Neuroevolution as a Tool for Microarray Gene Expression Pattern Identification in Cancer Research
Supplementary Data - Grisci, et al., 2018

S1-Figure: Example of NEAT crossover between two individuals.

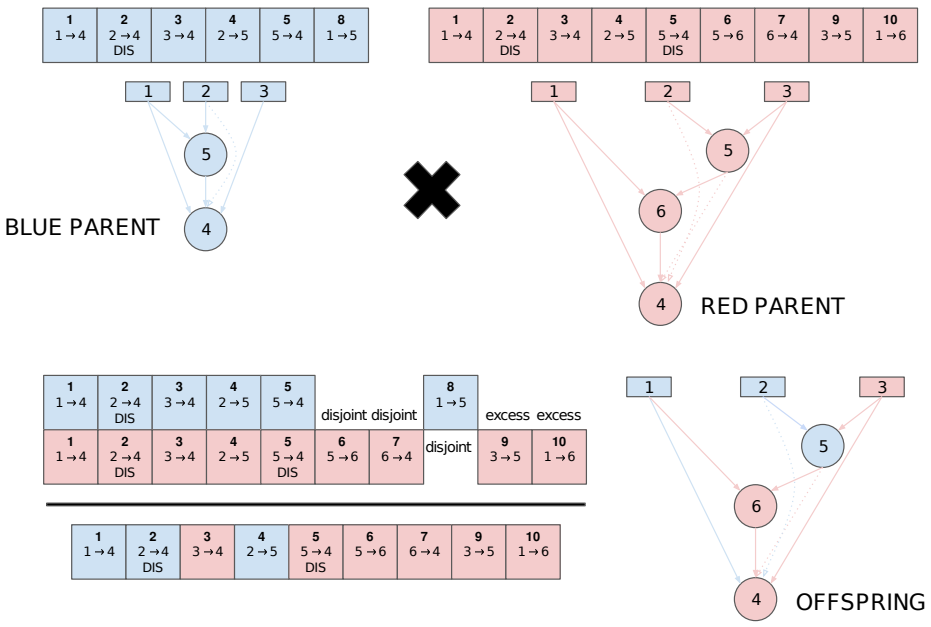

Figure 1: **Example of NEAT crossover between two individuals.** The red parent has better fitness than the blue parent. Their genes are aligned using the historical marker (numbers in bold) to avoid structural errors. The offspring receives genes with equal probability from any of the parents if they are present in both, or from the parent with better fitness if they are disjoint or excessive. Adapted from Stanley and Miikkulainen (2002).

S2-Figure: Illustration of the two possible structural mutations in NEAT.

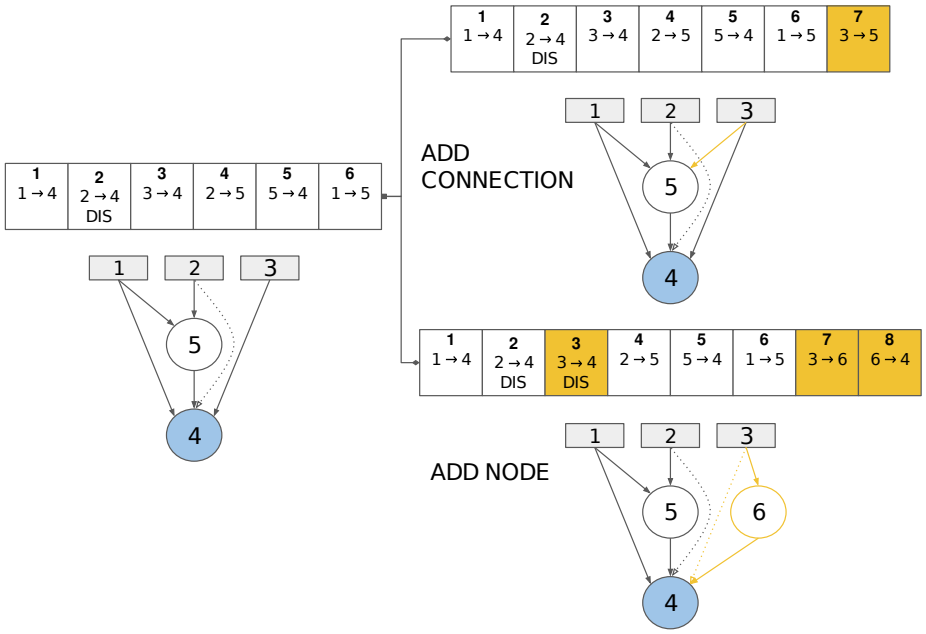

Figure 2: **Illustration of the two possible structural mutations in NEAT.** "Add connection" adds a connection with random weight between two randomly selected nodes in the network, in this case, nodes 3 and 5, and generates a new historical marker. "Add node" creates a new node with random bias in the place of an existing connection, that is disabled, and creates two new connections, one from the disabled connection origin node and the new node, that receives the weight value of the disabled connection. Finally, the connection from the new node to the disabled connection destination node receives a random weight value. In this example, the new node 6 is added between nodes 3 and 4, that were already connected. The changes are coloured in yellow. Adapted from Stanley and Miikkulainen (2002).

S3-Figure: Example of the extra FS-NEAT structural mutation.

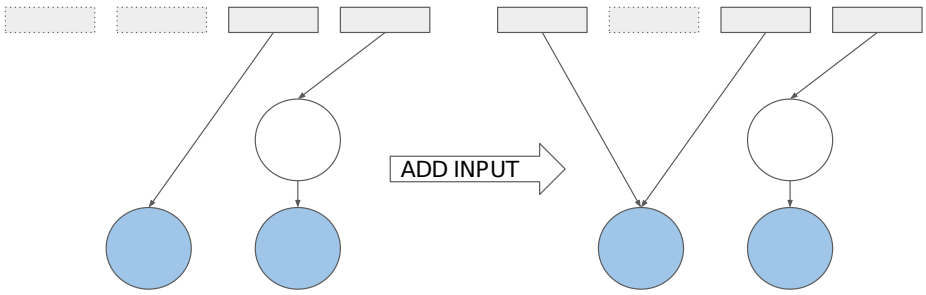

Figure 3: **Example of the extra FS-NEAT structural mutation.** A new input is added in a network by creating a connection with random weight value between the input being added and one of the outputs.

