Supplementary Information for: Identifying the optimal anticancer targets from the landscape of a cancer-immunity interaction network

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Parameter setting for ordinary differential equations

In this work, we set the parameter values in the models based on the following:

1, We chose parameter values according to some previous works on gene regulatory networks [1–3]. For example, the Hill coefficient reflects the degree of the nonlinearity. In this work we chose Hill coefficient $n = 4$ to represent high nonlinearity of cell-cell interactions following some previous works [4].

2, To reduce the complexity of the model, we set most of the parameters uniformly, since so far for cancer-immunity networks there is no such information about the regulatory strength among relevant cell types. For example, we set the same degradation or apoptosis rate for different cell types [4], and we set the same basal synthesis rate for different cell types.

3, We set parameter values that can satisfy certain biological constrains. For example, the apoptosis rate for each cell type is usually a few days [5,6], and the cell density is typically at the order of thousands cells per μL [7].

4, We performed the sensitivity analysis to the parameters, which supports the robustness of current parameter regions for our model.

5, Most of the parameters in the current model have not been determined by experiments. In this work we focus on the dynamics implications of the regulatory structure of the cancer-immune networks, i.e. the topology of the networks. We believe that the topology of the network governs the operating principles of the networks, as suggested by previous work [8, 9]. It is also possible to interrogate the robustness of the topology by random perturbations to the parameters, as suggested by some recent work [8].

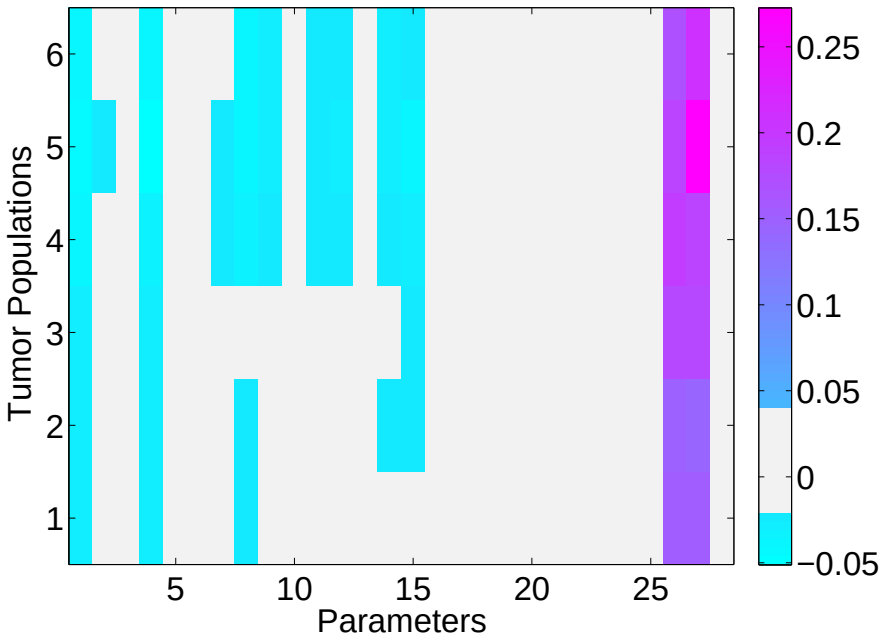

Figure S1. Predictions for anticancer targets based on the methods of optimizing transition actions. X axis shows 28 parameters (regulatory strength among different cell types, 17 activation parameters and 11 inhibition parameters, see Table S3 for the meaning of each parameter), and y axis shows the 6 different parameter sets, reflecting heterogeneity of tumor populations. The color indicates the influence of interventions on each target (links), with purple representing the increase of targets, and cyan representing the decrease of targets.

