# Supplementary Information

## Discovery of a kernel for controlling biomolecular regulatory networks

Junil Kim, Sang-Min Park, and Kwang-Hyun Cho*

Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

*Corresponding author, E-mail: ckh@kaist.ac.kr, Phone: +82-42-350-4325, Fax: +82-42-350-4310, Web: http://sbie.kaist.ac.kr/.

# Contents

## III. Supplementary Tables



## IV. Supplementary References

# I. Supplementary Methods

**Parameters of the genetic algorithm (GA)**

For the GA employed in the control kernel identification algorithm (Fig. S8), different values of *N* (the number of chromosomes) and *M* (generations for artificial evolution) were used depending on the network to ensure the convergence of average fitness for each chromosome: *N*=100 and *M*=100 for the *S. cerevisiae* cell cycle network, the *S. pombe* cell cycle network, the GRN underlying mammalian cortical area development, the GRN underlying *A. thaliana* development, the GRN underlying mouse myeloid development, and the mammalian cell cycle network; *N*=1000 and *M*=100 for the CREB signaling network; *N*=100 and *M*=2000 for the human fibroblast signaling network; and *N*=100 and *M*=100 for random networks. Mutation rate 0.01 and crossover rate 0.68 (1) were used.

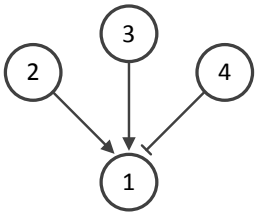
**Boolean network model based on four different types of logical rules for state transition**

We obtained the state transition diagram of each random network by simultaneously updating the Boolean functions based on four different types of logical rules (Rule 1~4). In Rule 1 adopted from Li *et al*. (2), the state of a node in the next time step depends on the present network states as follows:

$$x_i(t+1)=\begin{cases} 1, \sum_j a_{ij}x_j(t)>0 \\ 0, \sum_j a_{ij}x_j(t)<0 \\ x_i(t), \sum_j a_{ij}x_j(t)=0 \end{cases},$$

where $x_i(t)$ denotes the state of node $i$ at time step $t$, $a_{ij}=1$ if node $j$ activates node $i$, $a_{ij}=-1$ if node $j$ inhibits node $i$, and $a_{ij}=0$ if node $j$ does not regulate node $i$. Rule 2 is adopted from Abdi *et al*. (3), where every Boolean logic for activatory link is 'OR' whereas every Boolean logic for inhibitory link is 'AND'. Every Boolean logic is 'AND' in Rule 3 while every Boolean logic is 'OR' in Rule 4.

For instance, let us consider the following toy example network where node 2 and node 3 activate node 1 and node 4 inhibits node 1.




According to Rule 1, the state of node 1 at time step *t+1* is determined by the states of node 1, 2, 3, and 4 at time step *t* as follows:

| $x_1(t)$ | $x_2(t)$ | $x_3(t)$ | $x_4(t)$ | $x_1(t+1)$ |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| 0 | 0 | 0 | 1 | 0 |
| 0 | 0 | 1 | 0 | 1 |
| 0 | 0 | 1 | 1 | 0 |
| 0 | 1 | 0 | 0 | 1 |
| 0 | 1 | 0 | 1 | 0 |
| 0 | 1 | 1 | 0 | 1 |
| 0 | 1 | 1 | 1 | 1 |
| 1 | 0 | 0 | 0 | 1 |
| 1 | 0 | 0 | 1 | 0 |
| 1 | 0 | 1 | 0 | 1 |
| 1 | 0 | 1 | 1 | 1 |
| 1 | 1 | 0 | 0 | 1 |
| 1 | 1 | 0 | 1 | 1 |
| 1 | 1 | 1 | 0 | 1 |
| 1 | 1 | 1 | 1 | 1 |

According to Rule 2, the state of node 1 at time step *t+1* is determined by the states of node 2, 3, and 4 at time step *t* as follows:

| $x_2(t)$ | $x_3(t)$ | $x_4(t)$ | $x_1(t+1)$ |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 |
| 0 | 1 | 0 | 1 |
| 0 | 1 | 1 | 0 |
| 1 | 0 | 0 | 1 |
| 1 | 0 | 1 | 0 |
| 1 | 1 | 0 | 1 |
| 1 | 1 | 1 | 0 |
| 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 |

According to Rule 3, the state of node 1 at time step *t+1* is determined by the states of node 2, 3, and 4 at time step *t* as follows:

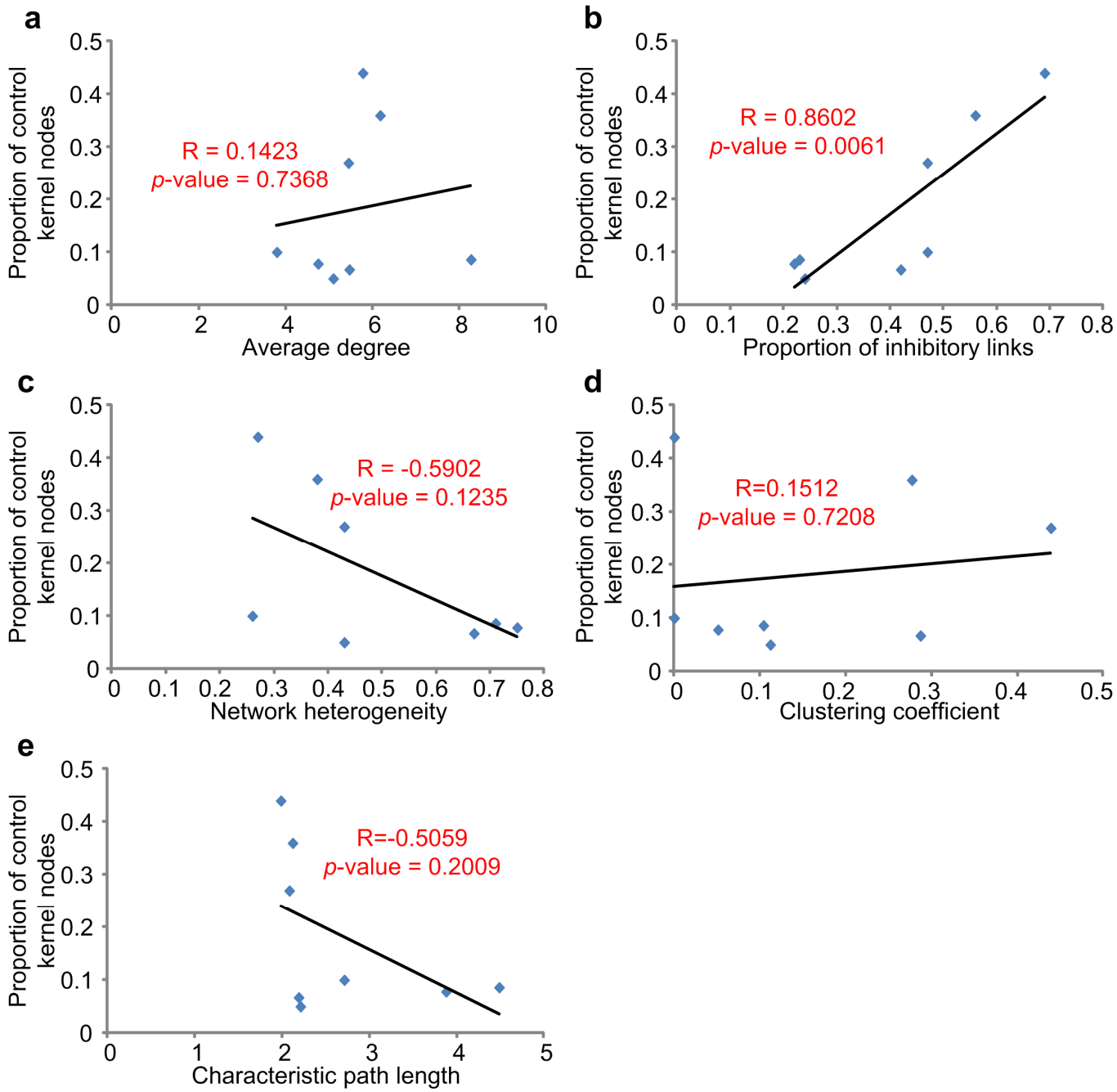
| $x_2(t)$ | $x_3(t)$ | $x_4(t)$ | $x_1(t+1)$ |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 |
| 0 | 1 | 0 | 0 |
| 0 | 1 | 1 | 0 |
| 1 | 0 | 0 | 0 |
| 1 | 0 | 1 | 0 |
| 1 | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| 1 | 1 | 1 | 0 |
| 0 | 0 | 0 | 0 |
| 0 | 0 | 1 | 0 |