S1-Table: List of used hyperparameters.

Table 1: **List of used hyperparameters.**

Hyperparameter	**Value**
Population size	1000
Number of generations	100
Aggregation function[1]	mean
Activation function[1]	tanh, Gaussian
L2 regularization λ[2]	0.5
Probability of mutation adding input[3]	0.05
Probability of mutation swapping input[3]	0.05
Probability of mutation adding connection	0.05
Probability of mutation adding node	0.03
Probability of mutation changing weight	0.04
Elitism proportion	0.1
k tournament selection	2
Coefficient 1[4]	1.0
Coefficient 2[4]	1.0
Coefficient 3[4]	0.4
Compatibility threshold[4]	3.0

[1] Eq. 5, [2] Eq. 4b, [3] Fig. 3, [4] Eq. 1

S2-Table: G-mean, accuracy and FS comparison of N3O with FS-NEAT.

Table 2: **G-mean, accuracy, and FS comparison of N3O with FS-NEAT.**

		G-mean		**Accuracy**		**FS**	
Datasets	**Class**	**N3O**	**FS-NEAT**	**N3O**	**FS-NEAT**	**N3O**	**FS-NEAT**
GSE10797	Cancer Epithelial	**0.724** ± .056	0.721 ± .040	**0.736** ± .058	0.725 ± .043	**13.65** ± 2.36	32.33 ± 10.77
	Cancer Stroma	**0.733** ± .039	0.730 ± .046	**0.744** ± .035	0.734 ± .044	**13.85** ± 2.76	37.12 ± 12.53
	Normal	0.806 ± .071	**0.809** ± .064	**0.930** ± .024	0.921 ± .024	**12.92** ± 4.19	20.09 ± 9.13
GSE8671		**0.983** ± .018	0.980 ± .020	**0.984** ± .018	0.980 ± .020	**15.16** ± 3.99	17.53 ± 7.98
GSE32323		**0.938** ± .041	0.933 ± .044	**0.939** ± .040	0.934 ± .043	**15.74** ± 4.02	20.29 ± 8.97
GSE41328		**0.963** ± .051	0.950 ± .080	**0.968** ± .045	0.955 ± .071	18.67 ± 6.35	**18.60** ± 9.24
GSE14317		**0.949** ± .063	0.946 ± .066	**0.964** ± .040	0.960 ± .044	**14.80** ± 4.76	20.77 ± 9.44
GSE71935		0.783 ± .126	**0.799** ± .096	**0.902** ± .046	0.860 ± .047	**14.60** ± 3.42	26.13 ± 11.54
Golub et al. (1999)		0.886 ± .036	**0.898** ± .040	0.900 ± .032	**0.901** ± .038	**12.51** ± 2.43	28.58 ± 11.97
Average		**0.863** ± .102	0.862 ± .099	**0.896** ± .093	0.886 ± .095	**14.65** ± 1.83	24.60 ± 6.84

Reported values from 31 runs of the stratified 3-fold cross-validation. N3O = average G-mean, accuracy, and FS of the proposed method. FS-NEAT = average G-mean, accuracy, and FS of regular FS-NEAT (same fitness function and neuron structure as N3O). In bold are the best average G-mean and accuracy, and smallest average FS of each dataset. Best results with statistical significance ($p < 0.01$) are marked in blue.

S3-Table: Stratified 3-fold cross-validation statistical report of accuracy for N3O.

Table 3: **Stratified 3-fold cross-validation statistical report of accuracy for N3O.**

Datasets	Class	Baseline	Mean±std	Median	Min-Max
GSE42568		0.87	0.978 ± .011	0.983	0.95 - 0.99
GSE45827	Basal	0.73	0.934 ± .016	0.934	0.89 - 0.97
	HER	0.80	0.946 ± .019	0.947	0.89 - 0.97
	Cell Line	0.91	0.994 ± .006	0.993	0.98 - 1.00
	Luminal A	0.81	0.934 ± .019	0.940	0.90 - 0.97
	Luminal B	0.80	0.890 ± .026	0.894	0.84 - 0.95
	Normal	0.95	0.988 ± .009	0.993	0.97 - 1.00
GSE10797	Cancer Epithelial	0.57	0.736 ± .058	0.727	0.58 - 0.83
	Cancer Stroma	0.57	0.744 ± .035	0.742	0.68 - 0.83
	Normal	0.85	0.930 ± .024	0.924	0.88 - 0.97
GSE44076		0.50	0.982 ± .009	0.985	0.97 - 1.00
GSE44861		0.50	0.823 ± .031	0.829	0.74 - 0.87
GSE8671		0.51	0.984 ± .018	0.984	0.94 - 1.00
GSE21510		0.58	0.956 ± .032	0.953	0.88 - 1.00
GSE32323		0.51	0.939 ± .040	0.939	0.85 - 1.00
GSE41328		0.55	0.968 ± .045	1.000	0.83 - 1.00
GSE9476	AML	0.59	0.901 ± .035	0.891	0.83 - 0.97
	Bone Marrow	0.84	0.989 ± .017	1.000	0.94 - 1.00
	Bone Marrow CD34	0.87	0.963 ± .023	0.969	0.92 - 1.00
	PB	0.84	0.994 ± .009	1.000	0.97 - 1.00
	PBSC CD34	0.84	0.976 ± .022	0.984	0.94 - 1.00
GSE14317		0.72	0.964 ± .040	0.960	0.84 - 1.00
GSE63270		0.59	0.969 ± .022	0.970	0.89 - 1.00
GSE71935		0.80	0.902 ± .046	0.891	0.83 - 0.98
Golub et al. (1999)		0.65	0.900 ± .032	0.903	0.83 - 0.97

Reported values from 31 runs of the stratified 3-fold cross-validation. Baseline = accuracy of a classifier that assigns all samples to the largest class. Std = Standard deviation; Min = Minimum value reported in all runs; Max = Maximum value reported in all runs.

