Gunnar Boldhaus

the yeast cell cycle network and its neutral mutants

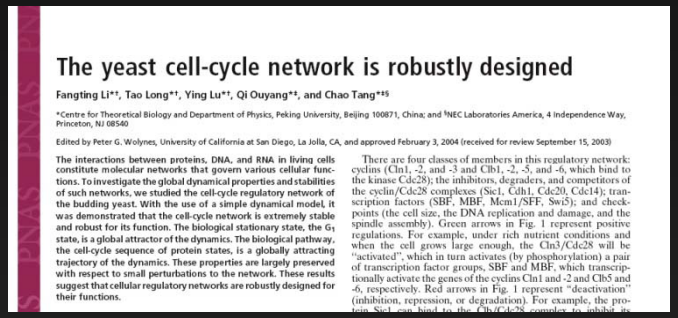
Cell cycle

Budding Yeast

Boolean Networks

Mutants

Neutral Graphs



The yeast cell-cycle network is robustly designed

Fangting Li*†, Tao Long*†, Ying Lu*†, Qi Ouyang*‡, and Chao Tang*‖§

*Centre for Theoretical Biology and Department of Physics, Peking University, Beijing 100871, China; and ‖NEC Laboratories America, 4 Independence Way, Princeton, NJ 08540

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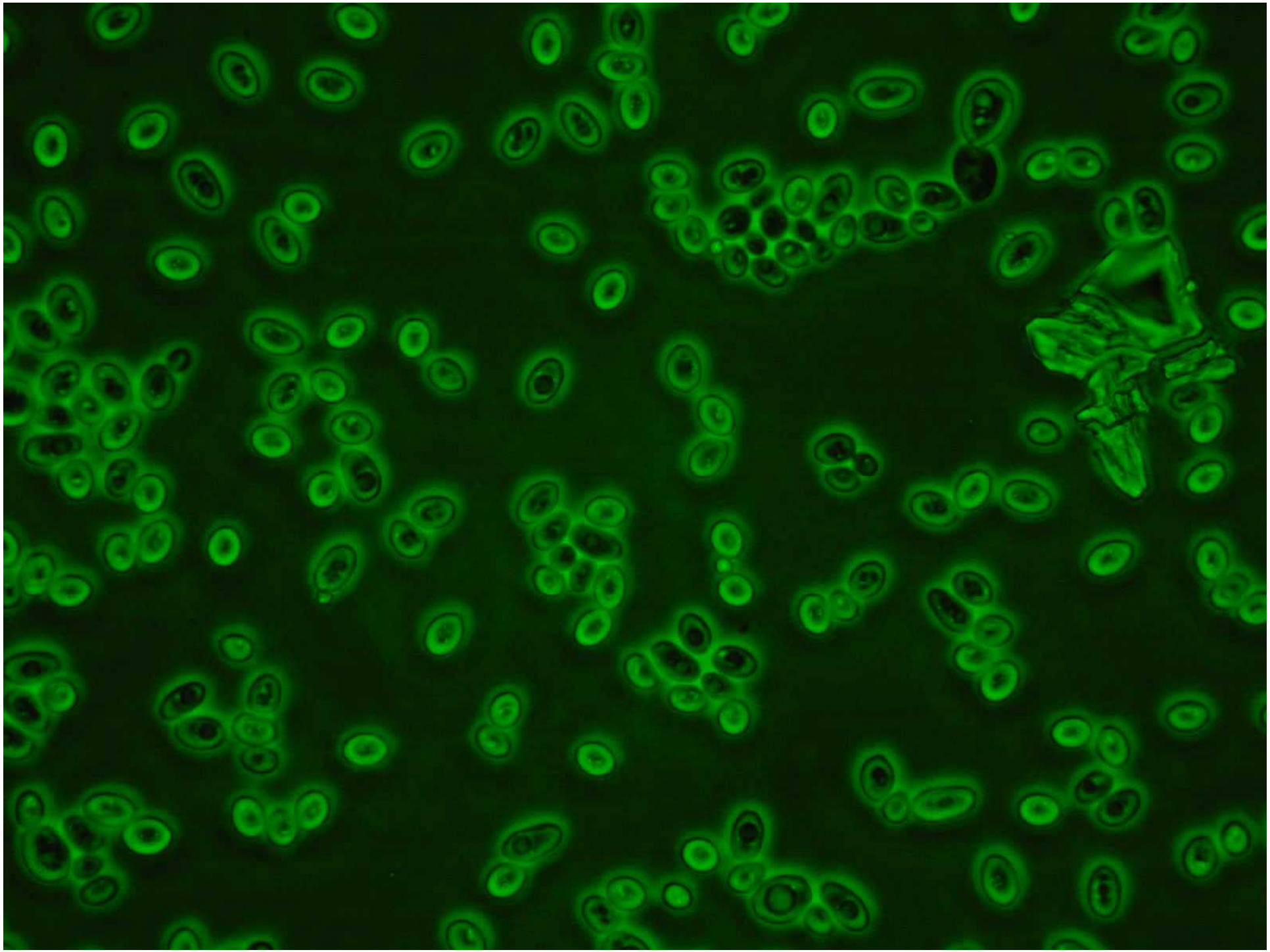
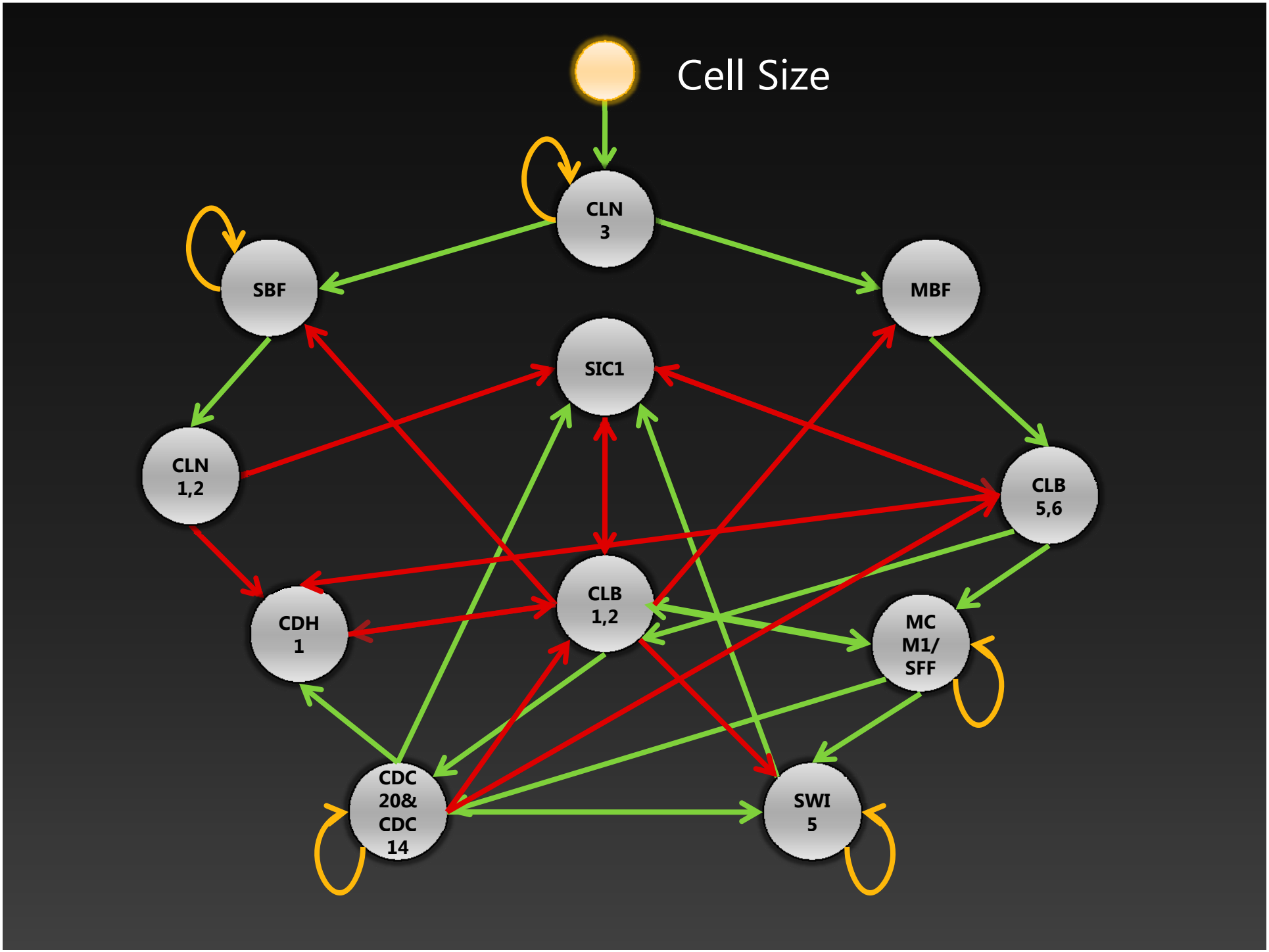
The interactions between proteins, DNA, and RNA in living cells constitute molecular networks that govern various cellular functions. To investigate the global dynamical properties and stabilities of such networks, we studied the cell-cycle regulatory network of the budding yeast. With the use of a simple dynamical model, it was demonstrated that the cell-cycle network is extremely stable and robust for its function. The biological stationary state, the G_1 state, is a global attractor of the dynamics. The biological pathway, the cell-cycle sequence of protein states, is a globally attracting trajectory of the dynamics. These properties are largely preserved with respect to small perturbations to the network. These results suggest that cellular regulatory networks are robustly designed for their functions.