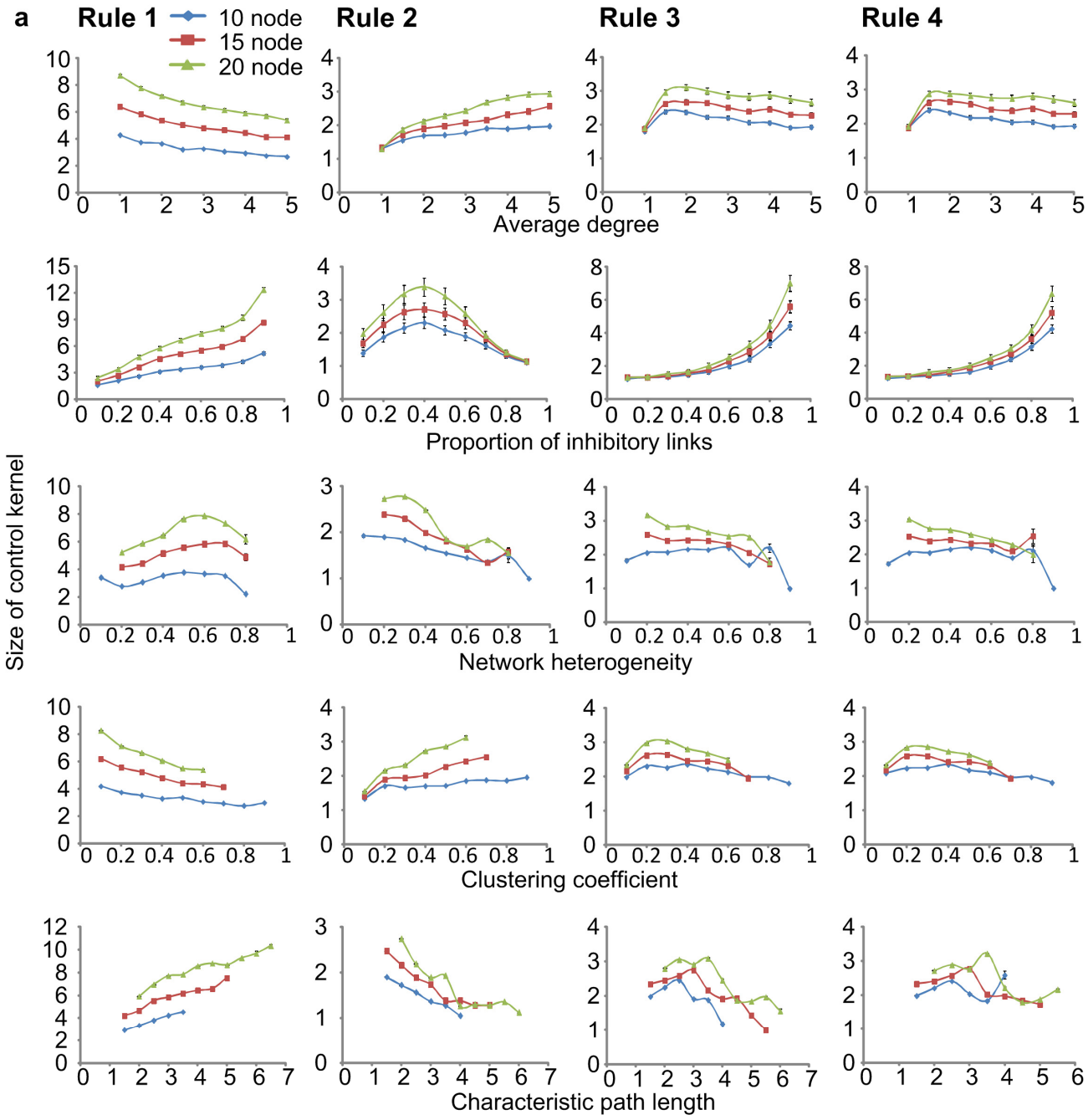
According to Rule 4, the state of node 1 at time step *t+1* is determined by the states of node 2, 3, and 4 at time step *t* as follows:

| $x_2(t)$ | $x_3(t)$ | $x_4(t)$ | $x_1(t+1)$ |
|---|---|---|---|
| 0 | 0 | 0 | 1 |
| 0 | 0 | 1 | 0 |
| 0 | 1 | 0 | 1 |
| 0 | 1 | 1 | 1 |
| 1 | 0 | 0 | 1 |
| 1 | 0 | 1 | 1 |
| 1 | 1 | 0 | 1 |
| 1 | 1 | 1 | 1 |
| 0 | 0 | 0 | 1 |
| 0 | 0 | 1 | 1 |

# II. Supplementary Figures



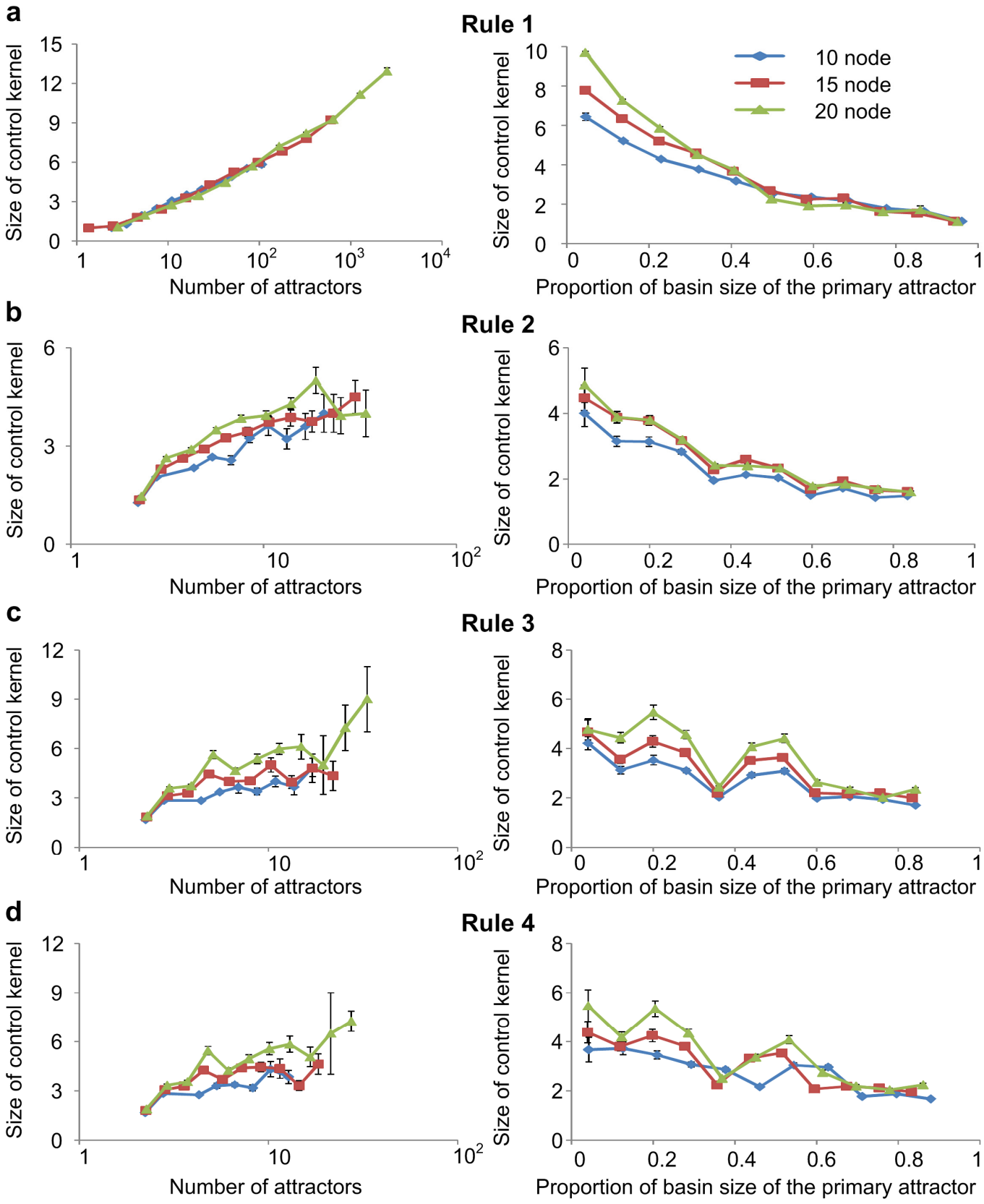

**Supplementary Figure S1**. **Relationship between the size of control kernel and the topological characteristics in the eight bimolecular regulatory networks.** (a) Average degree. (b) Proportion of inhibitory links. (c) Network heterogeneity. (d) Clustering coefficient. (e) Characteristic path length. $R$ denotes Pearson`s correlation coefficient.



