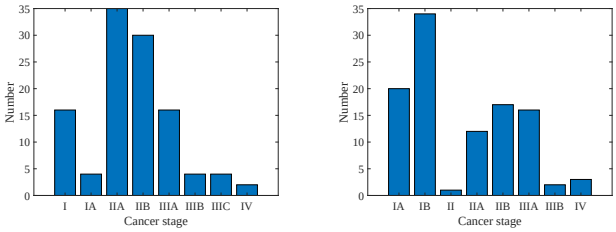
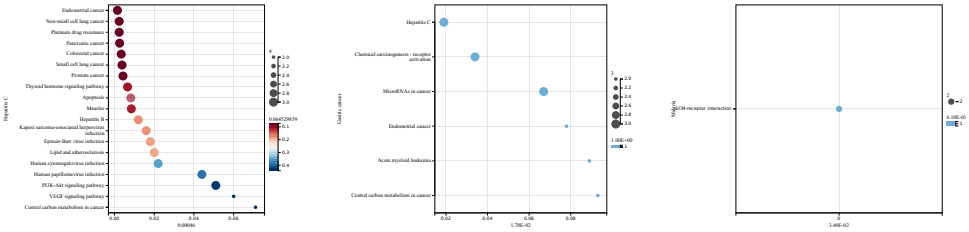
Supplementary File for "Constrained Multi-objective Optimization-Based Temporal Network Observability for Critical Biomarker Identification of Individual Patients"

S-I. Supplementary Results

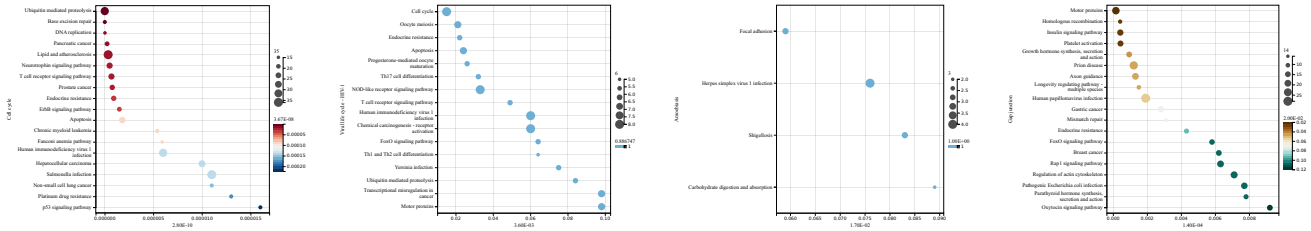


(a) BRCA (b) LUND

Fig. S-1. Number of patients in each stages for BRCA and LUND.

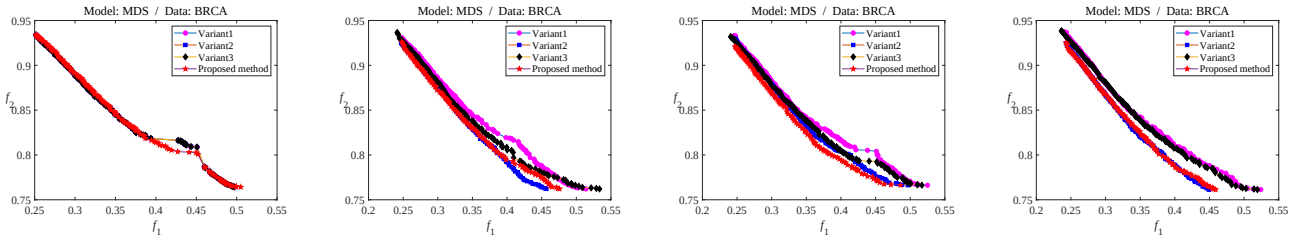


(a) MMPDNB on BRCA data (b) MMPDENB-RBM on BRCA data (c) MMPDENB-RBM on LUND data



(d) ELCEA on BRCA data under MDS model (e) ELCEA on BRCA data under NCUA model (f) ELCEA on LUND data under MDS model (g) ELCEA on LUND data under NCUA model

Fig. S-2. Pathway enrichment analysis. Since the result of MMPDNB on LUND data is not shown because it only finds one pathway.



(a) Stage I (b) Stage IA (c) Stage IIA (d) Stage IIB

(e) Stage IIIA (f) Stage IIIB (g) Stage IIIC (h) Stage IV

Fig. S-3. Populations of algorithms on the first patient data for each stage of BRCA data under MDS framework.

