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| **Identification of** **anticancer drug target genes using an outside competitive dynamics model on cancer signaling networks** Tien-Dzung Tran1,2,\* and Duc-Tinh Pham3,4 1Complex Systems and Bioinformatics Lab, Hanoi University of Industry, 298 Cau Dien street, Bac Tu Liem District, Hanoi, Vietnam;  2Department of Software Engineering, Faculty of Information and Communication Technology, Hanoi University of Industry, 298 Cau Dien street, Bac Tu Liem District, Hanoi, Vietnam.  3Graduate University of Science and Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam  4Hanoi University of Industry, 298 Cau Dien street, Bac Tu Liem District, Hanoi, Vietnam;  \*Corresponding: [trantd@haui.edu.vn](mailto:trantd@haui.edu.vn) |

Supplementary Information

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| **Algorithm S1.** Computation of total support of nodes in a network *G*(*V*,*E*) to a node *α* against outside impact | |
| 1 | **function** *[Xt]* *InsideCompetition(G(V,E), Leaders ⊂ V, AgainstLeaders ⊂ V)* |
| 2 | *maxIterations*←*10000;* |
| 3 | *Epsilon ← 4.94e-324;* |
| 4 | *ε* ←*1/(Max*(total weights of out-links of *v*, ∀*v*∈*V) - Epsilon;* |
| 5 | *Xt*←**new** *Dictionary<node,state>;* |
| 6 | *Xt+1* ←**new** *Dictionary<node,state>;* |
| 7 | **for** (*Node* **in** *V* ) **do** |
| 8 | *Xt[Node]* ←*0;* |
| 9 | **end for** |
| 10 | **for** (*Leader* **in** *Leaders*) **do** |
| 11 | *Xt[Leader] ←1;* |
| 12 | *Xt+1[Leader] ←1;* |
| 13 | **end for** |
| 14 | **for** (*AgainstLeader* **in** *AgainstLeaders*) **do** |
| 15 | *Xt[AgainstLeader]* ← *−1;* |
| 16 | *Xt+1[AgainstLeader]* ← *−1;* |
| 17 | **end for** |
| 18 | *Error ← 0;* |
| 19 | *t ← 0;* |
| 20 | **do** |
| 21 | *Error← 0;* |
| 22 | **for** (*u* **in** *V*) **do** |
| 23 | **if***(Leaders* contain *u* **or** *AgainstLeaders* contain *u)* **continue*;*** |
| 24 | **end if** |
| 25 | *r←0;* |
| 26 | **for** (*v* **in** *Neighbors of u*) **do** |
| 27 | *r← r + weight(u,v)\*(Xt[v]- Xt[u]);* |
| 28 | **end for** |
| 29 | *Xt+1[u]* ← *Xt[u]+ ε\* r;* |
| 30 | *Error ← Error + Math.Abs(Xt[u] - Xt+1[u]);* |
| 31 | **end for** |
| 32 | *Temp←Xt;* |
| 33 | *Xt← Xt+1;* |
| 34 | *Xt+1←Temp;* |
| 35 | *t ← t +1;* |
| 36 | **while** *(Error > Epsilon && t < maxIterations);* |
| 37 | **return** *Xt;* //Output as stable states of nodes as *t*→∞ |
| 38 | **end** |
| 39 | **function** *[Support]* *OutsideCompetition (G(V,E),* α *∈V)* |
| 40 | *Support←* **new** *Dictionary<node,state>;* |
| 41 | *β←* **new**Node |
| 42 | *NormalAgents← V \{β,*α*} ;* |
| 43 | **for** (*γ* **in** *NormalAgents* ) **do** |
| 44 | *e←* **new** *Edge(β, γ);* |
| 45 | *E= E ∪ {e};* |
| 46 | *← InsideCompetition(G(V,E), {*α*},{β});* |
| 47 | *Support[γ] ← [γ];* |
| 48 | *E= E \ {e};* |
| 49 | **end for** |
| 50 | **return** *Support;*//Support of nodes to α when connecting to *β* |
| 51 | **end** |
| 52 | **function** [*TotalSupport*] *ToS(G(V,E),* α *∈ V)* |
| 53 | *Support←* **new** *Dictionary<node,state>;* |
| 54 | *Support← OutsideCompetition (G(V,E),* α*);* |
| 55 | *TotalSupport ← 0;* |
| 56 | **for** (*γ* **in** *V*\{α}) **do** |
| 57 | *TotalSupport ← TotalSupport + Support[γ]* |
| 58 | **end for** |
| 59 | **return** *TotalSupport*; //Total support of nodes to α |
| 60 | **End** |