S4-Table: Accuracy comparison of N3O and SVM.

Table 4: **Accuracy comparison of N3O and SVM.**

Datasets	Class	N3O	SVM	KW&SVM	N3O&SVM
GSE42568		0.978 ± .011	0.985 ± .007	0.985 ± .006	**0.990** ± .006
GSE45827	Basal	0.934 ± .016	**0.972** ± .003	0.971 ± .004	0.968 ± .012
	HER	0.946 ± .019	0.962 ± .010	0.950 ± .011	**0.973** ± .026
	Cell Line	0.994 ± .006	**1.000** ± .000	**1.000** ± .000	0.999 ± .003
	Luminal A	0.934 ± .019	0.968 ± .014	**0.979** ± .007	0.965 ± .017
	Luminal B	0.890 ± .026	**0.931** ± .013	0.928 ± .016	0.923 ± .024
	Normal	0.988 ± .009	**0.995** ± .003	0.993 ± .000	0.994 ± .005
GSE10797	Cancer Epithelial	0.736 ± .058	**0.857** ± .028	**0.857** ± .028	0.850 ± .053
	Cancer Stroma	0.744 ± .035	0.761 ± .036	0.761 ± .036	**0.825** ± .062
	Normal	0.930 ± .024	0.924 ± .019	0.924 ± .019	**0.965** ± .018
GSE44076		0.982 ± .009	0.983 ± .003	0.984 ± .003	**0.987** ± .008
GSE44861		0.823 ± .031	**0.829** ± .045	**0.829** ± .045	**0.829** ± .059
GSE8671		**0.984** ± .018	0.698 ± .065	0.698 ± .065	0.667 ± .000
GSE21510		0.956 ± .032	**0.986** ± .021	**0.986** ± .021	**0.986** ± .039
GSE32323		**0.939** ± .040	0.692 ± .066	0.692 ± .066	0.686 ± .050
GSE41328		**0.968** ± .045	0.695 ± .061	0.697 ± .040	0.722 ± .000
GSE9476	AML	0.901 ± .035	0.947 ± .016	0.920 ± .019	**0.954** ± .039
	Bone Marrow	0.989 ± .017	0.984 ± .000	**0.998** ± .005	0.997 ± .007
	Bone Marrow CD34	0.963 ± .023	**0.997** ± .007	0.980 ± .019	0.984 ± .018
	PB	0.994 ± .009	0.985 ± .013	**1.000** ± .000	0.999 ± .004
	PBSC CD34	0.976 ± .022	0.984 ± .010	**0.997** ± .006	0.995 ± .012
GSE14317		0.964 ± .040	0.957 ± .044	0.991 ± .025	**0.996** ± .012
GSE63270		0.969 ± .022	**0.999** ± .003	0.998 ± .004	0.991 ± .011
GSE71935		0.902 ± .046	0.896 ± .034	0.923 ± .034	**0.966** ± .030
Golub et al. (1999)		0.900 ± .032	0.961 ± .022	**0.978** ± .012	0.943 ± .028
Average		**0.931** ± .070	0.918 ± .102	0.921 ± .103	0.926 ± .102

The accuracy is the result of 31 runs of the stratified 3-fold cross-validation. All SVM versions used the RBF kernel and had their hyperparameters tuned by grid search. N3O = average accuracy of the proposed method; SVM = average accuracy of SVM; KW&SVM = average accuracy of SVM after filtering the data with Kruskal-Wallis H Test; N3O&SVM = average accuracy of SVM using only the genes selected by the proposed method. In bold is the best average accuracy of each dataset. Best results with statistical significance ($p < 0.01$) are marked in blue.

S5-Table: Table listing all genes that were selected by our approach. The table brings the probe number, gene symbol, the biochemical function, the cancer type if it was already observed in the literature, the class in which it was selected and their respective references.