TABLE S-1
VERIFICATION RESULTS OF PROPOSED STRATEGIES REGARDING F-SCORE AND HV

Model+Data	Stages	F-score				HV			
		Variant1	Variant2	Variant3	ELCEA	Variant1	Variant2	Variant3	ELCEA
MDS+LUND	IA	0.5451 =	0.5439 =	0.5426 =	0.5419	0.2009 =	0.2009 =	0.2007 =	0.2004
	IB	0.5297 -	0.5911 =	0.4970 -	0.5930	0.1998 -	0.2076 =	0.1984 -	0.2077
	II	0.5475 -	0.5998 -	0.4821 -	0.6046	0.2049 -	0.2119 +	0.1976 -	0.2115
	IIA	0.5499 -	0.5800 -	0.4799 -	0.6064	0.2011 -	0.2065 -	0.1934 -	0.2095
	IIB	0.5398 -	0.5939 -	0.4858 -	0.6000	0.1999 -	0.2068 =	0.1939 -	0.2082
	IIIA	0.5335 -	0.5962 -	0.4898 -	0.6011	0.2006 -	0.2086 =	0.1957 -	0.2092
	IIIB	0.5099 -	0.5902 -	0.4781 -	0.5959	0.1968 -	0.2057 -	0.1917 -	0.2066
	IV	0.5424 -	0.5876 -	0.4882 -	0.6006	0.2013 -	0.2075 -	0.1948 -	0.2092
MDS+BRCA	I	0.5279 =	0.5279 =	0.5279 =	0.5287	0.2166 =	0.2166 =	0.2166 =	0.2165
	IA	0.5261 -	0.5680 =	0.5368 =	0.5601	0.2169 -	0.2212 =	0.2191 =	0.2207
	IIA	0.5257 -	0.5609 -	0.5328 -	0.5730	0.2167 -	0.2205 -	0.2192 -	0.2220
	IIB	0.5245 -	0.5741 =	0.5364 -	0.5765	0.2170 -	0.2219 =	0.2197 -	0.2225
	IIIA	0.5233 -	0.5756 =	0.5329 -	0.5812	0.2170 -	0.2226 =	0.2196 -	0.2231
	IIIB	0.5200 -	0.5694 =	0.5437 =	0.5769	0.2175 =	0.2220 =	0.2201 =	0.2229
	IIIC	0.5260 -	0.5555 -	0.5343 -	0.5866	0.2177 -	0.2205 =	0.2200 -	0.2239
	IV	0.5264 -	0.5663 -	0.5362 -	0.5892	0.2169 -	0.2219 -	0.2200 -	0.2244
NCUA+LUND	IA	0.5193 =	0.5181 =	0.5193 =	0.5191	0.1822 =	0.1819 =	0.1823 =	0.1821
	IB	0.5184 -	0.5350 =	0.5353 =	0.5367	0.1819 +	0.1815 +	0.1809 =	0.1800
	II	0.5187 -	0.5219 -	0.5302 +	0.5234	0.1849 +	0.1812 +	0.1809 +	0.1797
	IIA	0.5240 +	0.4906 +	0.4866 =	0.4775	0.1811 +	0.1747 =	0.1729 =	0.1751
	IIB	0.5143 -	0.5182 -	0.5274 =	0.5349	0.1820 +	0.1774 =	0.1759 -	0.1785
	IIIA	0.5162 -	0.5275 =	0.5049 -	0.5234	0.1805 +	0.1781 =	0.1778 =	0.1779
	IIIB	0.5168 +	0.5139 -	0.4923 -	0.5145	0.1771 +	0.1735 +	0.1720 -	0.1725
	IV	0.5193 +	0.5313 +	0.5231 +	0.5117	0.1806 +	0.1793 -	0.1793 -	0.1802
NCUA+BRCA	I	0.5220 =	0.5220 =	0.5237 =	0.5234	0.2074 =	0.2074 =	0.2076 =	0.2076
	IA	0.5210 -	0.5685 =	0.5765 =	0.5624	0.2077 =	0.2102 =	0.2103 =	0.2102
	IIA	0.5200 -	0.5709 =	0.5690 =	0.5708	0.2071 -	0.2116 =	0.2113 =	0.2116
	IIB	0.5226 -	0.5622 =	0.5573 -	0.5618	0.2076 -	0.2104 =	0.2098 =	0.2100
	IIIA	0.5213 -	0.5578 =	0.5673 +	0.5613	0.2077 -	0.2096 =	0.2100 =	0.2099
	IIIB	0.5231 -	0.5689 =	0.5594 =	0.5620	0.2082 =	0.2106 =	0.2106 =	0.2111
	IIIC	0.5225 -	0.5713 =	0.5744 =	0.5708	0.2078 -	0.2112 =	0.2101 =	0.2120
	IV	0.5228 -	0.5450 -	0.5490 -	0.5613	0.2068 -	0.2086 -	0.2087 -	0.2094
+/-/=		3/25/4	2/13/17	3/16/13		7/18/7	4/7/19	1/16/15	