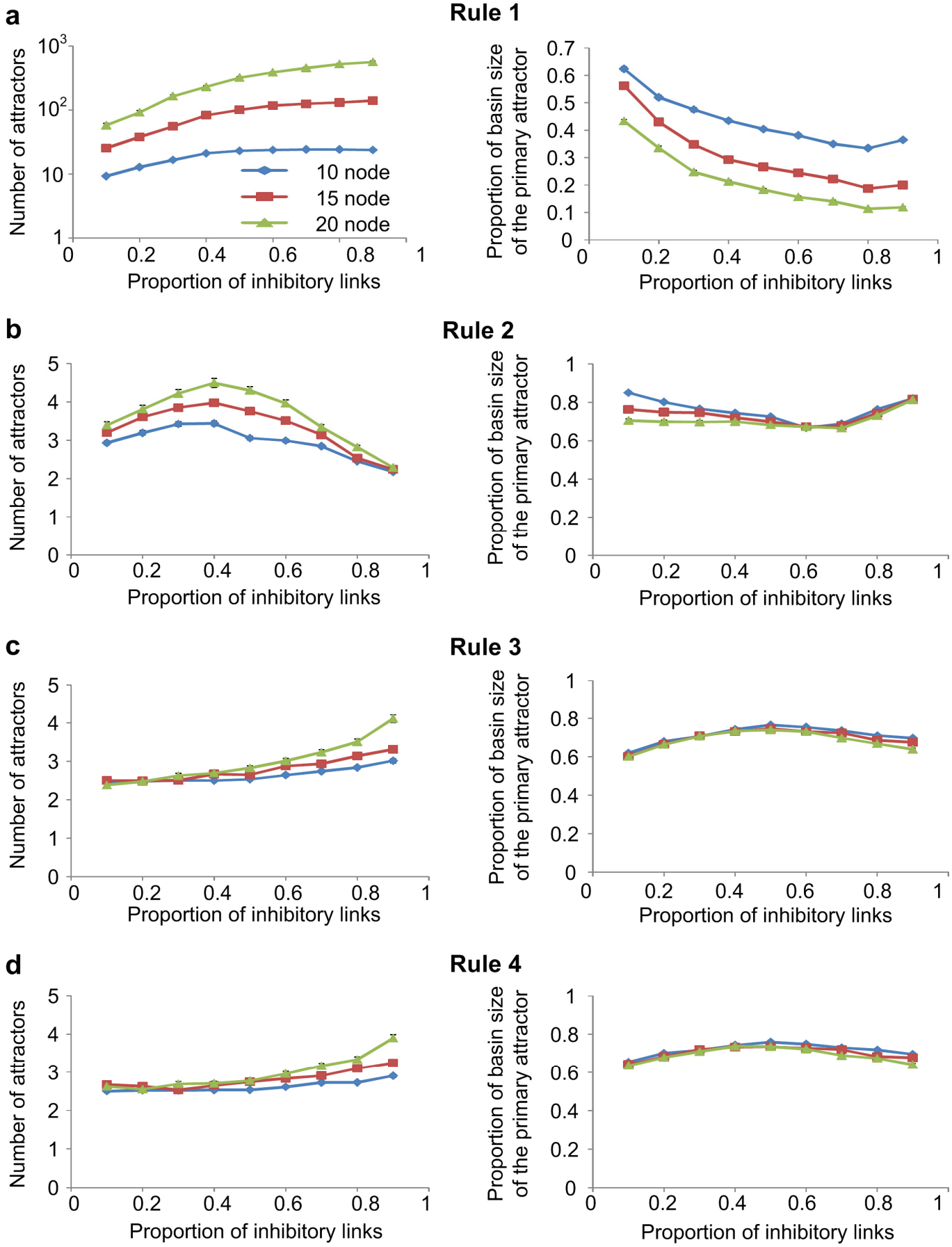

b

| Pearson`s correlation coefficient | Rule 1 | | | Rule 2 | | | Rule 3 | | | Rule 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 node | 15 node | 20 node | 10 node | 15 node | 20 node | 10 node | 15 node | 20 node | 10 node | 15 node | 20 node |
| Average degree | -0.283 | -0.268 | -0.272 | 0.166 | 0.225 | 0.253 | -0.043 | -0.000 | 0.027 | -0.049 | 0.001 | 0.033 |
| Proportion of inhibitory links | **0.613** | **0.733** | **0.783** | -0.158 | -0.191 | -0.224 | **0.563** | **0.554** | **0.557** | **0.520** | **0.503** | **0.514** |
| Network heterogeneity | 0.198 | 0.207 | 0.210 | -0.129 | -0.164 | -0.200 | -0.024 | -0.028 | -0.044 | 0.026 | -0.027 | -0.050 |
| Clustering coefficient | -0.263 | -0.247 | -0.260 | 0.147 | 0.217 | 0.243 | -0.033 | 0.001 | 0.031 | -0.047 | -0.005 | 0.031 |
| Characteristic path length | 0.285 | 0.261 | 0.268 | -0.163 | -0.207 | -0.241 | 0.008 | -0.045 | -0.079 | 0.024 | -0.041 | -0.074 |

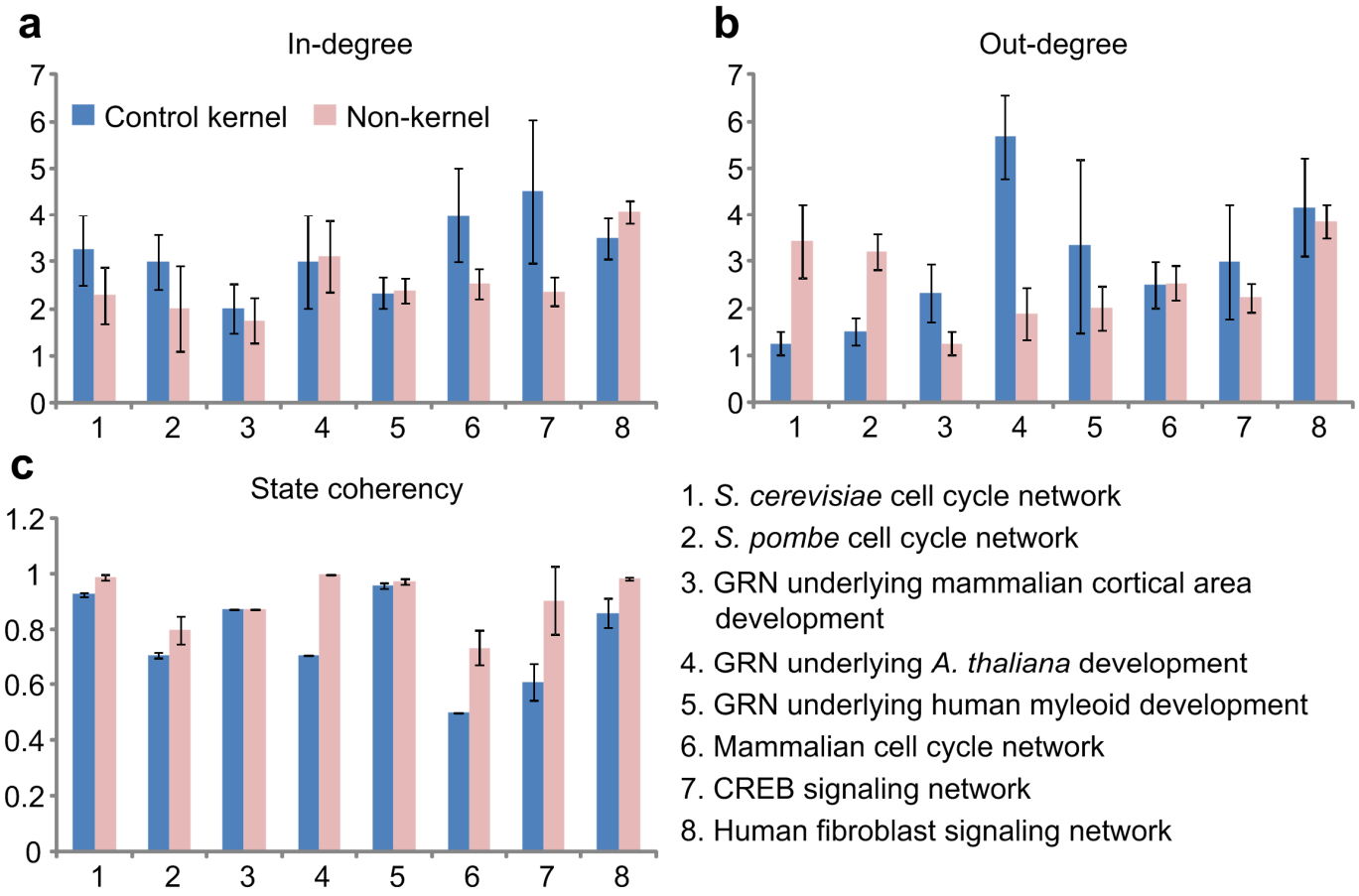
**Supplementary Figure S2**. **Relationship between the size of control kernel and the topological characteristics in random networks.** (a) Graphs for the average size of control kernel with respect to the five topological parameters (average degree, the proportion of inhibitory links, network heterogeneity, clustering coefficient, and characteristic path length). (b) Pearson`s correlation coefficients between the size of control kernel and each of the five topological parameters. Here the correlation coefficients greater than 0.5 are marked in red.



