76.7	-2.4	-4.7	98.5	0.8	0.8	95.4	0.3	0.0	0.802	0.010	-0.005
SRC	94.7	4.6	-2.7	88.7	0.7	8.1	92.4	3.1	1.5	0.839	0.064	0.029
TACR2	87.6	-1.6	-4.4	100.0	2.4	2.4	96.0	1.1	0.2	0.910	0.029	0.008
TBXA2R	88.8	-0.4	-2.1	94.9	-0.4	1.4	93.0	-0.4	0.3	0.838	-0.010	0.003
TEK	89.9	2.5	-4.1	97.8	2.6	1.9	94.5	2.6	-0.6	0.887	0.053	-0.013

Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

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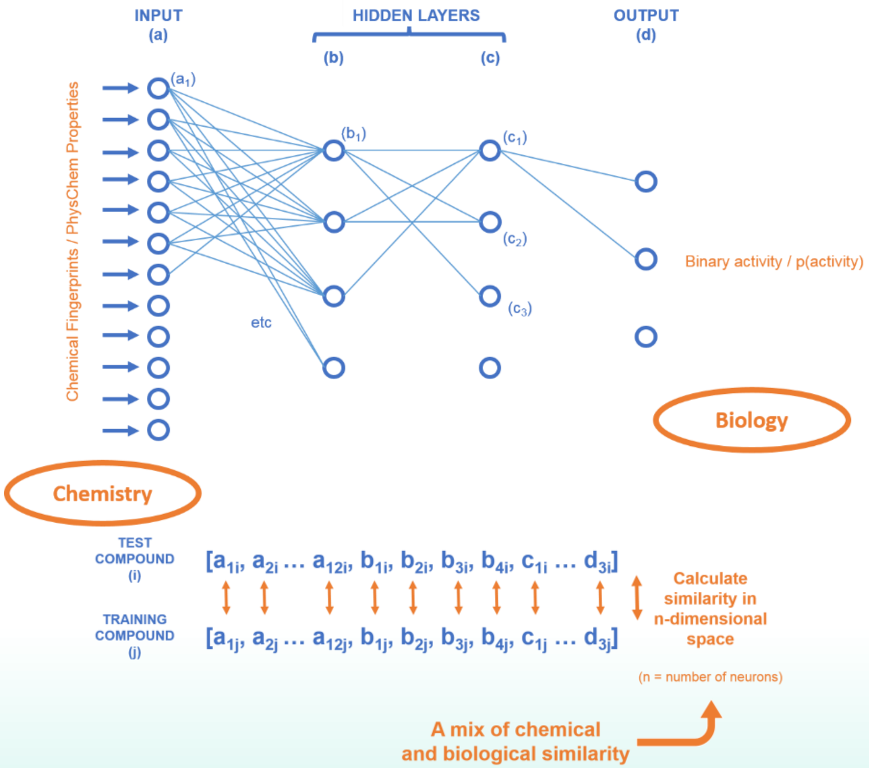
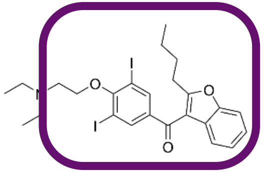
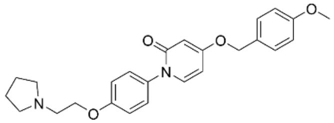
Neural Network Activation Similarity



Amiodarone (hERG)

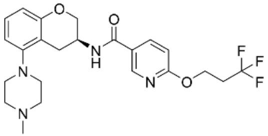


Amiodarone
KCNH2 Experimental Active
Predicted Probability Active: 90.1%



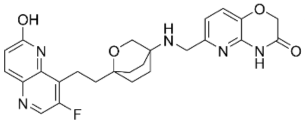
A
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.074



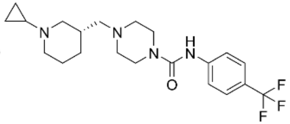
B
Experimental: Inactive

NNAS: 1.000*
Tanimoto: 0.084



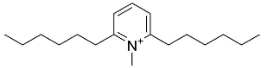
C
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.036