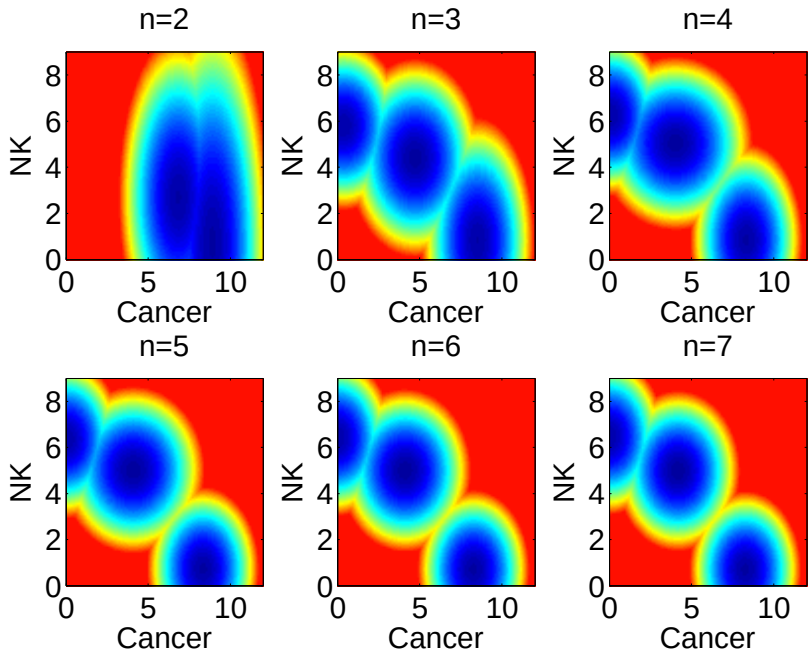

Figure S2. The landscape comparisons of different Hill coefficient n for cancer-immunity network. When Hill coefficient $n >= 3$, the landscape all show tristable states (cancer state, immune state and Hybrid state). Here, for $n = 5, 6, 7$, all other parameters are set as the default values (same as n=4). For $n = 3$, the activation constant a is set to 0.4 while keeping other parameters as default, and for $n = 2$, the activation constant a is set to 0.6 while keeping other parameters as default.