Probe	Gene Symbol	Biochemical Function	Cancer Type‡	Class	Refs*
1553243_at	ITIH5	Inter-alpha-Trypsin inhibitor	BC	BC	Rose et al. (2017); Benezeder et al. (2017)
201287_s_at	SDC1	Transmembrane Heparan Sulfate Proteoglycan	BC	BC	Cui et al. (2017)
220757_s_at	UBXN6/UBXD1	UBX Domain Protein	Several	BC	Rezvani (2016)
227530_at	AKAP12	A-Kinase Anchoring Protein	BC	BC	Marino et al. (2014)
235201_at	FOXP2	Transcription Factor	BC	BC	Wu et al. (2018b); Cuiffo and Karnoub (2015)
235362_at	LOC729970	LnC RNA	ND	BC	NA
237351_at	ENSG00000232079	ND	ND	BC	NA
237390_at	Hs.52931/ADRA1A	G protein-coupled receptor	HC	BC	Wang et al. (2013)
202908_at	WFS1	Transmembrane Glycoprotein	HC	BC-Estromal	Han et al. (2013)
205249_at	EGR2	Transcription Factor	BC	BC-Estromal	Kennedy and Harris (2018); Dillon et al. (2007)
205604_at	HOXD9	Transcription Factor	BC	BC-Estromal	DeInnocentes et al. (2015)
209194_at	CETN2	Calcium-binding protein	BC	BC-Estromal	Huan et al. (2014)
209392_at	ENPP2	Pyrophosphatase/Phosphodiesterase	BC	BC-Estromal	Schulte et al. (2012); Castellana et al. (2012a)
210031_at	CD247	T-cell receptor zeta	BC	BC-Estromal	Varchetta et al. (2007)
210455_at	C10orf28/R3HCC1L	ND	ND	BC-Estromal	NA
211635_x_at	IGHG1	Immunoglobulin	BC	BC-Estromal	Kabbage et al. (2008)
211915_s_at	TUBB7P	Pseudogene	ND	BC-Estromal	NA
213368_x_at	PPFIA3	Tyrosine phosphatase-interacting protein	GC	BC-Estromal	Li et al. (2016)
213893_x_at	PMS2P5	Pseudogene	ND	BC-Estromal	NA
220765_s_at	LIMS2/PINCH2	Focal adhesion proteins	GC, CRC	BC-Estromal	Park et al. (2015); Kim et al. (2006)
201438_at	COL6A3	Collagen	CRC	BC-Epithelium	Liu et al. (2018b)
201655_s_at	HSPG2	Proteoglycan	BC	BC-Epithelium	Valladares et al. (2006)
203371_s_at	NDUFB3	NADH: Ubiquinone Oxidoreductase	ND	BC-Epithelium	NA
205096_at	POM121/P145	Transmembrane Nucleoporin	BC	BC-Epithelium	Lawry et al. (1990)
205936_s_at	HK3	Hexokinase	BC	BC-Epithelium	Harami-Papp et al. (2016)
209758_s_at	MFAP5	Microfibril Associated Protein	BC	BC-Epithelium	Wu et al. (2018c)
214270_s_at	MAPRE3/EBF3	DNA-binding transcription factor	SC, AML	BC-Epithelium	Tao et al. (2015); Artomov et al. (2017)
216240_at	PVT1	LnC RNA	BC	BC-Epithelium	Tang et al. (2018)
201535_at	UBL3	Membrane-Anchored Ubiquitin-Fold Protein	TC	BC-Basal	Singh et al. (2015)
205376_at	INPP4B	Inositol Polyphosphate-4-Phosphatase	BC	BC-Basal	Croft et al. (2017); Tessier-Cloutier et al. (2017)
205819_at	MARCO	Macrophage Receptor	ND	BC-Basal	NA
206260_at	TGM4	Transglutaminase	PC	BC-Basal	Shaikhibrahim et al. (2011); Shan et al. (2017)
208894_at	HLA-DRA	Histocompatibility Complex, membrane-bound	BC	BC-Basal	Truax et al. (2012)
218211_s_at	MLPH	Rab effector protein	BC	BC-Basal	Thakkar et al. (2010, 2015)
221030_s_at	ARHGAP24	Rho GTPase Activating Protein	BC	BC-Basal	Uehara et al. (2017)
222457_s_at	LIMA1/EPLIN	Cytoskeleton-associated Protein	BC	BC-Basal	Jiang et al. (2008)
238865_at	PABPC4L	Poly(A) Binding Protein Cytoplasmic	ND	BC-Basal	NA
201262_s_at	BGN	Leucine-rich Proteoglycan	BC	BC-LuminalA	Valladares et al. (2006); Castellana et al. (2012b)

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Table 5 – *Continued from previous page*

Probe	Gene Symbol	Biochemical Function	Cancer Type‡	Class	Refs*
203930_s_at	MAPT	Microtubule Associated Protein	BC	BC-LuminalA	Lara-Padilla et al. (2016)
204092_s_at	AURKA	Kinase	BC	BC-LuminalA	Santpere et al. (2017); Lykkesfeldt et al. (2016)
211110_s_at	AR	Androgen Receptor	BC	BC-LuminalA	Khatun et al. (2018)
228554_at	PGR	Progesterone Receptor	BC	BC-LuminalA	Pirouzpanah et al. (2018); Kurozumi et al. (2017)
244035_at	AF086063	LnC RNA	ND	BC-LuminalA	NA
1558631_at	PPARA	Peroxisome Proliferator Receptor	BC	BC-LuminalB	Golembesky et al. (2008); Wu et al. (2012)
1566865_at	FAM200A	ND	ND	BC-LuminalB	NA
213557_at	Hs.444858	ND	ND	BC-LuminalB	NA
226363_at	ABCC5	ATP Binding Transporter	BC	BC-LuminalB	Lal et al. (2017)
231059_x_at	SCAND1	Zinc Finger proteins	ND	BC-LuminalB	NA
233003_at	Hs.677080	ND	ND	BC-LuminalB	NA
233571_x_at	PPDPF	Cell Differentiation And Proliferation Factor	ND	BC-LuminalB	NA
204914_s_at	SOX11	Transcription Factor	BC	BC-HER	Oliemuller et al. (2017)
210930_s_at	ERBB2	Tyrosine Kinase	BC	BC-HER	Keup et al. (2018)
227900_at	CBLB	Adenosyltransferase	BC	BC-HER	Chen et al. (2018)
240544_at	N23033	ND	ND	BC-HER	NA
241712_at	Hs.735278	ND	ND	BC-HER	NA
241978_at	Hs.731618	ND	ND	BC-HER	NA
202025_x_at	ACAA1	Acetyl-CoA Acyltransferase	CRC	CRC	Klimosch et al. (2013)
205697_at	SCGN	Calcium Binding Protein	CRC	CRC	Yang et al. (2018)
206409_at	TIAM1	Nucleotide exchange factor	CRC	CRC	Yu et al. (2013)
207003_at	GUCA2A	Guanylate Cyclase Activator	CRC	CRC	Lauriola et al. (2010)
209442_x_at	ANK3	Integral membrane protein	CRC	CRC	Yeon et al. (2017)
213389_at	ZNF592	Zinc Finger protein	ND	CRC	NA
216745_x_at	AK024606	ND	ND	CRC	NA
218599_at	REC8	Cohesin	GC, TRC	CRC	Liu et al. (2015); Yu et al. (2017b)
1558949_at	Hs.520638/TNRC18	ND	ND	CRC-Adenoma	NA
1563107_at	ENSG00000233215	LnC RNA	ND	CRC-Adenoma	NA
1569064_at	C15orf62	ND	ND	CRC-Adenoma	NA
201064_s_at	PABPC4	Poly(A) Binding Protein Cytoplasmic	PC, LC, BC	CRC-Adenoma	Kharaziha et al. (2015); Hsu et al. (2016); Kostianets et al. (2012)
201195_s_at	SLC7A5	Solute Carrier protein	CRC	CRC-Adenoma	Kalmar et al. (2013)
201970_s_at	NASP	H1 histone binding protein	GC, OC	CRC-Adenoma	Yu et al. (2017a); Ali-Fehmi et al. (2010)
202061_s_at	SEL1L	Ligase Adaptor Subunit	CRC	CRC-Adenoma	Ashktorab et al. (2012)
204272_at	LGALS4	Beta-galactoside-binding protein	CRC	CRC-Adenoma	Rodia et al. (2017)
205718_at	ITGB7	Integrin	CRC	CRC-Adenoma	Ortega et al. (2010)
205825_at	PCSK1	Proprotein Convertase	HC, PC, LC	CRC-Adenoma	Ramalingam et al. (2016); Malouf et al. (2014); Demidyuk et al. (2013)
207734_at	LAX1	Lymphocyte Transmembrane protein	CLL	CRC-Adenoma	Johnston et al. (2018)
207961_x_at	MYH11	Myosin	CRC	CRC-Adenoma	Jo et al. (2018)
208800_at	SRP72	Ribonucleoprotein	PC, TRC	CRC-Adenoma	Chai et al. (2016); Lyu et al. (2017)
213258_at	TFPI	Serine protease inhibitor	CRC	CRC-Adenoma	Kurer (2007)
213552_at	GLCE	Glucuronic Acid Epimerase	BC, PC	CRC-Adenoma	Belyavskaya et al. (2017); Suhovskih et al. (2014)
218694_at	ARMCX1/ALEX1	N-terminal transmembrane protein	CRC	CRC-Adenoma	Iseki et al. (2012)