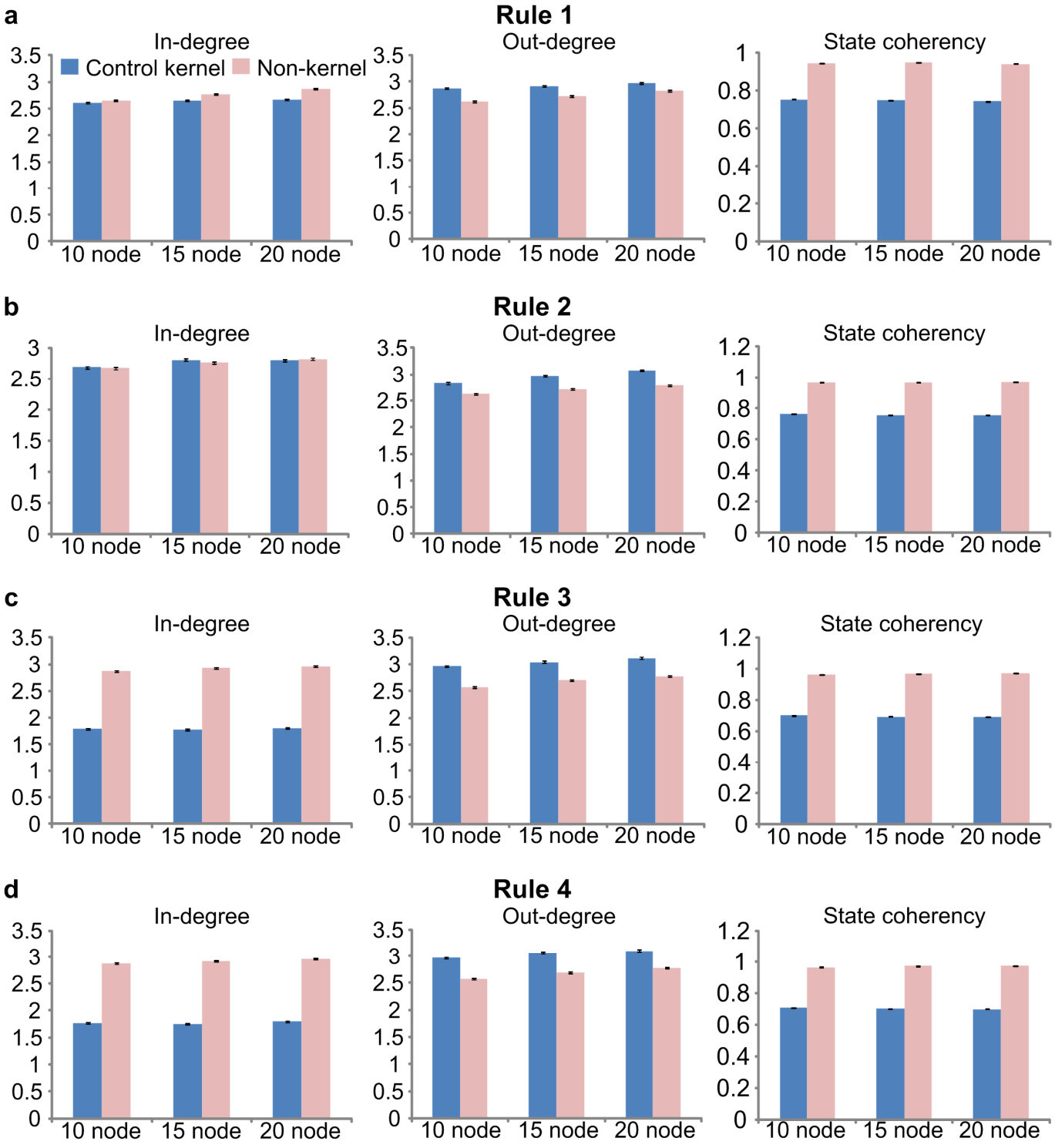

**Supplementary Figure S3. The average size of control kernel in the random networks with respect to the number of attractors and the proportion of basin size of the primary attractor.** (a) Rule 1. (b) Rule 2. (c) Rule 3. (d) Rule 4.



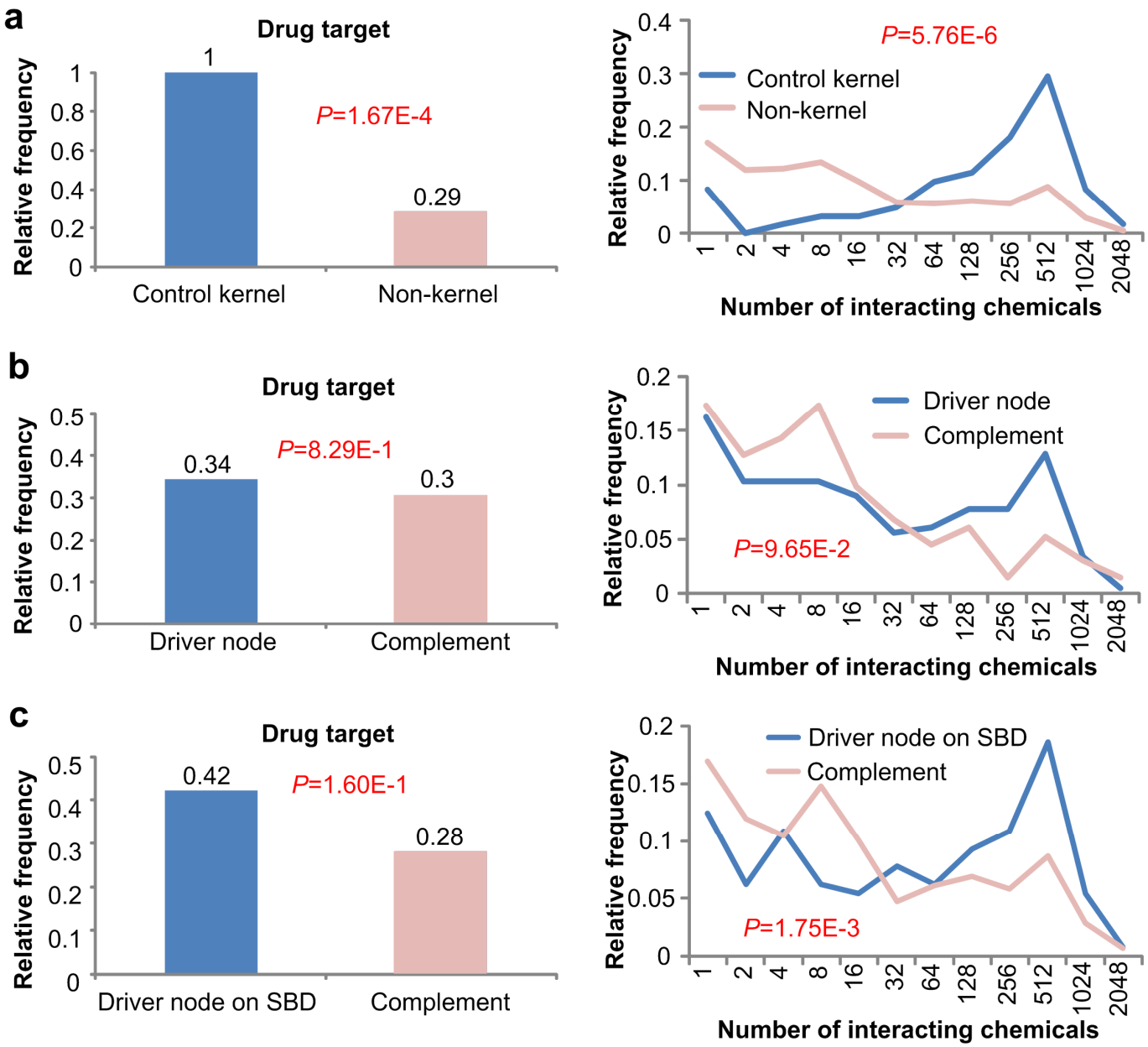

**Supplementary Figure S4. The average number of attractors and the proportion of basin size of the primary attractor in the random networks with respect to the proportion of inhibitory links.** (a) Rule 1. (b) Rule 2. (c) Rule 3. (d) Rule 4.