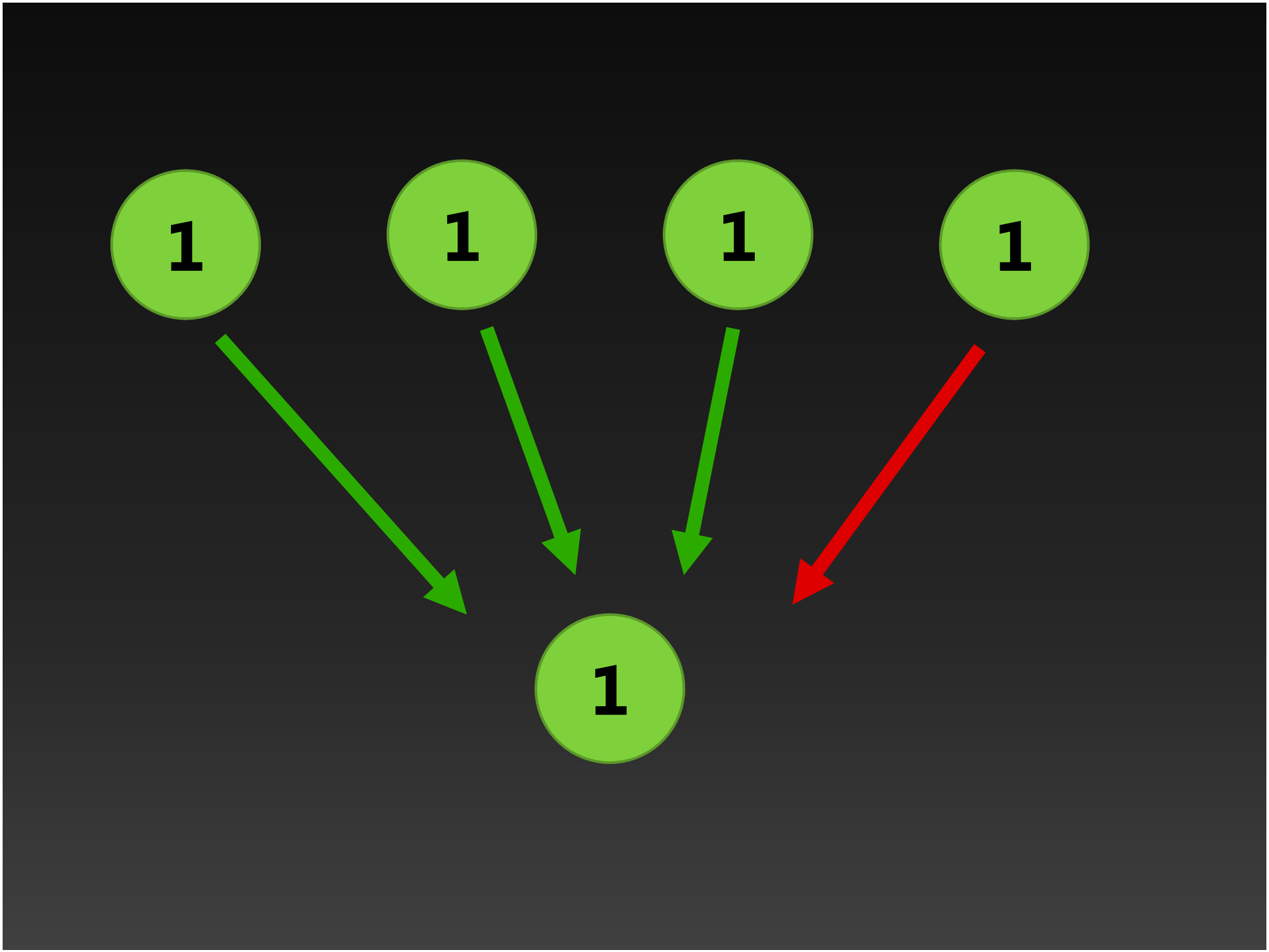
There are four classes of members in this regulatory network: cyclins (Cln1, -2, and -3 and Clb1, -2, -5, and -6, which bind to the kinase Cdc28); the inhibitors, degraders, and competitors of the cyclin/Cdc28 complexes (Sic1, Cdh1, Cdc20, Cdc14); transcription factors (SBF, MBF, Mcm1/SFF, Swi5); and checkpoints (the cell size, the DNA replication and damage, and the spindle assembly). Green arrows in Fig. 1 represent positive regulations. For example, under rich nutrient conditions and when the cell grows large enough, the Cln3/Cdc28 will be "activated", which in turn activates (by phosphorylation) a pair of transcription factor groups, SBF and MBF, which transcriptionally activate the genes of the cyclins Cln1 and -2 and Clb5 and -6, respectively. Red arrows in Fig. 1 represent "deactivation" (inhibition, repression, or degradation). For example, the protein Sic1 can bind to the Clb/Cdc28 complex to inhibit its