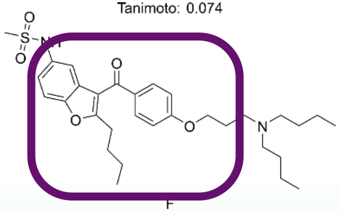
D
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.043



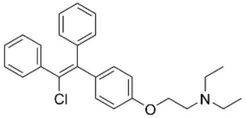
E
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.107



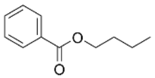
F
Experimental: Active

NNAS: 0.996
Tanimoto: 0.275



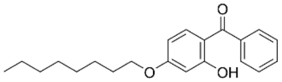
G
Experimental: Active

NNAS: 0.997
Tanimoto: 0.180



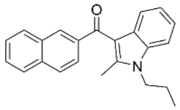
H
Experimental: Inactive

NNAS: 0.909
Tanimoto: 0.157



I
Experimental: Inactive

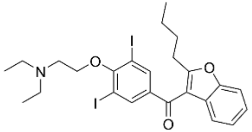
NNAS: 0.915
Tanimoto: 0.154



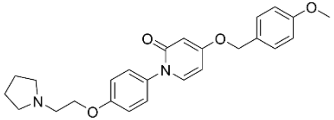
J
Experimental: Active

NNAS: 0.970
Tanimoto: 0.153

Amiodarone (hERG)

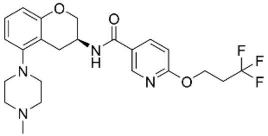


Amiodarone
KCNH2 Experimental Active
Predicted Probability Active: 90.1%



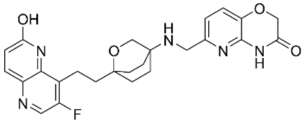
A
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.074



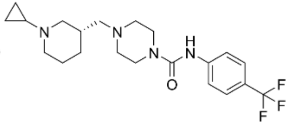
B
Experimental: Inactive

NNAS: 1.000*
Tanimoto: 0.084



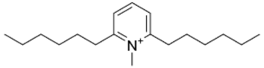
C
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.036



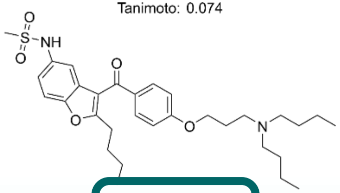
D
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.043



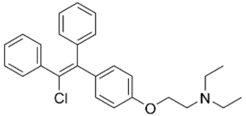
E
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.107



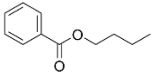
F
Experimental: Active

NNAS: 0.996
Tanimoto: 0.275



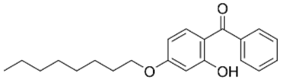
G
Experimental: Active

NNAS: 0.997
Tanimoto: 0.180



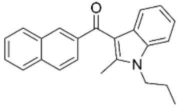
H
Experimental: Inactive

NNAS: 0.909
Tanimoto: 0.157



I
Experimental: Inactive

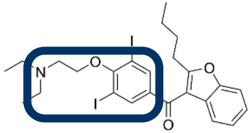
NNAS: 0.915
Tanimoto: 0.154



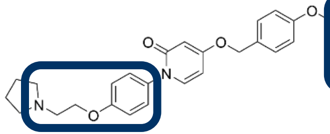
J
Experimental: Active

NNAS: 0.970
Tanimoto: 0.153

Amiodarone (hERG)

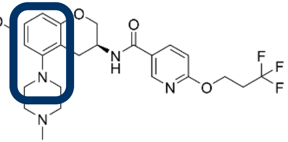


Amiodarone
KCNH2 Experimental Active
Predicted Probability Active: 90.1%



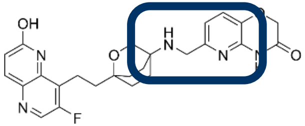
A
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.074