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| **Table S1**. Correlation coefficient (R) between total support and closeness/hierarchical closeness of 17 cancer types (all R have P < 0.0001) | | |
| **Cancer name** | **R(total support, hierarchical closeness)** | **R(total support, closeness)** |
| Acute myeloid leukemia | 0.919 | 0.836 |
| Basal cell carcinoma | 0.764 | 0.552 |
| Bladder cancer | 0.752 | 0.776 |
| Breast cancer | 0.837 | 0.948 |
| Chronic myeloid leukemia | 0.942 | 0.941 |
| Colorectal cancer | 0.834 | 0.760 |
| Endometrial cancer | 0.924 | 0.784 |
| Gastric cancer | 0.959 | 0.986 |
| Glioma | 0.610 | 0.646 |
| Hepatocellular carcinoma | 0.965 | 0.932 |
| Melanoma | 0.932 | 0.978 |
| Non-small-cell lung cancer | 0.719 | 0.721 |
| Pancreatic cancer | 0.805 | 0.787 |
| Prostate cancer | 0.783 | 0.773 |
| Renal cell carcinoma | 0.922 | 0.693 |
| Small cell lung cancer | 0.841 | 0.951 |
| Thyroid cancer | 0.797 | 0.830 |
| 100 random directed networks generated with  |V| = 50 and 49 ≤ |E| ≤ 100 | 0.866  (P = 0.0001) | 0.866  (P = 0.0001) |

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| **Table S2.**  Previously reported anticancer drug target genes among the top three genes with the highest total support. Genes in bold are approved for drug manufacture whereas the remaining ones are clinical trial/potential. | |
| **Cancer site** | **Anticancer drug target genes** |
| Acute myeloid leukemia | [GRB2](https://doi.org/10.1002/gcc.20344)[[1](#_ENREF_1)](#_ENREF_1); [**FLT3**](https://doi.org/10.2174/1381612043384394)[**2**](#_ENREF_2); **PML**[**3**](#_ENREF_3) |
| Basal cell carcinoma | SUFU[4](#_ENREF_4); **SMO**[**5**](#_ENREF_5); GLI3[6](#_ENREF_6) |
| Bladder cancer | RASSF1[9](#_ENREF_9" \o "Khandelwal, 2020 #583) **[10](#_ENREF_10" \o "Khandelwal, 2018 #584),[11](#_ENREF_11" \o "Sun, 2019 #585), FGFR3[8](#_ENREF_8" \o "Casadei, 2019 #582),** HRAS[7](#_ENREF_7" \o "Sugita, 2018 #581) |
| Breast cancer | **[LRP6](https://www.pnas.org/content/107/11/5136.short)**[12](#_ENREF_12" \o "Zhou, 2020 #551); [LRP5](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0004243)[13](#_ENREF_13),[14](#_ENREF_14); **[WNT](https://pubmed.ncbi.nlm.nih.gov/22846569/)1**[15](#_ENREF_15" \o "Wu, 2019 #554) |
| Chronic myeloid leukemia | [CRK](https://dx.doi.org/10.3889%2Foamjms.2018.420)[16](#_ENREF_16); [CRKL](https://dx.doi.org/10.18632%2Foncotarget.2072)[17](#_ENREF_17" \o "Frietsch, 2014 #133); [GAB2](https://www.nature.com/articles/leu2012222)[18](#_ENREF_18" \o "Wöhrle, 2013 #134) |
| Colorectal cancer | **[EGFR](https://doi.org/10.3978/j.issn.1000-9604.2014.01.10)**[19](#_ENREF_19),[20](#_ENREF_20); **[GRB2](https://doi.org/10.1007/s00432-009-0574-8)**[21](#_ENREF_21" \o "Ding, 2019 #558); [KRAS](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5850913/)[22](#_ENREF_22" \o "Porru, 2018 #97) |
| Endometrial cancer | [EGF](https://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-9-166)[23](#_ENREF_23" \o "Nishimura, 2015 #560); [EGFR](https://molecular-cancer.biomedcentral.com/articles/10.1186/1476-4598-9-166)[23](#_ENREF_23),[24](#_ENREF_24) |
| Gastric cancer | LRP6[25](#_ENREF_25" \o "Zhang, 2017 #140); [LRP5](https://dx.doi.org/10.3978%2Fj.issn.1000-9604.2014.08.22)[26](#_ENREF_26); WNT7A[27](#_ENREF_27) |
| Glioma | [CALM1](https://doi.org/10.1109/HIBIT.2013.6661681)[28](#_ENREF_28) |
| Hepatocellular carcinoma | [LRP6](https://doi.org/10.1186/s12967-014-0259-1)[30](#_ENREF_30),[31](#_ENREF_31), [WNT3A](https://www.spandidos-publications.com/10.3892/ijo.2017.4112)[29](#_ENREF_29) |
| Melanoma | FGF2[36](#_ENREF_36), FGF1[35](#_ENREF_35),[36](#_ENREF_36), [HGF](https://www.nature.com/articles/modpathol2013226)[32-34](#_ENREF_32) |
| Non-small-cell lung cancer | **ALK**[37](#_ENREF_37),[38](#_ENREF_38); EML4[39](#_ENREF_39), KRAS[40-42](#_ENREF_40" \o "Román, 2018 #576) |
| Pancreatic cancer | [**KRAS**](http://doi.org/10.1158/1535-7163.MCT-11-0269)[43](#_ENREF_43),[44](#_ENREF_44); [AKT2](https://doi.org/10.1152/ajprenal.00357.2012)[45](#_ENREF_45); AKT1[46](#_ENREF_46) |
| Prostate cancer | **IGF-1**[47-49](#_ENREF_47) |
| Renal cell carcinoma | [HGF](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3081175/)[50](#_ENREF_50); [**MET**](https://dx.doi.org/10.1200%2FJCO.2012.43.3383)[51](#_ENREF_51),[52](#_ENREF_52) |
| Small cell lung cancer | ITGB1[53](#_ENREF_53); COL4A1[54](#_ENREF_54) |
| Thyroid cancer | [NTRK1](https://doi.org/10.1016/j.mce.2009.10.009)[55-57](#_ENREF_55" \o "Greco, 2010 #101); [TPM3](https://www.nature.com/articles/6690920)[56](#_ENREF_56) |