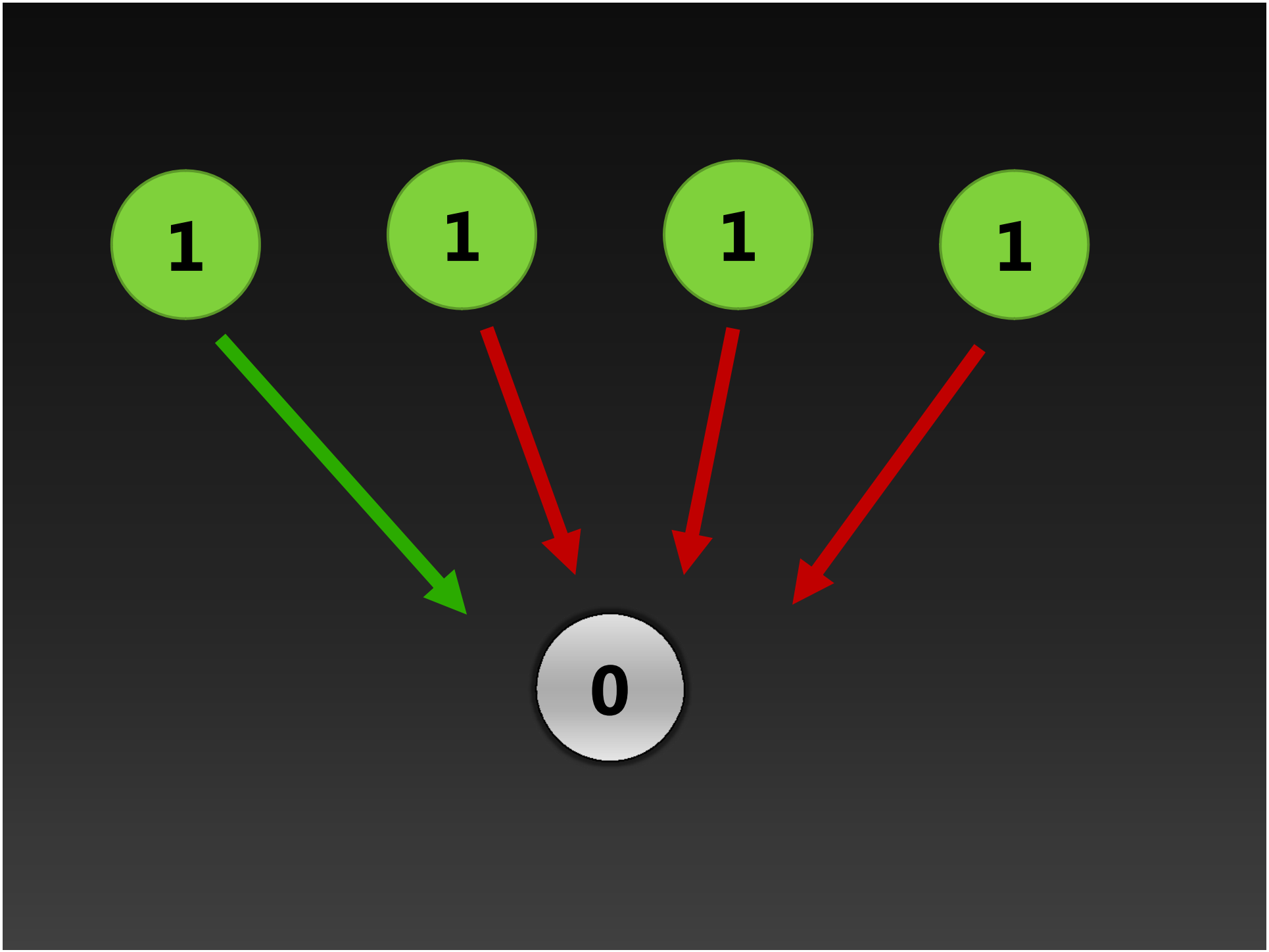
Li et al. (2004)