S-II. SUPPLEMENTARY CONTENTS

A. *Computational complexity*

In the proposed ELCEA, the main complexities come from the basic search algorithm and the operators related to experience learning. For the basic search algorithm, the complexities of mating selection, offspring generation, and environmental selection are $O(NP)$, $O(NP \cdot D)$, and $O(M \cdot NP^2)$, respectively. For the operators related to experience learning, the worst complexities of population initialization and archive updating are $O(NP \cdot D)$ and $O(D^2) + O(D) + O(D) = O(D^2)$, respectively. In addition, the complexity of the random population initialization method in the first stage is $O(NP \cdot D)$. Therefore, the worst complexities for the first stage and the remaining stages are $3 \cdot O(NP \cdot D) + 3 \cdot O(NP) + 3 \cdot O(NP \cdot D) + 3 \cdot O(M \cdot NP^2)$ and $O(NP \cdot D) + 2 \cdot O(NP \cdot D) + 3 \cdot O(NP) + 3 \cdot O(NP \cdot D) + 3 \cdot O(M \cdot NP^2) + O(D^2)$, respectively. Because D is significantly than NP, the final worst complexity of ELCEA is $O(D^2)$.

B. *Compared to network-based biomarker identification methods*

Two network-based biomarker identification methods (MDS and NCUA) are selected as compared algorithms to further verify the effectiveness of ELCEA. The warning score curves of MDS and NCUA on two datasets are plotted in Fig. S-4.

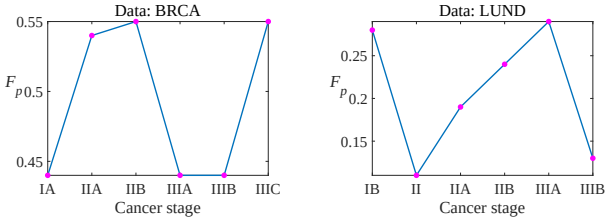
TABLE S-2
AVERAGE MACHINE TIME OF COMPARED ALGORITHMS ON ONE PATIENT

Algorithms	ELCEA	CCMO	IMTCMO	cDPEA	ICMA	LSCV_MCEA	MMPDENB-RBM	MMPDNB
Average machine time (s)	75.3908	62.788	97.395	74.99	66.274	55.844	131.6239	74.8522

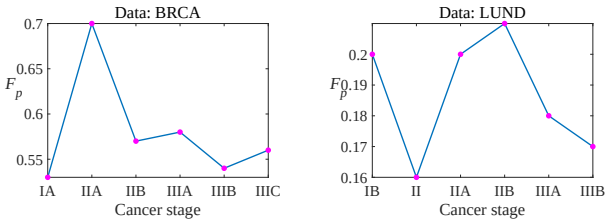
TABLE S-3
MEAN PRECISION AND RECALL VALUES OF ELCEA ON TWO DATASETS UNDER TWO FRAMEWORKS

Dataset	Model	Precision	Recall
BRCA	MDS	0.3875	0.3365
	NCUA	0.4419	0.3226
LUND	MDS	0.5683	0.3763
	NCUA	0.5908	0.3163

Because MDS and NCUA are constrained single-objective-based models, they identify different biomarkers and detect different critical states with ELCEA, MMPDNB, and MMPDENB-RBM. However, due to that the true critical states are unknown, it is difficult to judge the performance of ELCEA and compared algorithms, and we can observe that they have complementary abilities in identifying biomarkers. Furthermore, we calculate the F-score results of MDS and NCUA. The F-score values of MDS on BRCA and LUND range from 0.4 to 0.55 and 0.11 to 0.29, respectively. The F-score values of NCUA on BRCA and LUND range from 0.53 to 0.7 and 0.16 to 0.22, respectively. While, F-score values of ELCEA on BRCA dataset under MDS and NCUA framework range from 0.53 to 0.58 and 0.52 to 0.57, respectively. F-score values of ELCEA on LUND dataset under MDS and NCUA framework range from 0.54 to 0.61 and 0.50 to 0.55, respectively. Therefore, it can be observed that ELCEA is better than MDS and NCUA methods on F-score indicator.