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Table 5 – *Continued from previous page*

Probe	Gene Symbol	Biochemical Function	Cancer Type‡	Class	Refs*
219595_at	ZNF26	Zinc Finger Protein	ND	CRC-Adenoma	NA
219752_at	RASAL1	GTPase-activating protein	CRC	CRC-Adenoma	Aytekin et al. (2010)
225807_at	AJUBA	Complex Adapter protein	CRC	CRC-Adenoma	Jia et al. (2017); Yang et al. (2017)
225909_at	ZNF775	Zinc Finger Protein	ND	CRC-Adenoma	NA
227253_at	CP	Ferroxidase	CRC	CRC-Adenoma	Martín Mateo and Martín (1988)
241815_at	Hs.551393	ND	ND	CRC-Adenoma	NA
242384_at	Hs.605187	ND	ND	CRC-Adenoma	NA
11719018_at	CBFB	Transcription factor	CRC	CRC-Adenocarcinoma	Andersen et al. (2009)
11722527_s_at	PTPN21	Protein Tyrosine Phosphatase	CRC	CRC-Adenocarcinoma	Korff et al. (2008)
11724871_a_at	CLDN2	Integral membrane protein	CRC	CRC-Adenocarcinoma	Bujko et al. (2015)
11733581_a_at	CA7	Carbonic Anhydrase	CRC	CRC-Adenocarcinoma	Shangkuan et al. (2017)
11733707_x_at	COL11A1	Collagen	CRC	CRC-Adenocarcinoma	Zhang et al. (2016)
11740105_x_at	TMEM17	Transmembrane Protein	LC	CRC-Adenocarcinoma	Zhang et al. (2017c)
11740441_a_at	APOBEC3A	Cytidine deaminase	LC	CRC-Adenocarcinoma	Wang et al. (2018)
11744487_x_at	CNBP	Zinc Finger nucleic-acid binding protein	ND	CRC-Adenocarcinoma	NA
11744691_x_at	ARMC10	Transmembrane protein	SC	CRC-Adenocarcinoma	Turner et al. (2017)
11757530_a_at	C19orf53	ND	ND	CRC-Adenocarcinoma	NA
11758083_s_at	HPGD	15-Hydroxyprostaglandin Dehydrogenase	CRC	CRC-Adenocarcinoma	Pereira et al. (2016)
11762923_x_at	MT-CO2	Cytochrome C Oxidase	CRC	CRC-Adenocarcinoma	Errichiello et al. (2015)
1552906_at	FMR1NB	Cancer/Testis Antigen	TTC	CRC	Cappell et al. (2012)
1555230_a_at	KCNIP2	Potassium Voltage Channel Interacting Protein	ND	CRC	NA
1557531_a_at	C10orf55	ND	ND	CRC	NA
1568609_s_at	ENSG00000232151	ND	ND	CRC	NA
202228_s_at	NPTN	Transmembrane protein	LC	CRC	Kettunen et al. (2017)
212191_x_at	RPL13	Large Ribosomal Subunit	CRC	CRC	Xu et al. (2017)
212352_s_at	TMED10	Transmembrane protein	HC	CRC	Saran et al. (2016)
227435_at	KIAA2018	Transcription Factor	LC, TRC	CRC	Ni et al. (2017); Renieri et al. (2014)
230389_at	FNBP1	Formin-binding-protein	AML	CRC	Krumbholz et al. (2015)
1554575_a_at	BPNT1	5'-Bisphosphate Nucleotidase	HNC	CRC-Adenocarcinoma	An et al. (2015)
1554780_a_at	PHTF2	Transcription Factor	ND	CRC-Adenocarcinoma	NA
1861_at	BAD	BCL2 Associated Protein	Anti-tumor	CRC-Adenocarcinoma	Stickles et al. (2015)
200001_at	CAPNS1	Calcium-Dependent Protease	BC	CRC-Adenocarcinoma	Raimondi et al. (2016)
201105_at	LGALS1	Beta-galactoside-binding protein	CRC	CRC-Adenocarcinoma	Li et al. (2017)
201161_s_at	CSDA/YBX3	DNA-Binding Protein	RC	CRC-Adenocarcinoma	Dupasquier et al. (2014)
201327_s_at	CCT6A	Chaperone	SC, RC	CRC-Adenocarcinoma	Zhu et al. (2017); Tanic et al. (2006)
205757_at	ENTPD5	Triphosphate Diphosphohydrolase	CRC	CRC-Adenocarcinoma	Pizzini et al. (2013)
206173_x_at	GABPB1	Transcription Factor	SC	CRC-Adenocarcinoma	Zhang et al. (2017b)
209842_at	SOX10	Transcription Factor	CRC	CRC-Adenocarcinoma	Tong et al. (2014)
213857_s_at	CD47	Membrane protein	CRC	CRC-Adenocarcinoma	Thean et al. (2018)
214430_at	GLA	Galactosidase	ND	CRC-Adenocarcinoma	NA
214665_s_at	CHP1	Phosphoprotein	CRC	CRC-Adenocarcinoma	Galamb et al. (2016)
214845_s_at	CALU	Calcium-binding protein	CRC	CRC-Adenocarcinoma	Torres et al. (2013)