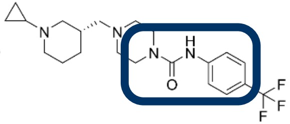
B
Experimental: Inactive

NNAS: 1.000*
Tanimoto: 0.084



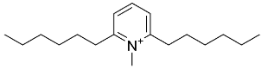
C
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.036



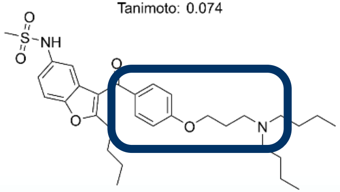
D
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.043



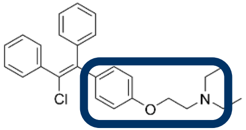
E
Experimental: Active

NNAS: 1.000*
Tanimoto: 0.107



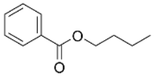
F
Experimental: Active

NNAS: 0.996
Tanimoto: 0.275



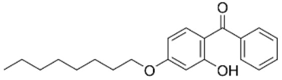
G
Experimental: Active

NNAS: 0.997
Tanimoto: 0.180



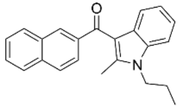
H
Experimental: Inactive

NNAS: 0.909
Tanimoto: 0.157



I
Experimental: Inactive

NNAS: 0.915
Tanimoto: 0.154



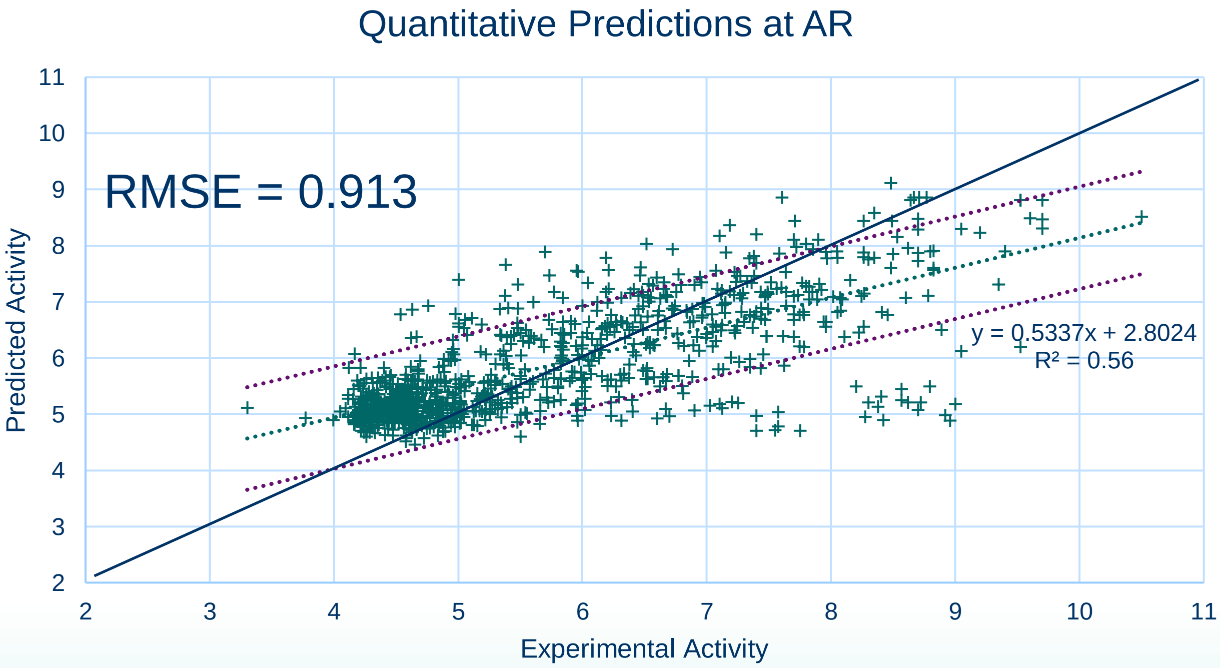
J
Experimental: Active

NNAS: 0.970
Tanimoto: 0.153

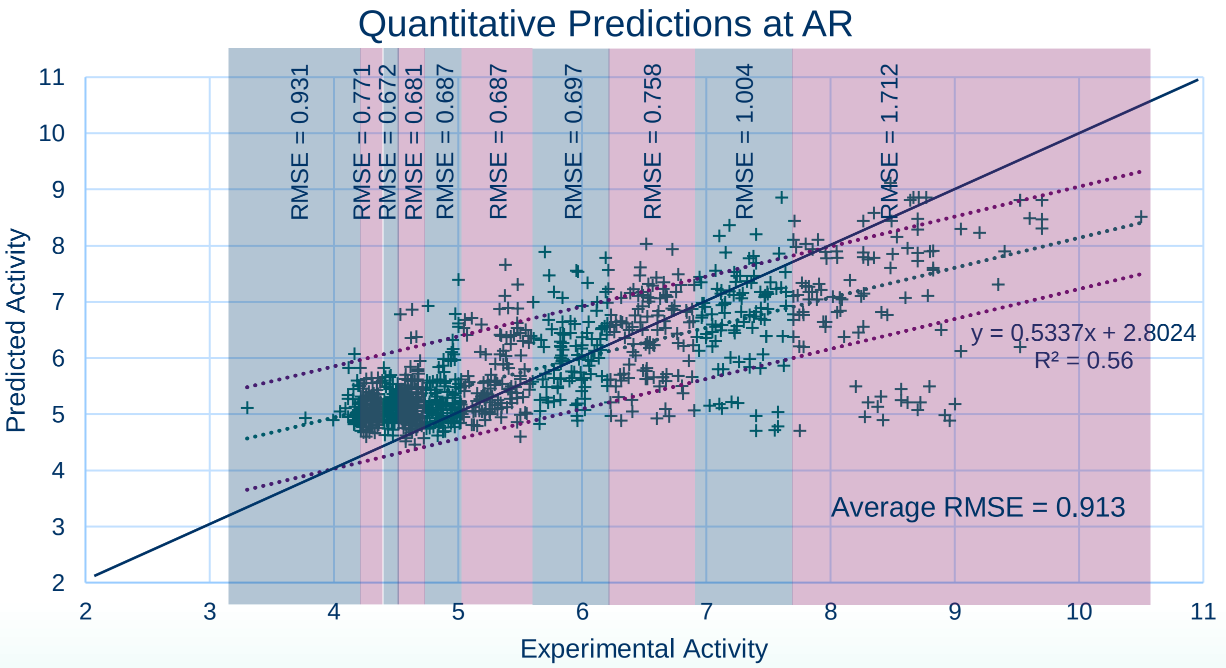
Quantitative Predictions

- Dose-Response Relationships and Risk Assessment Procedures require Quantitative Information
- Adjustment of AR dataset to contain only quantitative activity vales (p(Activity), 4880 values)
- Change of loss function to MSE
- Single output node with linear activation function
- Models evaluated using MSE and RMSE

Quantitative Predictions



Quantitative Predictions



Summary

- Neural Networks are a class of Machine Learning Algorithms that can provide both binary and quantitative predictions
- Structural Alerts, Random Forests and Neural Networks have been used to try and predict binary activity at Human MIEs
- A combination of these models and understanding of their workings is key to highest performance and model use in toxicology decision making
- Quantitative predictions help push this methodology closer to use in risk assessment, rather than just hazard identification

References

- Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment, Ankley, G.T., *et al.* (**2010**) *Environ. Toxicol. Chem.*, 29; 730.
- A next generation risk assessment case study for coumarin in cosmetic products, Baltazar, M.T. *et al.* (**2020**) *Toxicol. Sci., Accepted Manuscript.*
- Using 2D Structural Alerts to Define Chemical Categories for Molecular Initiating Events, Allen, T.E.H. *et al.* (**2018**) *Toxicol. Sci.*, 165; 213.
- Structural Alerts and Random Forest Models in a Consensus Approach for Receptor Binding Molecular Initiating Events. Wedlake, A.J. *et al.* (**2019**) *Chem. Res. Toxicol.*, 33; 388.

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