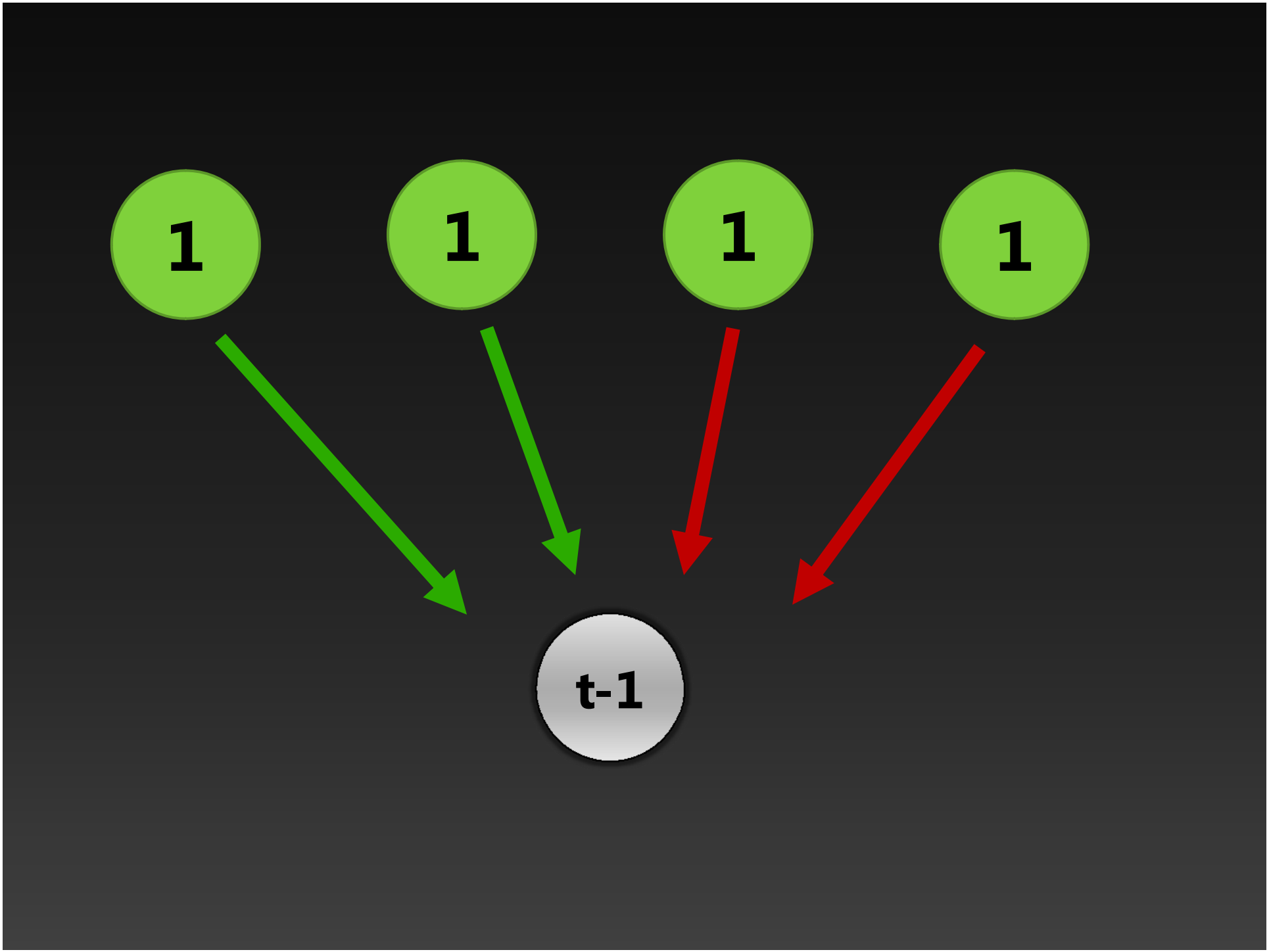


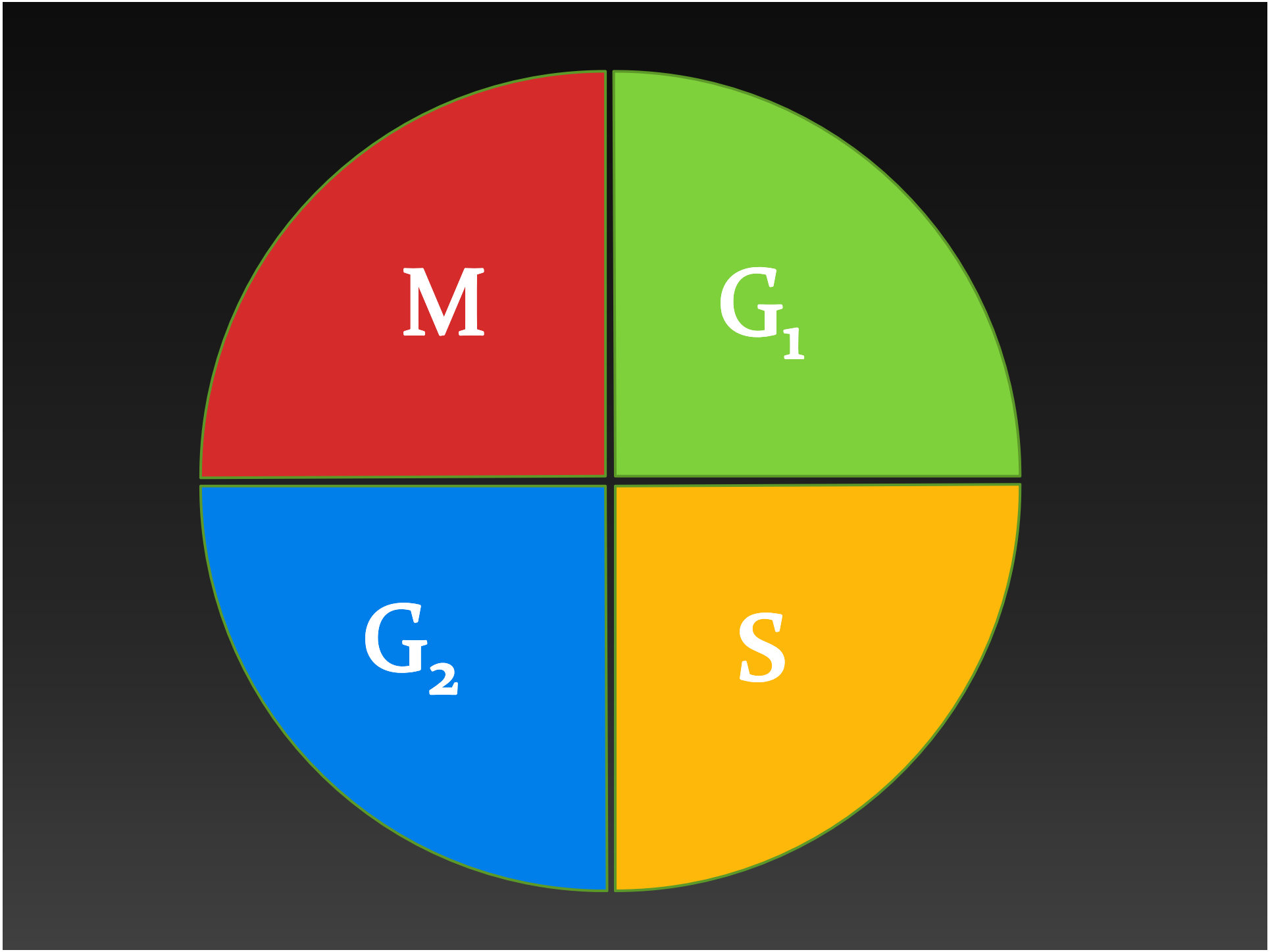

Cell Size
CLN 3
SBF