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Table 5 – *Continued from previous page*

Probe	Gene Symbol	Biochemical Function	Cancer Type‡	Class	Refs*
215894_at	PTGDR	Prostaglandin D2 Receptor	CRC	CRC-Adenocarcinoma	Kalmar et al. (2013)
218184_at	TULP4	ND	ND	CRC-Adenocarcinoma	NA
222449_at	PMEPA1	Transmembrane Protein	CRC	CRC-Adenocarcinoma	Sheffer et al. (2009)
225575_at	LIFR	Type I cytokine receptor	CRC	CRC-Adenocarcinoma	Wu et al. (2018a)
228194_s_at	SORCS1	Vacuolar protein receptor	CRC	CRC-Adenocarcinoma	Hua et al. (2017)
228671_at	TMEM201	Transmembrane Protein	ND	CRC-Adenocarcinoma	NA
235299_at	SLC41A2	Solute Carrier protein	ND	CRC-Adenocarcinoma	NA
235372_at	FCRLA	Fc Receptor-Related Protein	CLL	CRC-Adenocarcinoma	Li et al. (2008)
235784_at	N32155	ND	ND	CRC-Adenocarcinoma	NA
238169_at	AI307778	ND	ND	CRC-Adenocarcinoma	NA
203110_at	PTK2B	Tyrosine Kinase	CRC	CRC	Oh et al. (2017)
207643_s_at	TNFRSF1A	TNF Receptor	CRC	CRC	Yu et al. (2014)
214670_at	ZKSCAN1	Transcription Factor	HC	CRC	Z et al. (2017)
219202_at	RHBDF2	ND	GC	CRC	Ishimoto et al. (2017)
227955_s_at	EFNA5	Tyrosine Kinase Ligand	GC, PC	CRC	Zhu et al. (2015a); Rosenberg et al. (2017)
230081_at	PLCXD3	Phospholipase	ND	CRC	NA
204793_at	GPRASP1	G Protein-Coupled Receptor	ND	LKM-ATL	NA
205109_s_at	ARHGEF4	Rho Guanine Nucleotide Exchange Factor	ALL	LKM-ATL	Lyons et al. (2010)
212091_s_at	COL6A1	Collagen	PC, RC, CC	LKM-ATL	Zhu et al. (2015b); Wan et al. (2015); Hou et al. (2016)
218925_s_at	C11orf1	ND	ND	LKM-ATL	NA
204924_at	TLR2	Toll-like receptor	AML, CLL	LKM-AML	Eriksson et al. (2017); Williams and Ariza (2018)
218493_at	SNRNP25	Nuclear Ribonucleoprotein	ND	LKM-AML	NA
218599_at	REC8	Meiotic structural protein	GC, TRC	LKM-AML	Liu et al. (2015); Yu et al. (2017b)
230351_at	LOC283481	LnC RNA	ND	LKM-AML	NA
231772_x_at	CENPH	Kinetochore protein	MDS	LKM-AML	Lee et al. (2012)
239082_at	FZD3	Transmembrane Receptor	AML, CLL	LKM-AML	Kaucká et al. (2013); Zhang et al. (2017a)
1570115_at	Hs.684470	ND	ND	LKM-JMML	NA
201118_at	PGD/6PGD	Phosphogluconate Dehydrogenase	AML	LKM-JMML	Bhanot et al. (2017)
203820_s_at	IGF2BP3	Insulin-Like Growth Factor	ALL	LKM-JMML	Stoskus et al. (2011)
204906_at	RPS6KA2	Serine/threonine kinase	CRC, PCC	LKM-JMML	Milosevic et al. (2013); Slattery et al. (2011)
207802_at	CRISP3	Cysteine Rich Secretory Protein	PC	LKM-JMML	Pathak et al. (2018)
212332_at	RBL2	Transcriptional Corepressor	ATL	LKM-JMML	Takeuchi et al. (2003)
213603_s_at	RAC2	GTP-metabolizing protein	JMML, CLL	LKM-JMML	Caye et al. (2015); Nieborowska-Skorska et al. (2012)
219892_at	TM6SF1	Transmembrane protein	BC	LKM-JMML	de Groot et al. (2014)
225681_at	CTHRC1	Collagen-associated protein	LC, CRC, HC	LKM-JMML	He et al. (2018); Liu et al. (2018a); Wang et al. (2018)
231406_at	ORAI2	Calcium-release Channel	AML	LKM-JMML	Diez-Bello et al. (2017)
242013_at	BCL2L15	ND	Several	LKM-JMML	Niavarani et al. (2018)
200742_s_at	TPP1	Tripeptidyl Peptidase	CLL	LKM-AML	Guièze et al. (2017)
203042_at	LAMP2	Membrane glycoprotein	AML	LKM-AML	Sukhai et al. (2013)
203770_s_at	STS	Steroid Sulfatase	AML	LKM-AML	Hughes et al. (2005)
205054_at	NEB	Cytoskeleton structural component	ND	LKM-AML	NA
206493_at	ITGA2B	Fibronectin receptor	AML	LKM-AML	Huang et al. (2017)