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| **Table S3.** Comparison between Our top 1 prediction and four previous network-based approaches. | | |
| **Input**: | | |
| **List names** | **Number of elements** | **Number of unique elements** |
| Our top1 prediction | 15 | 15 |
| Liu's prediction | 27 | 27 |
| Emig's prediction | 17 | 17 |
| Li's prediction | 16 | 16 |
| Wang's prediction | 25 | 25 |
| **Overall number of unique elements** | | **93** |
| **Output:** | | |
| **Name** | **Total** | **Elements** |
| Liu's prediction Our top1 prediction | 3 | HGF FGF2 ITGB1 |
| Emig's prediction Our top1 prediction | 1 | EGFR |
| Li's prediction Our top1 prediction | 1 | GRB2 |
| Liu's prediction Wang's prediction | 2 | CDK1 PLK1 |
| Our top1 prediction | 10 | KRAS SUFU NTRK1 RASSF1 EGF LRP6 ALK CRK IGF-1 CALM1 |
| Liu's prediction | 22 | LYN YES1 BID IGF1 XIAP APAF1 IL6 PTGS2 TH PRKAB1 TNF HDAC1 NFKB1 WEE1 CD4 PRKCZ CDK2 CDC42 CDK5 PPARA CASP3 E2F1 |
| Wang's prediction | 23 | CHKA BUB1 MTOR PDGFRA PRKCSH CHEK2 CDK16 MARK2 STK17B NEK2 CSNK2B RAF1 CDC7 AURKA AK2 CERK BRD2 STK38 PLK4 SRPK1 UCK2 TTK PKC |
| Emig's prediction | 16 | c-Fos NF-kB p50/p65 AP-1 STAT3 GCR-alpha HIF1A RelA (p65 NF-kB subunit) c-Jun STAT5 STAT5B p53 c-Src STAT5A CDK1 (p34) NF-kB JAK1 |
| Li's prediction | 15 | TRAF2 NOTCH2 NL N2N MTUS2 ASH KRT40 LAPSER1 SIRT1 KA36 GOLGA2 NCK1 KRT31 KIAA1813 LZTS2 NCK |

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