MBF
SIC1
CLN 1,2
CLB 5,6
CDH 1
CLB 1,2
MC M1/ SFF
CDC 20& CDC 14
SWI 5

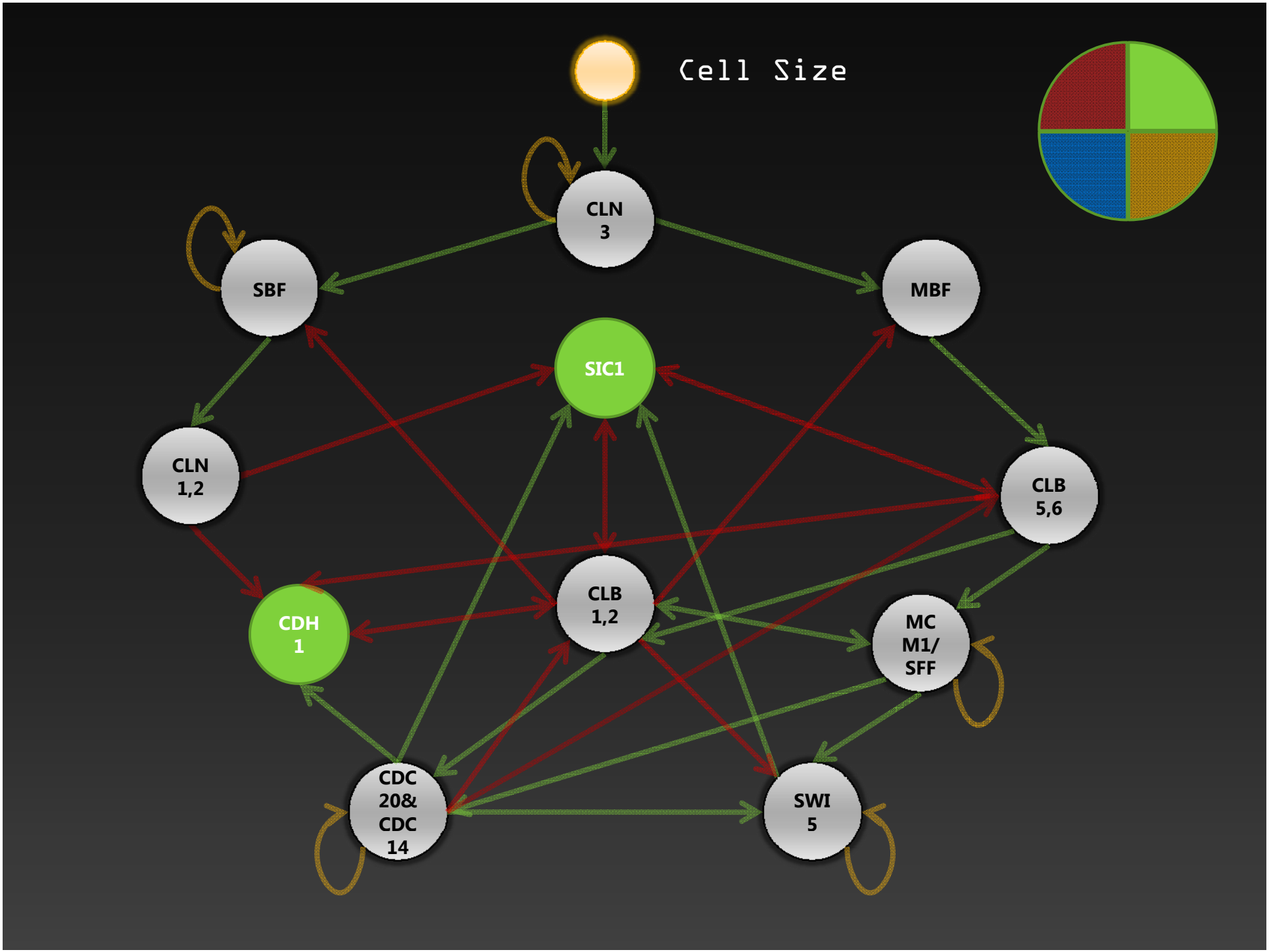
