Trustworthy Deep Neural Network for Inferring Anticancer Synergistic Combinations

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Supplementary file

Content

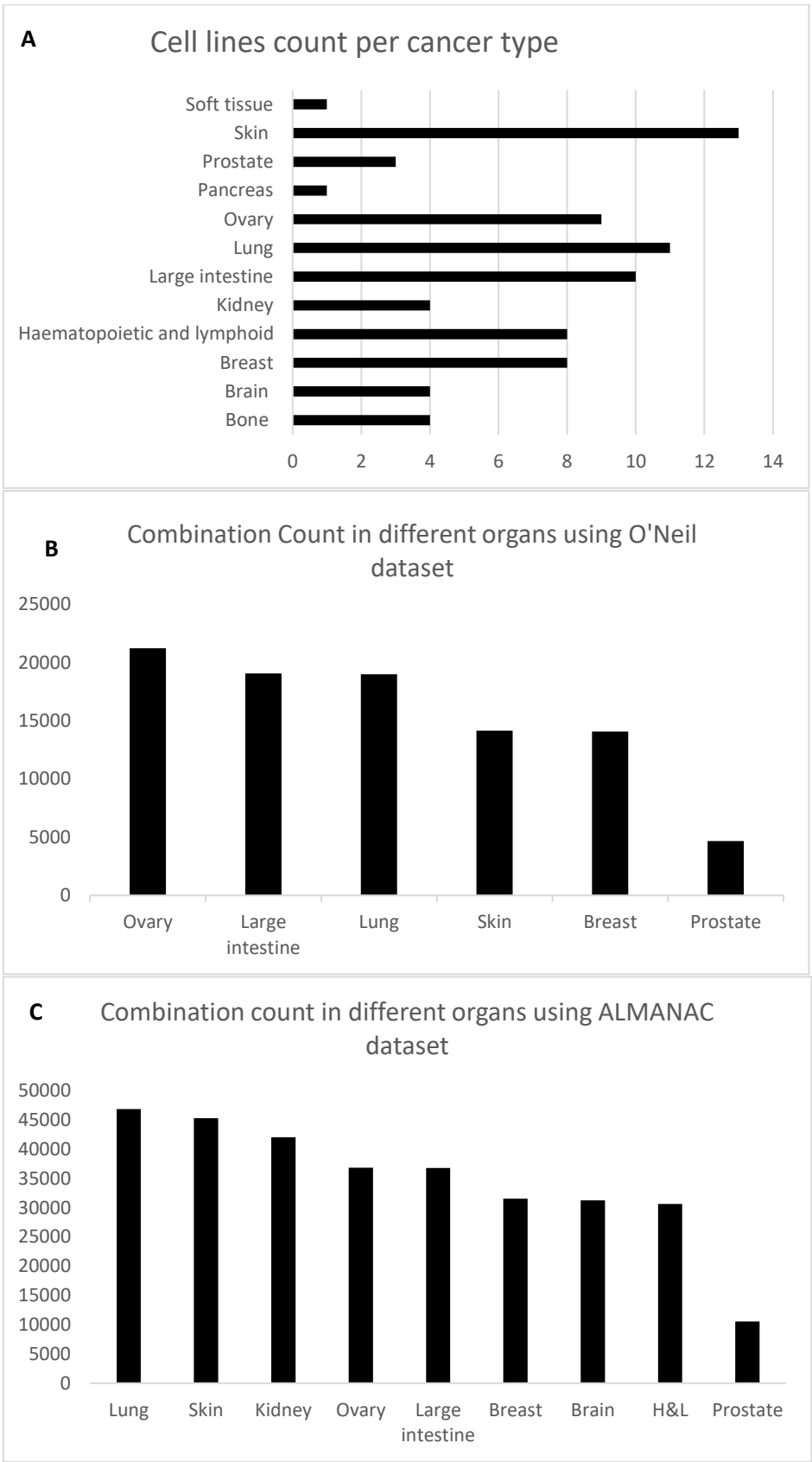

Figure S1 Cell lines and combination count used for training per cancer type in different datasets. A) Allocation of the total 76 cell lines used in SynPredict variants per various cancer types, B) and C) representing the counts of studied anticancer combinations per organ in ONEIL and ALMANAC datasets, respectively. H&L; Haematopoietic and lymphoid cancers.

