**Supplementary Files**

***for***

***Network Activity Evaluation Reveals Significant Gene Regulatory Architectures during SARS-CoV-2 Viral Infection from Dynamic scRNA-seq Data***

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## *S1. FPCA fits time-course gene expression data*

Functional Principal Component Analysis (FPCA is a flexible non-parametric method for analyzing continuous trajectory data [1]. It models the data as a time process, and its characteristic basis functions reflect the main change patterns underlying the data. Recently, FPCA has been utilized to identify time-course gene expression profile trajectories for subsequent analysis. Moreover, the smooth continuous curve derived by FPCA can easily obtain the derivative value at any time, which facilitates downstream ODE system modeling [2, 3]. Specifically, FPCA approximates the gene expression curve with the following equation:

, (1)

where  is the mean expression level over time,  is an orthonormal eigenfunction,  is corresponding coefficient, and  represents unexplained temporal variation.

Taking the simulation dataset D1 in the main text as an example, FPCA analysis is conducted on cell type I. We plotted the fitted curve of expression values for one gene, as shown in Fig. 1, where we uniformly sampled eight time points along the curve (marked by red dots). Thus, the discrete time points of gene expression values of individual genes have been fitted into a smoothed continuous function curve. For simplicity, FPCA values for all genes are computed by the same time intervals. The derivation values of each gene expression at each time point (left hand side of Equation (1) in the main text) can be obtained easily after continuous fitting. Then the differential equations in ODE system can be transformed as a linear system with algebraic equations.