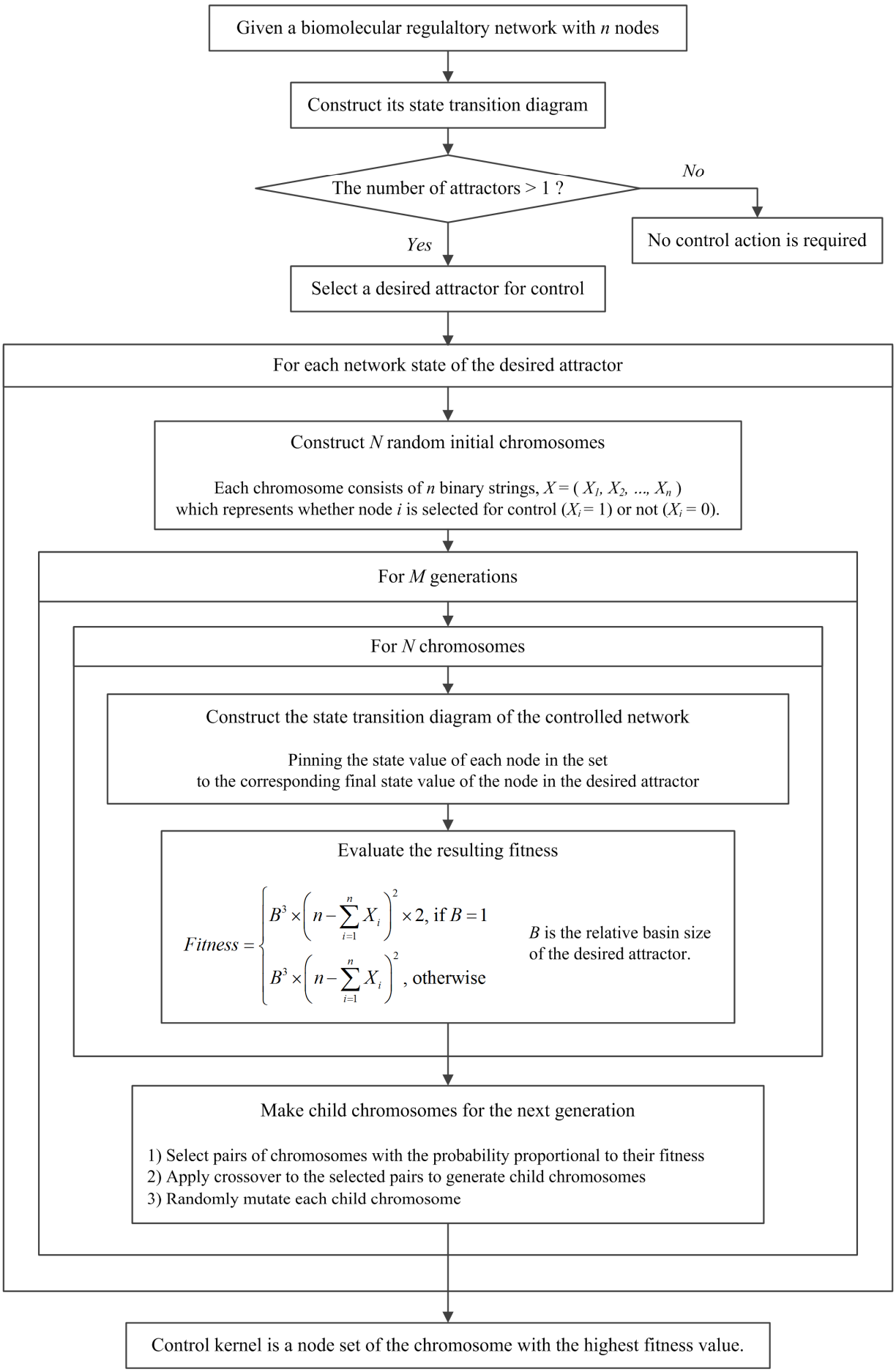

**Supplementary Figure S5**. **Topological and dynamical characteristics of the control kernel nodes in the eight biomolecular regulatory networks.** (a) In-degree (the number of incoming links). (b) Out-degree (the number of out-going links). (c) State coherency.



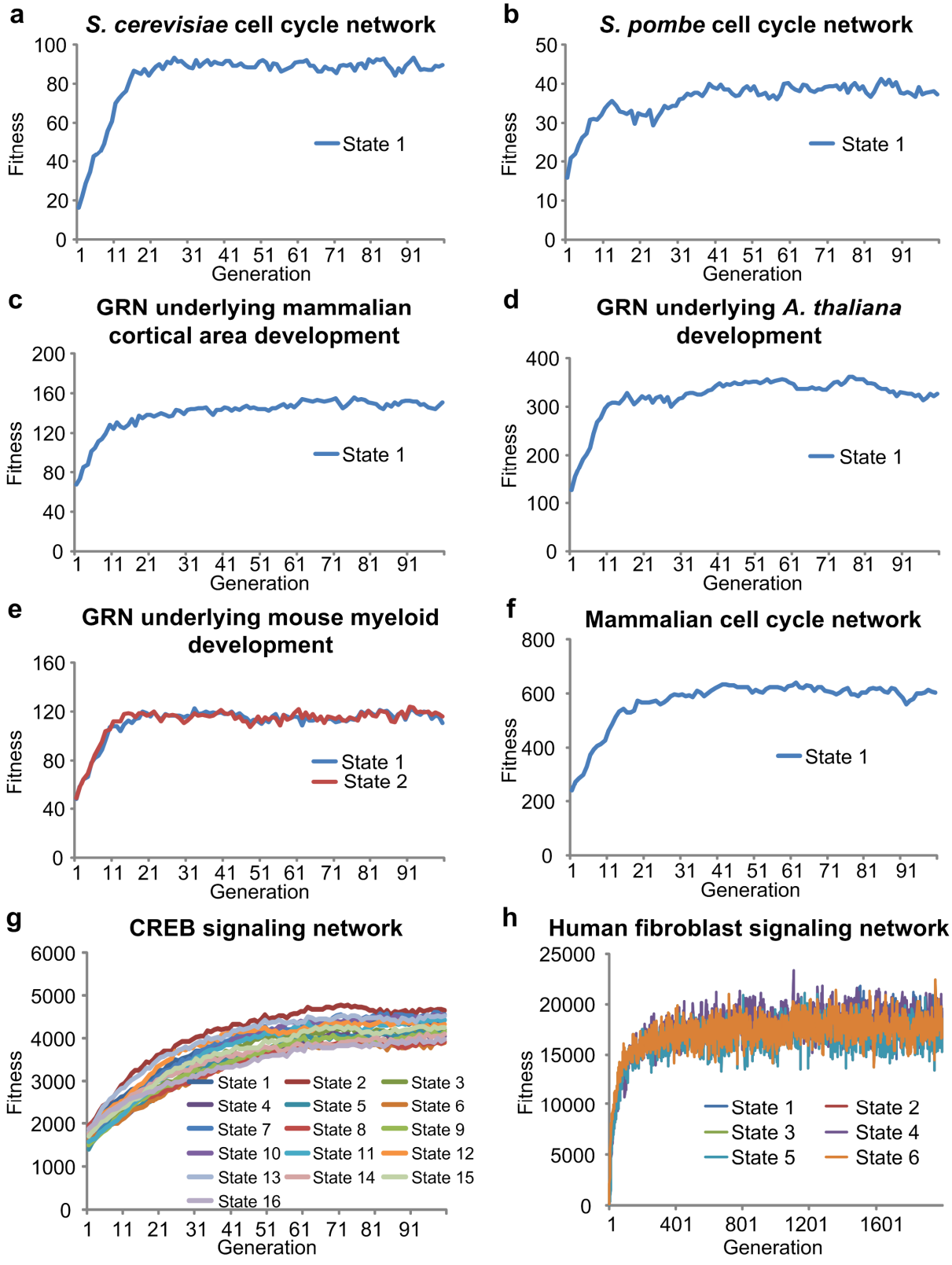

**Supplementary Figure S6. Topological and dynamical properties of the control kernel nodes in the random networks.** In-degree, out-degree, and state coherency of the control kernel nodes and non-kernel nodes in the random networks with four different logical rules. (a) Rule 1. (b) Rule 2. (c) Rule 3. (d) Rule 4.