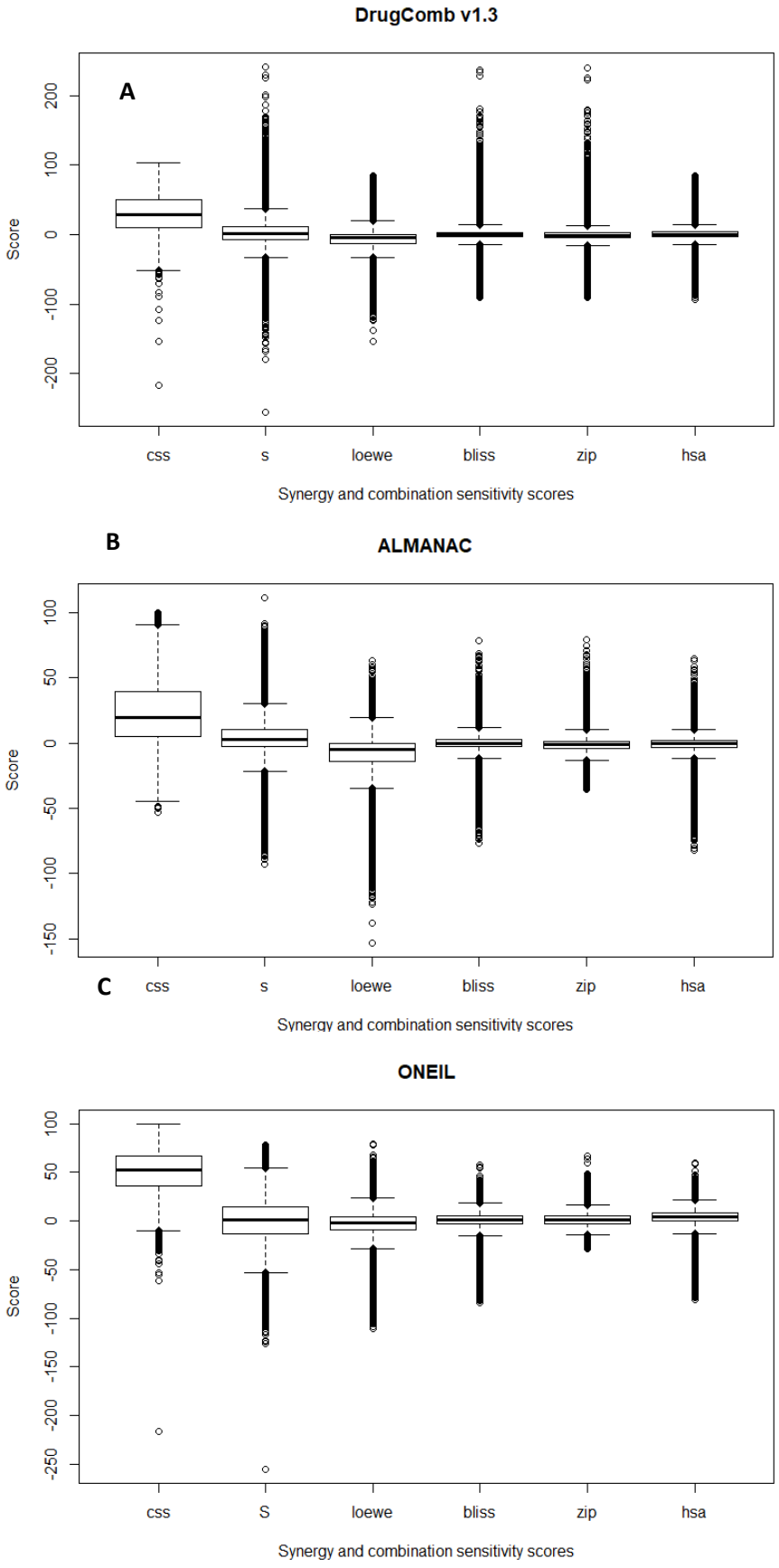

Figure S2 Boxplot frequency distribution of Combination sensitivity and different synergy scores in (A) the processed DrugComb v1.3 dataset and its ALMANAC (B) and ONEIL(C) subsets.

Table S1 Common models of synergy quantitation.

Models	Theory and/or assumption	Limitation	Equation	software	Ref.
Loewe additivity	The sham mixture, no interaction expected of the drug with itself, and assume drugs have a constant potency ratio	Constant Potency ratio and parallel dose-response curves are rare	(1)	SynergyFinder, Chalice, CombiTool, Combenefit, GeneData DrugComb	[1]
Bliss independence	**Non-interaction,** combination effect is due to 2 drugs don't interfere with each other and different site of action	Drug interactions in some drugs can't be excluded	(2)		[2]
Highest single agent (HSA) = Gaddum's pharmacological independence	The combination effect is superior to that achieved by single individual components	Any extra effect over the higher single drug will be considered as synergy Drug added to itself can produce an excess over HAS Too optimistic as the lowest threshold for synergy is considered	(3)		[3]
Zero interaction potency (ZIP),	-The combined effect is observed when the dose-response curve remains unchanged upon addition of the second drug -Hybrid model based on both Loewe additivity and Bliss independence	Dependence of accurate fitting of the dose-response curve to log-logistic curve which may be challenging for complex and low-quality dose-response data	(4)	DrugComb SynergyFinder	[4]
Median effect (Chou-Talalay)	Theorised based on median-effect equation and mass action low, and assume drugs have a constant potency ratio	Difficulty in the correct calculation of median effect doses due to nonlinearity and sigmoidicity of the dose-response curves	(5)	CompuSyn, Calcusyn, GeneData, PharmacoGx	[5]