(a) MDS



(b) NCUA

Fig. S-4. Compared F_P results of ELCEA, MDS, and NCUA on BRCA and LUND datasets.

C. Compared results regarding machine time

The average machine time of compared algorithms on one patient is provided in Table S-2. Among all algorithms, MMPDENB-RBM and IMTCMO consume significantly more machine time than other algorithms because MMPDENB-RBM contains one complex machine learning technique (restricted Boltzmann machine) and IMTCMO includes neighbor-based mating selection operator. For the remaining algorithms, LSCV_MCEA consumes the least amount of machine time, and the other algorithms consume similar machine time.

D. Precision and recall values of ELCEA and compared algorithms

To further analyze F-score results, we calculate the mean precision and recall values of ELCEA on two datasets, and the results are provided in Table S-3. It can be seen that for most cases, precision values are larger than recall values, which shows that most prior nodes are significant to satisfy constraints. In addition, we plot the precision and recall values of different individuals in the population on the first BRCA patient network. First, we sort the population based on their second objective

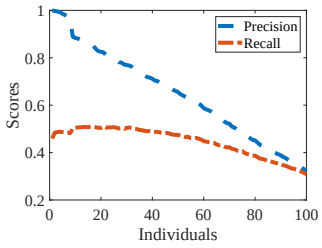


Fig. S-5. Precision and recall values of sorted individual on the first BRCA patient network.

values in ascending order. In this case, the smaller the index of individuals, the more prior nodes it contains. Then, the precision and recall values of each individual is plotted in Fig. S-5. It can be seen that the more prior nodes the individual contains, the larger the precision and recall values. Specially, when the number of prior nodes is small, it is difficult for the algorithm to use these prior nodes to satisfy constraints. Therefore, the precision and recall values become small.

In addition, we compare the precision and recall values between ELCEA and five compared CMOEAs, and results are provided in Figs. S-6 and S-7 respectively. First, for each algorithm, its precision values are larger than its recall values, which indicates that the algorithm selects a large number of prior nodes to satisfy constraints. Second, for precision results, IMCA and IMTCMO get relatively better results than other compared algorithms, while they are significantly worse than ELCEA. For recall results, ELCEA, ICMA, and LSCV_MCEA get relatively better results than other compared algorithms. Therefore, ELCEA is better than other compared algorithms regarding precision and recall indicators.

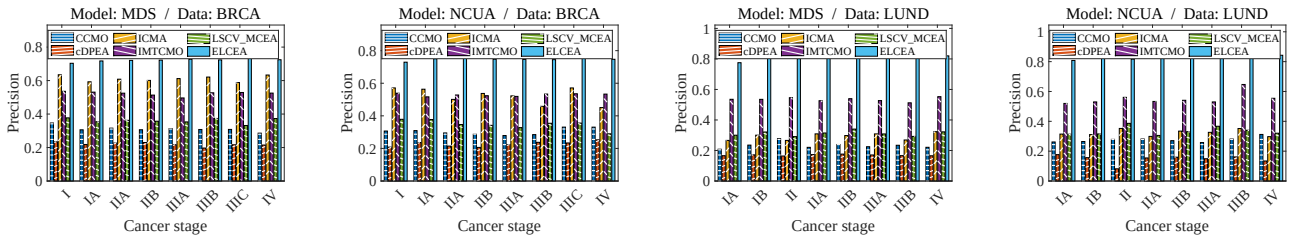


Fig. S-6. Precision results of the proposed algorithm and CMOEAs.

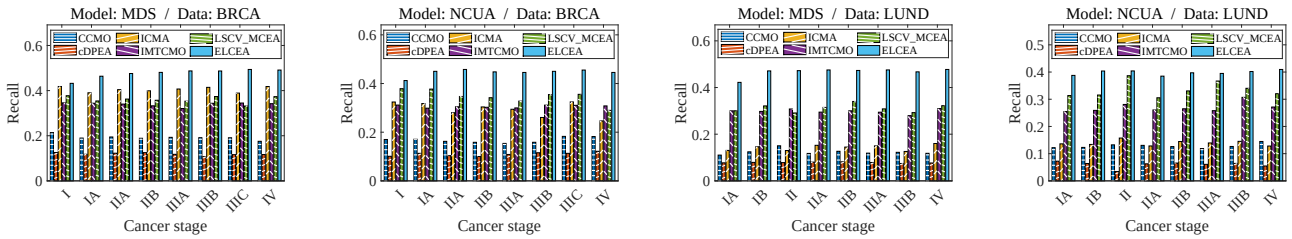


Fig. S-7. Recall results of the proposed algorithm and CMOEAs.