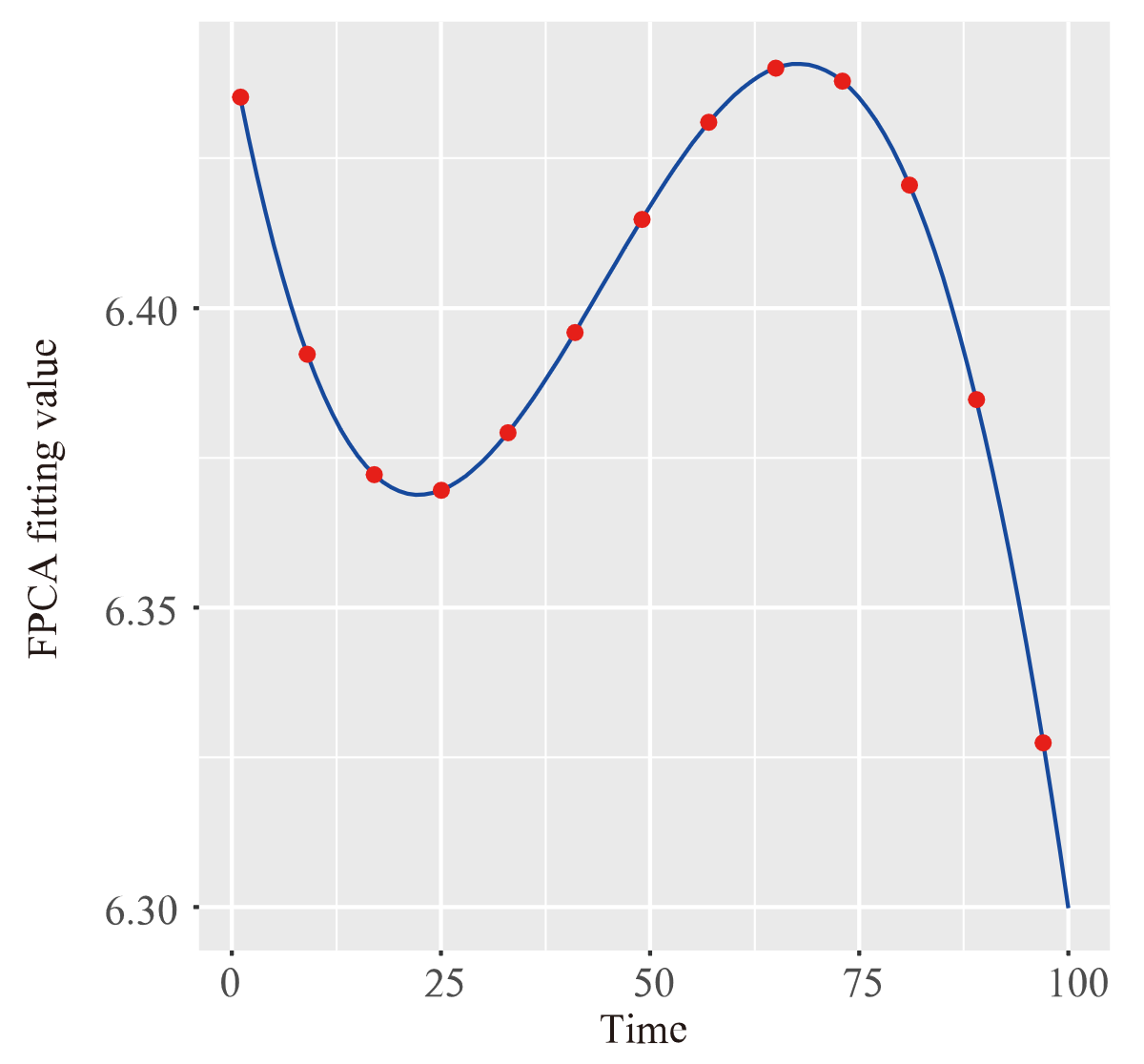


Fig. S1 An example of the fitted expression curves by FPCA on the D1 dataset. Fitted gene expression values are plotted as a continuous curve and the sampled time points are shown in red.

## *S2. Evaluation results of gold network activity in simulaion datasets*

We used the SERGIO tool to generate a total of 12 simulation datasets D1...D12. For comparison, we ran the network activity evaluation tasks using scNAE, topologyGSA [4], SPIA [5], netGO[6] and NetGSA[7], respectively. Tables SI, SII, and SIII list the evaluation results on the simulation data.

TABLE SII

Experimental results in the D7-D9 datasets.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Datasets  (Nodes, Cell Type) | scNAE with different parameters *p* | | | | | | topolo  gyGSA | SPIA | netGO | NetGSA |
| 0 | 1/3 | 1/2 | 2/3 | 1 | 2 |
| D7(30, I) | 0.011 | 0.013 | 0.011 | 0.013 | 0.004 | 0.008 | **0.001** | 0.991 | 0.072 | 0.412 |
| D7(30, II) | 0.014 | 0.004 | 0.007 | 0.008 | **0.007** | **0.007** | 0.059 | 0.987 | 0.142 | 0.145 |
| D7(30, III) | 0.003 | 0.001 | 0.001 | 0.001 | **0.001** | **0.001** | 0.82 | 0.489 | 0.140 | 0.820 |
| D7(30, IV) | 0.005 | **0.004** | 0.049 | 0.052 | 0.059 | 0.045 | 0.015 | 0.538 | 0.207 | 0.748 |
| D8(50, I) | 0.032 | 0.03 | 0.029 | 0.022 | **0.020** | 0.033 | 0.302 | 0.698 | 0.049 | 0.041 |
| D8(50, II) | 0.012 | 0.023 | 0.027 | 0.022 | **0.012** | 0.025 | 0.048 | 0.565 | 0.234 | 0.063 |
| D8(50, III) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.017 | 0.272 | 0.289 | 0.015 |
| D8(50, IV) | 0.006 | 0.011 | 0.007 | 0.008 | 0.01 | **0.004** | 0.01 | 0.272 | 0.332 | 0.009 |
| D9(100, I) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.039 | 0.992 | 0.093 | 0.410 |
| D9(100, II) | 0.369 | 0.384 | 0.344 | 0.312 | 0.335 | 0.399 | **0.241** | 0.998 | 0.108 | 0.131 |
| D9(100, III) | **0.001** | 0.002 | 0.002 | **0.001** | **0.001** | **0.001** | 0.081 | 0.321 | 0.167 | 0.652 |
| D9(100, IV) | 0.011 | 0.017 | 0.013 | **0.009** | 0.013 | 0.013 | 1.000 | 0.485 | 0.288 | 0.020 |