**Supplementary Figure S7. The enrichment of drug targets and chemical-binding interactions in the control kernel nodes and the driver nodes in the human fibroblast signaling network.** (a, b) Control kernel nodes. (c, d) Driver nodes. (e, f) Driver nodes on switchboard dynamics (SBD).




**Supplementary Figure S8. The flow diagram illustrating the control kernerl identification algorithm.**




**Supplementary Figure S9. Average fitness trajectories during the artificial evolution of chromosomes for the identification of control kernel in the eight biomolecular regulatory networks.** (a) *Saccharomyces cerevisiae* cell cycle network. (b) *Schizosaccharomyces pombe* cell cycle network. (c) The GRN underlying mammalian cortical area development. (d) The GRN underlying *Arabidopsis thaliana* development. (e) The GRN underlying mouse myeloid development. (f) Mammalian cell cycle network. (g) CREB signaling network. (h) The human fibroblast signaling network. 'State' in the legend of each figure denotes the respective network state of the desired attractor. The desired attractors of (e), (g), and (h) are cyclic attractors with the period length greater than two.

# III. Supplementary Tables

**Supplementary Table S1. State coherency and attractor states of the *Saccharomyces cerevisiae* cell cycle network.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernel of the *Saccharomyces cerevisiae* cell cycle network is $\{\text{Cdh1, MBF, SBF, Sic1}\}$.

| Node name | Cdc20_Cdc14 | Cdh1 | Clb1_2 | Clb5_6 | Cln1_2 | Cln3 | MBF | Mcm1_SFF | SBF | Sic1 | Swi5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| State coherency | 1 | 0.915 | 1 | 1 | 0.926 | 1 | 0.943 | 1 | 0.926 | 0.922 | 1 |
| Attractor 1 (1764) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Attractor 2 (151) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Attractor 3 (109) | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Attractor 4 (9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Attractor 5 (7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Attractor 6 (7) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Attractor 7 (1) | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Supplementary Table S2. State coherency and attractor states of the *Schizosaccharomyces pombe* cell cycle network.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernel of the *Schizosaccharomyces pombe* cell cycle network is $\{\text{Cdc25, Rum1, Ste9, Wee1}\}$.

| Node name | Cdc2/13 | Cdc2/13* | Cdc25 | PP | Rum1 | SK | Slp1 | Ste9 | Wee1 |
|---|---|---|---|---|---|---|---|---|---|
| State coherency | 0.75 | 0.75 | 0.723 | 0.75 | 0.693 | 1 | 0.75 | 0.693 | 0.723 |
| Attractor 1 (341) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Attractor 2 (128) | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Attractor 3 (9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Attractor 4 (6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Attractor 5 (6) | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Attractor 6 (5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Attractor 7 (5) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Attractor 8 (2) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Attractor 9 (2) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 |
| Attractor 10 (2) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 |
| Attractor 11 (1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Attractor 12 (1) | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Attractor 13 (1) | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Attractor 14 (1) | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| Attractor 15 (1) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| Attractor 16 (1) | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |

**Supplementary Table S3. State coherency and attractor states of the GRN underlying mammalian cortical area development.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernels of the GRN underlying mammalian cortical area development are $\{Fgf8\_g\}$, $\{Emx2\_g\}$, $\{Sp8\_g\}$, $\{Fgf8\_p\}$, $\{Emx2\_p\}$, and $\{Sp8\_p\}$.

| Node name | Fgf8_g | Emx2_g | Pax6_g | Coup_g | Sp8_g | Fgf8_p | Emx2_p | Pax6_p | Coup_p | Sp8_p |
|---|---|---|---|---|---|---|---|---|---|---|
| State coherency | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 | 0.875 |
| Attractor 1 (784) | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| Attractor 2 (224) | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Attractor 3 (16) | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 |

**Supplementary Table S4. State coherency and attractor states of the GRN underlying *Arabidopsis thaliana* development.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernels of the GRN underlying *Arabidopsis thaliana* development are $\{AP1\}$, $\{LFY\}$, and $\{SEP\}$.

| Node name | AG | AP1 | AP2 | AP3 | CLF | EMF1 | FT | FUL | LFY | LUG | Pl | SEP | TFL1 | UFO | WUS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| State coherency | 1 | 0.71 | 1 | 1 | 1 | 1 | 1 | 1 | 0.71 | 1 | 1 | 0.71 | 1 | 1 | 1 |
| Attractor 1 (23200) | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 |
| Attractor 2 (9480) | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Attractor 3 (88) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Supplementary Table S5. State coherency and attractor states of the GRN underlying mouse myeloid development.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernels of the GRN underlying mouse myeloid development are $\{GATA\_1, EKLF, Fli\_1\}$ and $\{EKLF, Fli\_1, PU1\}$.

| Node name | GATA_2 | GATA_1 | FOG_1 | EKLF | Fli_1 | SCL | CEBPA | PU1 | cJun | EgrNab | Gfi_1 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| State coherency | 1 | 0.9313 | 0.9313 | 0.9641 | 0.9641 | 0.9344 | 0.9813 | 0.9781 | 0.993 | 0.993 | 0.982 |
| Attractor 1 (1088) | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Attractor 2 (240) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| Attractoror 3 (192) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Attractor 4 (128) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 |
| Attractor 5 (128) | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| Attractor 6 (128) | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Attractor 7 (128) | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Attractor 8 (16) | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 |

**Supplementary Table S6. State coherency and attractor states of the mammalian cell cycle network.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernels of the mammalian cell cycle network are $\{\text{MEK1}\}$ and $\{\text{IGF1R}\}$.

| Node name | State coherency | Attractor 1 (9984) | Attractor 2 (16) |
|---|---|---|---|
| Akt1 | 0.5008 | 1 | 0 |
| CDK2 | 0.5008 | 1 | 0 |
| CDK4 | 0.5008 | 1 | 0 |
| CDK6 | 0.5008 | 1 | 0 |
| cMYC | 0.5008 | 1 | 0 |
| CycD1 | 0.5008 | 1 | 0 |
| CycE1 | 0.5008 | 1 | 0 |
| Era | 0.5008 | 1 | 0 |
| ErbB1 | 1 | 0 | 0 |
| ErbB1_2 | 1 | 0 | 0 |
| ErbB1_3 | 1 | 0 | 0 |
| ErbB2 | 1 | 0 | 0 |
| ErbB2_3 | 1 | 0 | 0 |
| ErbB3 | 1 | 0 | 0 |
| IGF1R | 0.5008 | 1 | 0 |
| MEK1 | 0.5008 | 1 | 0 |
| p21 | 1 | 0 | 0 |
| p27 | 1 | 0 | 0 |
| pRB | 0.5008 | 1 | 0 |
| EGF | 1 | 0 | 0 |

**Supplementary Table S7. State coherency and primary attractor states of the CREB signaling network.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernels of the CREB signaling network are $\{\text{AC2, AC5, Calmodulin, M2R, PKA}\}$ and $\{\text{CREB, CaMKI, Calmodulin, Galphai, PKA}\}$.