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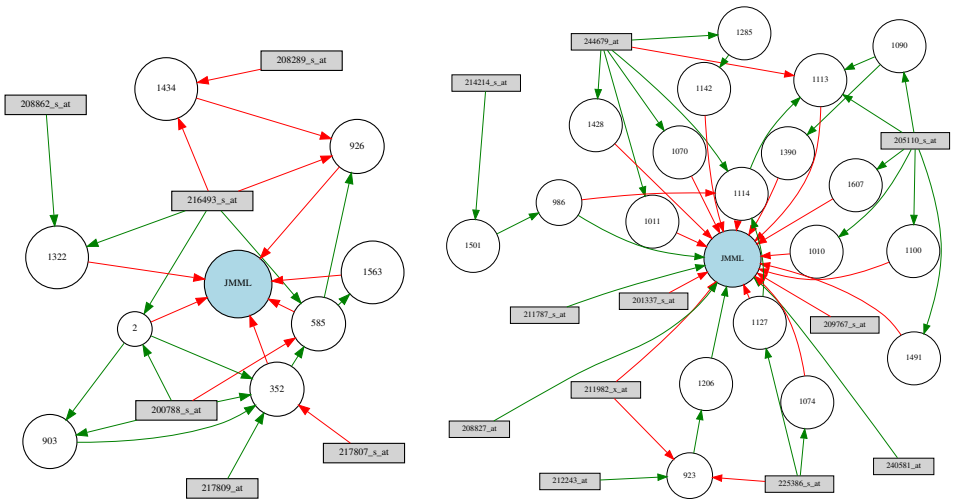
Table 5 – *Continued from previous page*

Probe	Gene Symbol	Biochemical Function	Cancer Type‡	Class	Refs*
209389_x_at	DBI/ACBP	Diazepam Binding Inhibitor	TC	LKM-AML	Dlamini et al. (2017)
210123_s_at	CHRNA7	Cholinergic Receptor	T-ALL	LKM-AML	Chakhachiro et al. (2013)
212224_at	ALDH1A1	Aldehyde Dehydrogenase	AML	LKM-AML	Gasparetto and Smith (2017)
212792_at	DPY19L1	C-mannosyltransferase	CRC	LKM-AML	Márquez et al. (2013)
212914_at	CBX7	Polycomb repressive complex component	CML	LKM-AML	Crea et al. (2015)
215116_s_at	DNM1	GTP-binding protein	BRC	LKM-AML	Patel et al. (2013)
215823_x_at	RLIM	E3 ubiquitin protein ligase	BOC, BC	LKM-AML	Johnsen et al. (2009); Chen et al. (2014)
216726_at	Hs.447377	ND	ND	LKM-AML	NA
217825_s_at	UBE2J1	Ubiquitin Conjugating Enzyme	ND	LKM-AML	NA
219394_at	PGS1	Phosphatidylglycerophosphate Synthase	ND	LKM-AML	NA
219450_at	C4orf19	ND	ND	LKM-AML	NA
220589_s_at	ITFG2	ND	ND	LKM-AML	NA
221477_s_at	SOD2	Superoxide Dismutase	ALL, ABL	LKM-AML	Alachkar et al. (2017); Girerd et al. (2018)

‡= Other cancer types that the selected genes were observed to be altered in some way; * = when multiple references were available we gave preference to citations from the last 5 years, except when they could be complementary; ABL = Chronic Myeloid Leukemia BCR-ABL fusion; ALL = Acute Myeloid Leukemia; ATL = Acute T-cell Leukemia; BC = Breast Cancer; BOC = Bone Cancer; BRC = Brain Cancer; CC = Cervical Cancer; CLL = Chronic Lymphocytic Leukemia; CRC = Colorectal Cancer; GC = Gastric Cancer; HC = Hepatic Cancer; HNC = Head and Neck Cancer; JMML = Juvenile Myelomonocytic Leukemia; LC = Lung Cancer; MDS = Myelodysplastic Syndrome; NA = Not Applicable; ND = Not Defined; OC = Ovarian Cancer; PC = Prostate Cancer; PCC = Pancreatic Cancer; RC = Renal Cancer; SC = Skin Cancer; T-ALL = T-lymphoblastic Leukemia; TC = Throat Cancer; TRC = Thyroid Cancer; TTC = testicular Cancer.

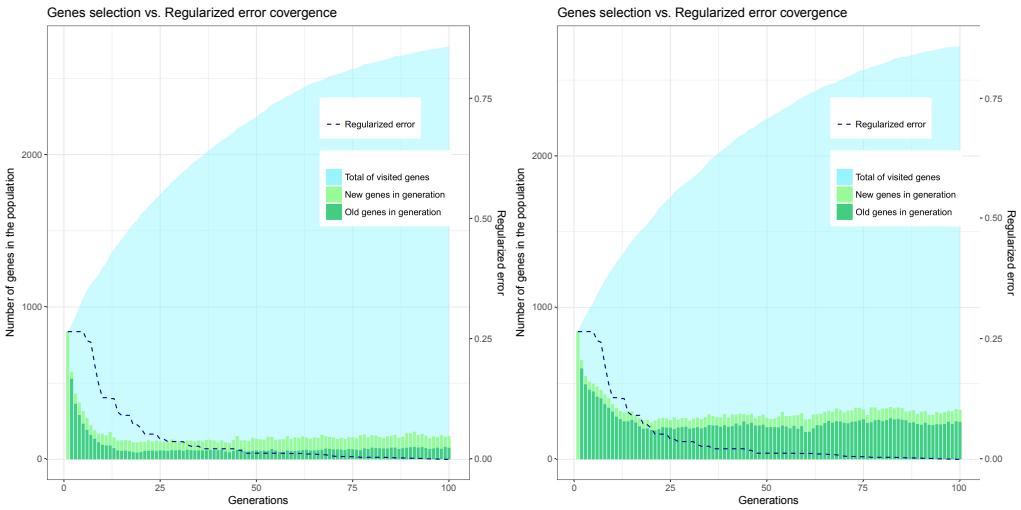
S4-Figure: ANNs created with N3O and FS-NEAT for the same data.