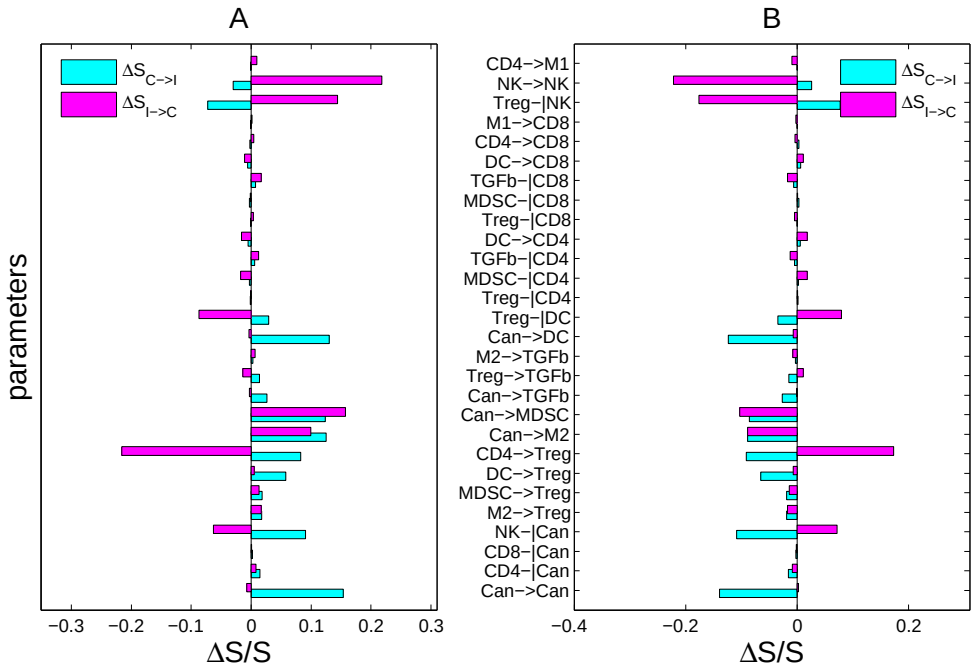

Figure S3. Sensitivity analysis for the 28 key parameters (regulatory strengths among different cell types, including 17 activation constant and 11 inhibition constant) on the transition action ($S_{C->I}$ and $S_{I->C}$) at Hill coefficient n=5. Y-axis represents the 28 parameters. X-axis represents the percentage of transition action (S) changed relative to S without parameter changes. Here, $S_{C->I}$ represents the transition action from attractor C to attractor I (cyan bars), and $S_{I->C}$ represents the transition action from attractor I to attractor C (magenta bars). M1 represents M1TAM and M2 represents M2TAM. (A) Each parameter is increased by 15%, individually. (B) Each parameter is decreased by 15%, individually.

Table S1. Interaction matrix M. The element $M(j,i)$ (the jth row and the ith column of the matrix M) represents the interaction type from node j to node i. 1 represents activation, -1 represents inhibition, and 0 represents no interaction. Can: Cancer cells; Treg: regulatory T cells; M1: M1TAM; M2: M2TAM; MDSC: Myeloid Derived Suppressor Cells; DC: dendritic cells; CD4: CD4+ Tcells; CD8: CD8+ Tcells; NK: natural killer cells.

Cell types	Can	Treg	M2	MDSC	TGFβ	DC	CD4	CD8	NK	M1
	1	2	3	4	5	6	7	8	9	10
1	1	0	1	1	1	1	0	0	0	0
2	0	0	0	0	1	-1	-1	-1	-1	0
3	0	1	0	0	1	0	0	0	0	0
4	0	1	0	0	0	0	-1	-1	0	0
5	0	0	0	0	0	0	-1	-1	0	0
6	0	1	0	0	0	0	1	1	0	0
7	-1	1	0	0	0	0	0	1	0	1
8	-1	0	0	0	0	0	0	0	0	0
9	-1	0	0	0	0	0	0	0	1	0
10	0	0	0	0	0	0	0	1	0	0

Table S2. Parameter values for Cancer-Immunity model with tristability

Symbol	Value	Unit	Description
k	0.2	Day^{-1}	apoptosis rate of cells
a	0.36	10^3 cells/($\mu L\cdot$ Day)	activation rate
b	0.8	10^3 cells/($\mu L\cdot$ Day)	inhibition rate
ρ_C, ρ_N	0.85	10^3 cells/($\mu L\cdot$ Day)	proliferation rate of cancer and NK cells
n	4		Hill coefficient
S	2.5		Threshold for Hill function

Table S3. Target ID (link ID) and corresponding interaction links (17 activation regulations and 11 inhibition regulations), as well as related references. Here, $->$ represent activation, and $-|$ represent inhibition.

Target ID	Interaction	References
1	Can $->$ Can	[10]
2	CD4 $-|$ Can	[11]
3	CD8 $-|$ Can	[12]
4	NK $-|$ Can	[12, 13]
5	M2TAM $->$ Treg	[14]
6	MDSC $->$ Treg	[14]
7	DC $->$ Treg	[15]
8	CD4$->$Treg	[16]
9	Can$->$M2TAM	[14]
10	Can$->$MDSC	[14]
11	Can$->$TGFb	[17]
12	Treg$->$TGFb	[18, 19]
13	M2TAM$->$TGFb	[14, 20]
14	Can$->$DC	[21]
15	Treg$-|$DC	[19]
16	Treg$-|$CD4	[19]
17	MDSC $-|$CD4	[14]
18	TGFb $-|$CD4	[19]
19	DC$->$CD4	[15]
20	Treg $-|$CD8	[19]
21	MDSC $-|$CD8	[14]
22	TGFb $-|$CD8	[19]
23	DC $->$CD8	[15]
24	CD4 $->$CD8	[19]
25	M1TAM $->$CD8	[14, 20]
26	Treg $-|$NK	[19]
27	NK $->$ NK	[22]
28	CD4 $->$ M1TAM	[23]

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