TABLE SI

Experimental results in the D1-D6 datasets.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Datasets  (Nodes, Cell Type) | scNAE with different parameters *p* | | | | | | topolo  gyGSA | SPIA | netGO | NetGSA |
| 0 | 1/3 | 1/2 | 2/3 | 1 | 2 |
| D1(30, I) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.599 | 0.559 | 0.061 | 0.704 |
| D1(30, II) | 0.007 | 0.008 | 0.008 | 0.005 | 0.015 | 0.008 | 0.005 | 0.272 | 0.490 | **0.005** |
| D2(50, I) | **0.001** | **0.001** | **0.001** | **0.001** | 0.006 | **0.001** | 0.008 | 0.065 | 0.019 | 0.037 |
| D2(50, II) | 0.011 | 0.017 | 0.013 | 0.018 | 0.033 | 0.021 | 0.009 | **0.001** | 0.127 | 0.008 |
| D3(100, I) | **0.001** | 0.001 | **0.001** | **0.001** | 0.015 | **0.001** | 1.000 | 0.272 | 0.218 | 0.003 |
| D3(100, II) | 0.003 | 0.002 | **0.001** | **0.001** | 0.001 | 0.002 | 0.504 | 0.047 | 0.349 | 0.645 |
| D4(30, I) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.136 | 0.786 | 0.089 | 0.349 |
| D4(30, II) | **0.001** | **0.001** | **0.001** | **0.001** | 0.005 | **0.001** | 0.011 | 0.845 | 0.107 | 0.077 |
| D4(30, III) | **0.002** | **0.002** | 0.002 | 0.005 | 0.003 | 0.003 | 0.009 | 0.562 | 0.030 | 0.631 |
| D5(50, I) | 0.002 | 0.002 | **0.001** | 0.002 | **0.001** | 0.002 | 0.006 | 0.438 | 0.053 | 0.121 |
| D5(50, II) | 0.044 | 0.054 | 0.055 | 0.052 | 0.064 | **0.042** | 0.068 | 0.330 | 0.164 | 0.926 |
| D5(50, III) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.043 | 0.0738 | 0.069 | 0.026 |
| D6(100, I) | **0.001** | **0.001** | **0.001** | 0.002 | **0.001** | **0.001** | 0.019 | 0.890 | 0.293 | 0.347 |
| D6(100, II) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.012 | 0.565 | 0.283 | 0.003 |
| D6(100, III) | 0.029 | 0.042 | 0.048 | 0.046 | 0.041 | 0.029 | 0.039 | 0.610 | 0.524 | **0.002** |

TABLE III

Experimental results in the D10-D12 datasets.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Datasets  (Nodes, Cell Type) | scNAE with different parameters *p* | | | | | | topolo  gyGSA | SPIA | netGO | NetGSA |
| 0 | 1/3 | 1/2 | 2/3 | 1 | 2 |
| D10(30, I) | 0.106 | 0.145 | 0.125 | 0.123 | 0.120 | 0.136 | **0.045** | 0.963 | 0.085 | 0.512 |
| D10(30, II) | 0.013 | 0.066 | 0.028 | 0.017 | **0.006** | 0.081 | 0.714 | 0.811 | 0.127 | 0.505 |
| D10(30, III) | 0.012 | **0.001** | 0.006 | 0.007 | 0.015 | **0.001** | 0.007 | 0.927 | 0.216 | 0.095 |
| D10(30, IV) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.005 | 0.594 | 0.207 | 0.945 |
| D10(30, V) | 0.006 | **0.001** | 0.006 | 0.005 | 0.008 | **0.001** | 0.016 | 0.908 | 0.359 | 0.001 |
| D11(50, I) | 0.468 | 0.408 | 0.402 | 0.413 | 0.156 | 0.123 | **0.030** | 0.995 | 0.043 | 0.129 |
| D11(50, II) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.089 | 0.993 | 0.243 | 0.020 |
| D11(50, III) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.007 | 0.919 | 0.299 | 0.160 |
| D11(50, IV) | 0.004 | 0.002 | **0.001** | 0.004 | 0.005 | 0.004 | 0.044 | 0.562 | 0.310 | 0.018 |
| D11(50, V) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 0.032 | 0.999 | 0.300 | 0.006 |
| D12(100, I) | 0.010 | **0.007** | 0.009 | 0.013 | 0.011 | 0.010 | 1.000 | 0.928 | 0.063 | 0.241 |
| D12(100, II) | 0.372 | 0.412 | 0.353 | 0.322 | 0.414 | 0.388 | **0.018** | 0.984 | 0.164 | 0.097 |
| D12(100, III) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 1.000 | 0.687 | 0.130 | **0.001** |
| D12(100, IV) | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | **0.001** | 1.000 | 0.738 | 0.221 | **0.001** |
| D12(100, V) | 0.012 | 0.007 | 0.008 | 0.010 | **0.006** | 0.010 | 0.014 | 0.924 | 0.135 | 0.404 |

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