(1) $E_{AB} = E_A\,(a + a_b) = E_B\,(b_a + b)$ & CI = a/A + b/B+ c/C……n/N

(2) $E_A + E_B(1-E_A) = E_A + E_B\text{-}E_AE_B$ & CI = $(E_A + E_B\text{-}E_A \times E_B)/E_{AB}$

(3) $E_{AB} = \max(E_A, E_B)$ & CI = $\max(E_A, E_B)/E_{AB}$

(4)
$$E_{AB} = \frac{\left(\frac{[A]}{EC_{50,A}}\right)^{\lambda_A}}{1+\left(\frac{[A]}{EC_{50,A}}\right)^{\lambda_A}} + \frac{\left(\frac{[B]}{EC_{50,B}}\right)^{\lambda_B}}{1+\left(\frac{[B]}{EC_{50,B}}\right)^{\lambda_B}} - \frac{\left(\frac{[A]}{EC_{50,A}}\right)^{\lambda_A}}{1+\left(\frac{[A]}{EC_{50,A}}\right)^{\lambda_A}} \frac{\left(\frac{[B]}{EC_{50,B}}\right)^{\lambda_B}}{1+\left(\frac{[B]}{EC_{50,B}}\right)^{\lambda_B}}$$

(5) $f_a/f_u = (D/D_m)^{m^*}$ and CI = $D_1/E_1 + D_2/E_2$

a + ab; dose a giving the effect E_{AB}, ba + b; dose b giving the effect $E_{AB,}$ CI; combination index (CI > 1 antagonism; CI = 1 additivity; CI < 1 synergy), D; a dose of the drug given, Dm; median-effect dose, D_1 and D_2; actual drug doses used, E_1 and E_2; the theoretical individual drug levels that would be expected to be needed to achieve the experimentally measured response, E_A; effect of drug A, E_B; effect of drug B, E_{AB}; effect of the combination of drug A and drug B, E_1 and E_2; theoretically individual drug levels expected to be required to produce the experimentally measured effect, EC_{50},A and EC_{50},B; the half-maximal response of drug A and drug B, fa; the fraction of cells killed, fu; the fraction of living cells, m; sigmoidicity of the dose-effect curve, R; potency ratio =A/B, 'Sham mixture'; drug mixed with itself, λ_A and λ_B; slope parameters of A and B dose response curves *; median effect equation.

Table S2 Synpredict MSE change % compared with other SynPredict variants or state of art regression models.

A				
	SynPredict1	**SynPredict2**	**SynPredict3**	**SynPredict4**
TransSynergy-LOEWE	21.4	23.6	26.8	27
AuDNN-LOEWE	24.7	26.7	29.8	30
DeepSynergy-LOEWE	29	30.9	33.8	34
DrugComb-LOEWE	-100.13	-94.71	-86.44	-86
DrugComb-BLISS	3	67.3	-5.2	55.4
DrugComb-HSA	-1	72.2	10.6	73.5
DrugComb-ZIP	-0.79	45.24	-12.07	64.17
B				
	ONEIL to ALMANAC (IF)	**ONEIL to ALMANAC (EF)**	**EF to IF (ONEIL)**	**EF to IF (ALMANAC)**
LOEWE	2.715954	0.266115	-7.34477	-4.70798
BLISS	66.29075	57.64859	7.843456	26.64877
HSA	65.79028	63.21839	-11.58	-3.77799
S	63.66042	61.85795	-3.48035	1.409791
ZIP	45.6753	68.03245	10.06656	-52.8302
CSS	72.5846	70.80917	-124.529	-110.873

EF; early fusion, IF; intermediate fusion. The positive and negative values indicate enhancement and deterioration of the model performance, respectively. MSE change % = (MSE of the baseline- MSE of SynPredict variant)/MSE of the baseline x 100, where the state of art model's MSE or other SynPredict variant's MSE was considered as a baseline of comparison in A and B, respectively.

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Deep Buhyan Dr Bhuyan received his PhD in pancreatic cancer therapeutics from The University of Newcastle, Australia in 2018 and has been working at NICM Health Research Institute, Western Sydney University as a Postdoctoral Research Fellow since then. His research centres on the development of novel antimicrobial and anticancer agents from natural sources and deciphering their molecular mechanisms of action. His current research is aimed at understanding the complex synergistic interactions among various phytochemicals and standard drugs on specific biological targets and how this can be utilised as therapeutic strategies against infectious/metabolic diseases and cancer. He has a strong research background investigating the anticancer and antimicrobial properties of plant extracts and bioactive compounds.

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Chun Guang Li. Professor Li commenced his current full-time role as Pharmacology leader at NICM in late 2012. In the previous five years he worked as a full time academic in the School of Health Sciences at RMIT University where he held the position of Director of the Chinese Medicine Research Group from 2007-2009 and was the leader of the Herbal Pharmacology and Toxicology group from 2008-2012. Li has directed a number of funded research projects and established an international reputation in the fields of pharmacology of complementary medicine in cancer and inflammation research. He conceptualised and managed various collaborative research projects with national and international institutions, and pharmaceutical industries. His main research interests include pharmacology of natural products, drug discovery, and traditional medicines.