| Node name | State coherency | Attractor 1 (0.2925) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5-HT1AR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5-HT2AR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5-HT4R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| A1R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| A2AR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AC1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| AC2 | 0.5 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AC5 | 0.5 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |
| AKT | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Ach | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adenosine | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CBP | 0.5 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 |
| CREB | 0.559 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 |
| CREM | 0.787 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Ca2 | 0.5 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| CaMKI | 0.825 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CaMKII | 0.5 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| CaMKIV | 0.787 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| CaMKK | 0.825 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Calmodulin | 0.5 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 |
| D1R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D2R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| D3R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DAG | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DOR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dopamine | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enkephalin | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GABA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GABABR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GSK3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Galphai | 0.5 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 |
| Galphas | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Galphaz | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gbetagamma | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Glutamate | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Grb2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ILK | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| KOR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| M1R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| M2R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| M4R | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MOR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| N-typeCaCh | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NMDAR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NOR | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| P/QtypeCaCh | 0.5 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PDK1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PI3K | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PIP2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PIP3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PKA | 0.5 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 |
| PKC | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PLCβ | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PLCγ | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PP2A | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PP2B | 0.5 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 |
| RSK | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| RasGAP | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| SAM68 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Serotonin | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cAMP | 0.5 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| cJun | 0.5 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| mGluR1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| mGluR7 | 0.5 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |

**Supplementary Table S8. State coherency and primary attractor states of the human fibroblast signaling network.** The control kernel nodes are marked in red and the number in the parenthese denotes the basin size of the corresponding attractor. The control kernel of the human fibroblast signaling network is {DAG, PIP_4, PIP2_45, alpha_s_R, Gbg_s, cAMP, Rho, alpha_q_R, alpha_12_13_R, Raf_DeP, PKC_primed, Raf_Loc} .

| Node name | State coherency | Attractor 1 (0.5554) | | | | | |
|---|---|---|---|---|---|---|---|
| EGFR | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PLC_B | 0.948 | 0 | 0 | 0 | 0 | 0 | 0 |
| PLC_g | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| IP3 | 0.951 | 0 | 0 | 0 | 0 | 0 | 0 |
| DAG | 0.845 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ca | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| CaM | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| CaMKK | 0.999 | 0 | 0 | 0 | 0 | 0 | 0 |
| CaMK | 0.999 | 0 | 0 | 0 | 0 | 0 | 0 |
| RGS | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rap1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Shc | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Grb2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sos | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ras | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PKC | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| AA | 0.999 | 0 | 0 | 0 | 0 | 0 | 0 |
| Raf | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mek | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Erk | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PLA2 | 0.999 | 0 | 0 | 0 | 0 | 0 | 0 |
| PI3K | 0.997 | 0 | 0 | 0 | 0 | 0 | 0 |
| Akt | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PDK1 | 0.983 | 0 | 0 | 0 | 0 | 0 | 0 |
| PIP_4 | 0.500 | 0 | 1 | 0 | 1 | 0 | 1 |
| PIP2_45 | 0.995 | 1 | 1 | 1 | 1 | 1 | 1 |
| PIP2_34 | 0.996 | 0 | 0 | 0 | 0 | 0 | 0 |
| PIP3_345 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PI4K | 0.999 | 1 | 1 | 1 | 1 | 1 | 1 |
| PI5K | 0.995 | 1 | 1 | 1 | 1 | 1 | 1 |
| alpha_s_R | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gbg_s | 0.870 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gai | 0.997 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gas | 0.870 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gaq | 0.950 | 0 | 0 | 0 | 0 | 0 | 0 |
| GRK | 0.771 | 0 | 0 | 0 | 0 | 0 | 0 |
| B_Arrestin | 0.916 | 0 | 0 | 0 | 0 | 0 | 0 |
| AC | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| cAMP | 0.995 | 0 | 0 | 0 | 0 | 0 | 0 |
| PKA | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| RasGRF_GRP | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| p120RasGAP | 0.983 | 1 | 1 | 1 | 1 | 1 | 1 |
| Rho | 0.945 | 0 | 0 | 0 | 0 | 0 | 0 |
| RhoGDI | 0.996 | 0 | 0 | 0 | 0 | 0 | 0 |
| p190RhoGAP | 0.984 | 0 | 0 | 0 | 0 | 0 | 0 |
| p115RhoGEF | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| RhoK | 0.945 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fak | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cas | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Src | 0.984 | 0 | 0 | 0 | 0 | 0 | 0 |
| Csk | 0.984 | 0 | 0 | 0 | 0 | 0 | 0 |
| Myosin | 0.944 | 0 | 0 | 0 | 0 | 0 | 0 |
| Actin | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Integrins | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| RKIP | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vinc | 0.984 | 0 | 0 | 0 | 0 | 0 | 0 |
| Crk | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nck | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| DOCK180 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rac | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tiam | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| RalGDS | 0.916 | 0 | 0 | 0 | 0 | 0 | 0 |
| AND_3_4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ral | 0.914 | 0 | 0 | 0 | 0 | 0 | 0 |
| RalBP1 | 0.914 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cdc42 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| NIK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Talin | 0.979 | 1 | 1 | 1 | 1 | 1 | 1 |
| ILK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Arp_2_3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pix_Cool | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PAK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| WASP | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Graf | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MLCK | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| MLCP | 0.945 | 1 | 1 | 1 | 1 | 1 | 1 |
| IL1_TNFR | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Trafs | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| GCK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gab1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tab_1_2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mekk1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mekk2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mekk3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mekk4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| ASK1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Trx | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| TAK1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tpl2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MLK1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MLK2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MLK3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| TAO_1_2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sek1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MKK7 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MKK3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MKK6 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| SAPK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| p38 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| p90RSK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PP2A | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| SHP2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| MKPs | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PTEN | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PTP1b | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| PTPPEST | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PTPa | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| PLD | 0.995 | 1 | 1 | 1 | 1 | 1 | 1 |
| PA | 0.995 | 1 | 1 | 1 | 1 | 1 | 1 |
| ARF | 0.995 | 1 | 1 | 1 | 1 | 1 | 1 |
| DGK | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| B_Parvin | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_i_R | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_q_R | 0.899 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_12_13_R | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ga_12_13 | 0.907 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gbg_i | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gbg_q | 0.924 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gbg_12_13 | 0.907 | 0 | 0 | 0 | 0 | 0 | 0 |
| PDE4 | 0.916 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cbp | 0.984 | 0 | 0 | 0 | 0 | 0 | 0 |
| IP3R1 | 0.998 | 0 | 0 | 0 | 0 | 0 | 0 |
| Raf_DeP | 0.514 | 0 | 1 | 0 | 0 | 1 | 0 |
| PKC_primed | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Raf_Loc | 0.771 | 1 | 1 | 1 | 1 | 1 | 1 |
| Raf_Rest | 0.628 | 1 | 1 | 0 | 1 | 1 | 0 |
| Palpha_s_R | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Palpha_q_R | 0.916 | 0 | 0 | 0 | 0 | 0 | 0 |
| Palpha_i_R | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Palpha_12_13_R | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| EGF | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ECM | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_q_lig | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_i_lig | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_s_lig | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| alpha_12_13_lig | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Stress | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| IL1_TNF | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| ExtPump | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

**Supplementary Table S9. Comparison of the control kernel, driver node set, driver node set on switchboard dynamics (SBD), and optimal sensor set of the human fibroblast signaling network.** In the table, '1' indicates that the node in the corresponding row belongs to the group of the corresponding column, and '0' indicates that the node in the corresponding row does not belong to the group of the corresponding column. Since the set of the driver nodes are not unique, the union and intersection of the sets obtained from 1,000 repetitions are considered.