(a) N3O (b) FS-NEAT

Figure 4: **ANNs created with N3O and FS-NEAT for the same data.** Two neural networks with best fitness in the population at the final generation for a run of N3O and regular FS-NEAT with dataset GSE71935 (leukemia). Grey rectangles are input nodes, white circles are hidden nodes, and blue circles are output nodes. The number inside the hidden nodes inform the order in which they were created. Arrows are green if they are connections with positive weight, or they are red otherwise. Their thickness is proportional to the absolute values of their weights. Dotted arrows are disabled connections.

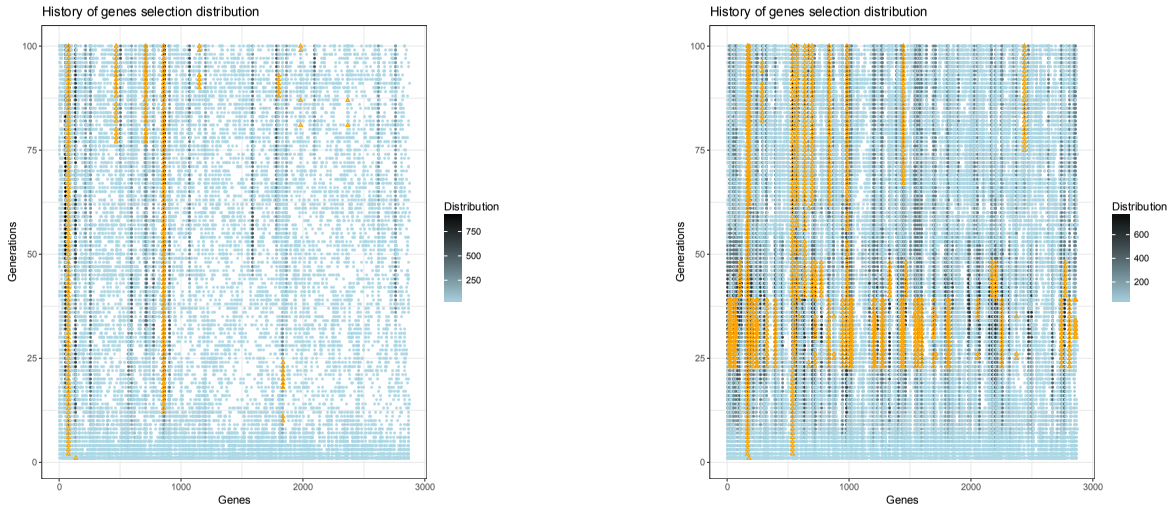
S5-Figure: Genes selection and error convergence for N3O and FS-NEAT.



(a) N3O (b) FS-NEAT

Figure 5: **Genes selection and error convergence for N3O and FS-NEAT** for a run with dataset GSE71935 (leukemia). Chart showing the convergence of both the best regularized error ($-fitness$) in the dashed line, and the selection of genes in the population in green bars. Each green bar represents the number of genes present in at least one individual of the population at a given generation. The darker bar is the number of genes that were already present in the previous generation, and the lighter bar the number of genes new to the population when compared with the previous generation. The light blue curve represents the total exploration of genes, counting the number of genes that were present in at least one individual during at least one generation.

S6-Figure: Selection history of candidate genes for N3O and FS-NEAT.



(a) N3O (b) FS-NEAT

Figure 6: **Selection history of candidate genes for N3O and FS-NEAT** for a run with dataset GSE71935 (leukemia). This chart brings all the genes allowed to be selected during the evolution (after filtering with Kruskal-Wallis H Test and $p < 0.01$), ordered in the x axis from the smallest p-value (left) to the highest p-value (right), and the generations in the y axis, from the beginning (bottom) to the end (top). If a gene was present in the population (selected by at least one individual) at a given generation, it will be marked with a circle in the respective position. The darker the point, the larger the number of individuals selecting this gene at the same generation. If a point is marked with an orange triangle, that gene, at that generation, was present in the individual with best fitness.

S7-Figure: The number of genes related to the major cellular components.

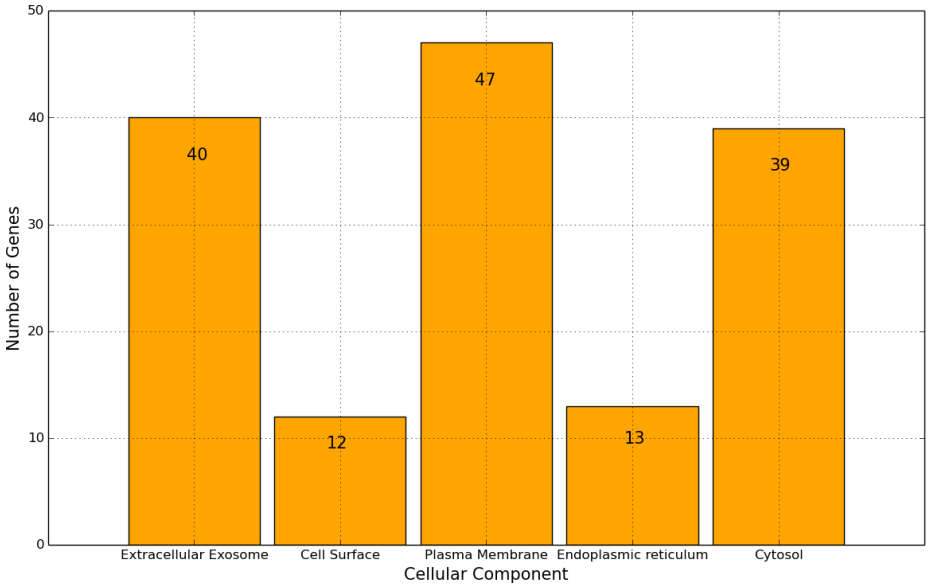


Figure 7: **The number of genes related to the major cellular components.** The five most significant and abundant categories that the selected genes were classified are related to the extracellular exosomes, cell surface, plasma membrane, endoplasmatic reticulum and the cytosol.

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