| Node name | Control kernel | Driver node set | | Driver node set on SBD | Optimal sensor set |
|---|---|---|---|---|---|
| | | Union | Intersection | | |
| AA | 0 | 0 | 0 | 1 | 0 |
| AC | 0 | 1 | 0 | 0 | 0 |
| AND_3_4 | 0 | 1 | 0 | 0 | 0 |
| ARF | 0 | 1 | 0 | 1 | 0 |
| ASK1 | 0 | 1 | 0 | 1 | 0 |
| Actin | 0 | 0 | 0 | 0 | 0 |
| Akt | 0 | 1 | 0 | 0 | 0 |
| Arp_2_3 | 0 | 0 | 0 | 0 | 0 |
| B_Arrestin | 0 | 0 | 0 | 1 | 0 |
| B_Parvin | 0 | 1 | 0 | 0 | 0 |
| Ca | 0 | 0 | 0 | 1 | 0 |
| CaM | 0 | 1 | 0 | 1 | 0 |
| CaMK | 0 | 1 | 0 | 0 | 0 |
| CaMKK | 0 | 1 | 0 | 0 | 0 |
| Cas | 0 | 1 | 0 | 1 | 0 |
| Cbp | 0 | 1 | 0 | 0 | 0 |
| Cdc42 | 0 | 0 | 0 | 1 | 0 |
| Crk | 0 | 1 | 0 | 0 | 0 |
| Csk | 0 | 0 | 0 | 0 | 0 |
| DAG | 1 | 0 | 0 | 0 | 0 |
| DGK | 0 | 1 | 0 | 0 | 0 |
| DOCK180 | 0 | 1 | 0 | 0 | 0 |
| EGFR | 0 | 1 | 0 | 1 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Erk | 0 | 0 | 0 | 1 | 0 |
| Fak | 0 | 1 | 0 | 1 | 0 |
| GCK | 0 | 1 | 0 | 0 | 0 |
| GRK | 0 | 1 | 0 | 0 | 0 |
| Ga_12_13 | 0 | 0 | 0 | 0 | 0 |
| Gab1 | 0 | 1 | 0 | 0 | 0 |
| Gai | 0 | 1 | 0 | 0 | 0 |
| Gaq | 0 | 1 | 0 | 0 | 0 |
| Gas | 0 | 1 | 0 | 0 | 0 |
| Gbg_12_13 | 0 | 1 | 0 | 1 | 0 |
| Gbg_i | 0 | 1 | 0 | 1 | 0 |
| Gbg_q | 0 | 1 | 0 | 1 | 0 |
| Gbg_s | 1 | 1 | 0 | 0 | 0 |
| Graf | 0 | 1 | 0 | 0 | 0 |
| Grb2 | 0 | 1 | 0 | 1 | 0 |
| IL1_TNFR | 0 | 1 | 1 | 1 | 0 |
| ILK | 0 | 1 | 0 | 1 | 0 |
| IP3 | 0 | 1 | 0 | 0 | 0 |
| IP3R1 | 0 | 0 | 0 | 0 | 0 |
| 0Integrins | 0 | 1 | 0 | 0 | 0 |
| MKK3 | 0 | 0 | 0 | 0 | 0 |
| MKK6 | 0 | 0 | 0 | 0 | 0 |
| MKK7 | 0 | 0 | 0 | 0 | 0 |
| MKPs | 0 | 1 | 0 | 0 | 0 |
| MLCK | 0 | 1 | 0 | 0 | 0 |
| MLCP | 0 | 1 | 0 | 0 | 0 |
| MLK1 | 0 | 1 | 0 | 1 | 0 |
| MLK2 | 0 | 1 | 0 | 0 | 0 |
| MLK3 | 0 | 1 | 0 | 1 | 0 |
| Mek | 0 | 0 | 0 | 0 | 0 |
| Mekk1 | 0 | 0 | 0 | 0 | 0 |
| Mekk2 | 0 | 0 | 0 | 0 | 0 |
| Mekk3 | 0 | 1 | 0 | 0 | 0 |
| Mekk4 | 0 | 1 | 0 | 1 | 0 |
| Myosin | 0 | 0 | 0 | 0 | 0 |
| NIK | 0 | 0 | 0 | 0 | 0 |
| Nck | 0 | 1 | 0 | 1 | 0 |
| PA | 0 | 0 | 0 | 1 | 0 |
| PAK | 0 | 1 | 0 | 0 | 0 |
| PDE4 | 0 | 1 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| PDK1 | 0 | 1 | 0 | 1 | 0 |
| PI3K | 0 | 1 | 0 | 0 | 0 |
| PI4K | 0 | 1 | 0 | 0 | 0 |
| PI5K | 0 | 1 | 0 | 0 | 0 |
| PIP2_34 | 0 | 1 | 0 | 1 | 0 |
| PIP2_45 | 1 | 1 | 0 | 1 | 0 |
| PIP3_345 | 0 | 1 | 0 | 1 | 0 |
| PIP_4 | 1 | 0 | 0 | 0 | 1 |
| PKA | 0 | 1 | 0 | 1 | 0 |
| PKC | 0 | 1 | 0 | 1 | 0 |
| PKC_primed | 1 | 1 | 0 | 0 | 0 |
| PLA2 | 0 | 1 | 0 | 0 | 0 |
| PLC_B | 0 | 1 | 0 | 1 | 0 |
| PLC_g | 0 | 1 | 0 | 0 | 0 |
| PLD | 0 | 0 | 0 | 0 | 0 |
| PP2A | 0 | 1 | 0 | 1 | 0 |
| PTEN | 0 | 0 | 0 | 1 | 0 |
| PTP1b | 0 | 1 | 0 | 1 | 0 |
| PTPPEST | 0 | 1 | 0 | 0 | 0 |
| PTPa | 0 | 1 | 0 | 0 | 0 |
| Palpha_12_13_R | 0 | 1 | 0 | 0 | 0 |
| 0Palpha_i_R | 0 | 1 | 0 | 1 | 0 |
| Palpha_q_R | 0 | 1 | 0 | 0 | 0 |
| Palpha_s_R | 0 | 1 | 0 | 0 | 0 |
| Pix_Cool | 0 | 0 | 0 | 0 | 0 |
| RGS | 0 | 1 | 0 | 1 | 0 |
| RKIP | 0 | 1 | 0 | 1 | 0 |
| Rac | 0 | 0 | 0 | 0 | 0 |
| Raf | 0 | 1 | 0 | 0 | 0 |
| Raf_DeP | 1 | 1 | 0 | 0 | 0 |
| Raf_Loc | 1 | 1 | 0 | 0 | 0 |
| Raf_Rest | 0 | 1 | 0 | 0 | 0 |
| Ral | 0 | 0 | 0 | 0 | 0 |
| RalBP1 | 0 | 0 | 0 | 1 | 0 |
| RalGDS | 0 | 1 | 0 | 0 | 0 |
| Rap1 | 0 | 1 | 0 | 0 | 0 |
| Ras | 0 | 0 | 0 | 1 | 0 |
| RasGRF_GRP | 0 | 1 | 0 | 0 | 0 |
| Rho | 1 | 0 | 0 | 1 | 0 |
| RhoGDI | 0 | 1 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| RhoK | 0 | 1 | 0 | 1 | 0 |
| SAPK | 0 | 0 | 0 | 0 | 0 |
| SHP2 | 0 | 1 | 0 | 1 | 0 |
| Sek1 | 0 | 0 | 0 | 0 | 0 |
| Shc | 0 | 1 | 0 | 0 | 0 |
| Sos | 0 | 1 | 0 | 0 | 0 |
| Src | 0 | 0 | 0 | 1 | 0 |
| TAK1 | 0 | 0 | 0 | 1 | 0 |
| TAO_1_2 | 0 | 1 | 1 | 1 | 0 |
| Tab_1_2 | 0 | 1 | 0 | 0 | 0 |
| Talin | 0 | 1 | 0 | 1 | 0 |
| Tiam | 0 | 1 | 0 | 0 | 0 |
| Tpl2 | 0 | 1 | 0 | 1 | 0 |
| Trafs | 0 | 1 | 0 | 1 | 0 |
| Trx | 0 | 1 | 0 | 1 | 0 |
| Vinc | 0 | 0 | 0 | 0 | 1 |
| WASP | 0 | 1 | 0 | 0 | 0 |
| alpha_12_13_R | 1 | 0 | 0 | 1 | 0 |
| alpha_i_R | 0 | 1 | 0 | 1 | 0 |
| alpha_q_R | 1 | 1 | 0 | 1 | 0 |
| alpha_s_R | 1 | 0 | 0 | 1 | 0 |
| cAMP | 1 | 0 | 0 | 1 | 0 |
| p115RhoGEF | 0 | 1 | 0 | 0 | 0 |
| p120RasGAP | 0 | 1 | 0 | 0 | 0 |
| p190RhoGAP | 0 | 0 | 0 | 0 | 0 |
| p38 | 0 | 0 | 0 | 0 | 0 |
| p90RSK | 0 | 1 | 0 | 0 | 0 |

# IV. Supplementary References


1. J. Kim, T. G. Kim, S. H. Jung, J. R. Kim, T. Park, P. Heslop-Harrison, K. H. Cho, Evolutionary design principles of modules that control cellular differentiation: consequences for hysteresis and multistationarity. *Bioinformatics* **24**, 1516 (2008).
2. F. Li, T. Long, Y. Lu, Q. Ouyang, C. Tang, The yeast cell-cycle network is robustly designed. *Proc Natl Acad Sci U S A* **101**, 4781 (2004).
3. A. Abdi, M. B. Tahoori, E. S. Emamian, Fault diagnosis engineering of digital circuits can identify vulnerable molecules in complex cellular pathways. *Sci Signal* **1**, ra10 (2008).