the dynamics


1
1
1
1
1


1
1
1
1
0


1
1
1
1
t-1


M
G1
G2
S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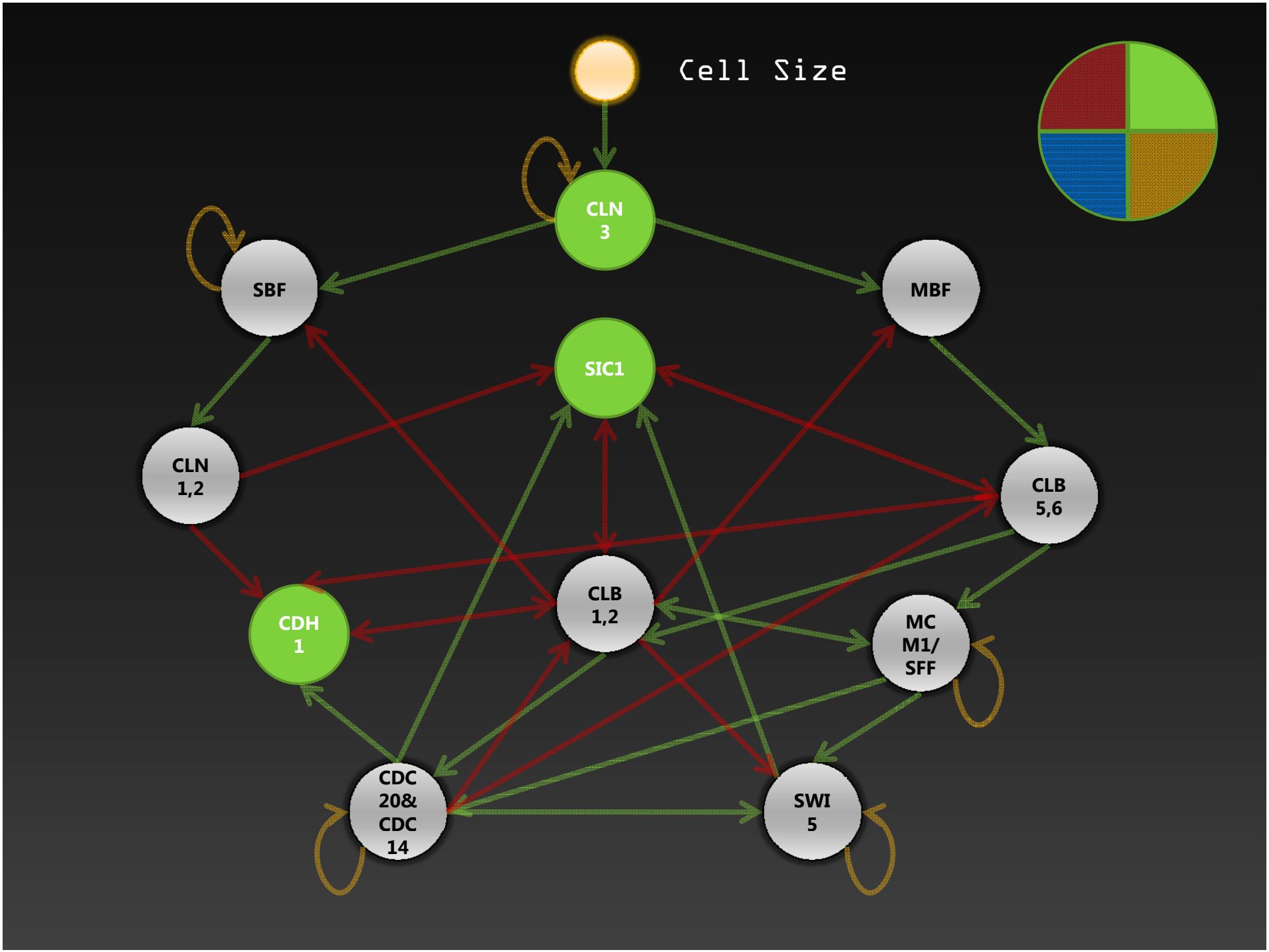
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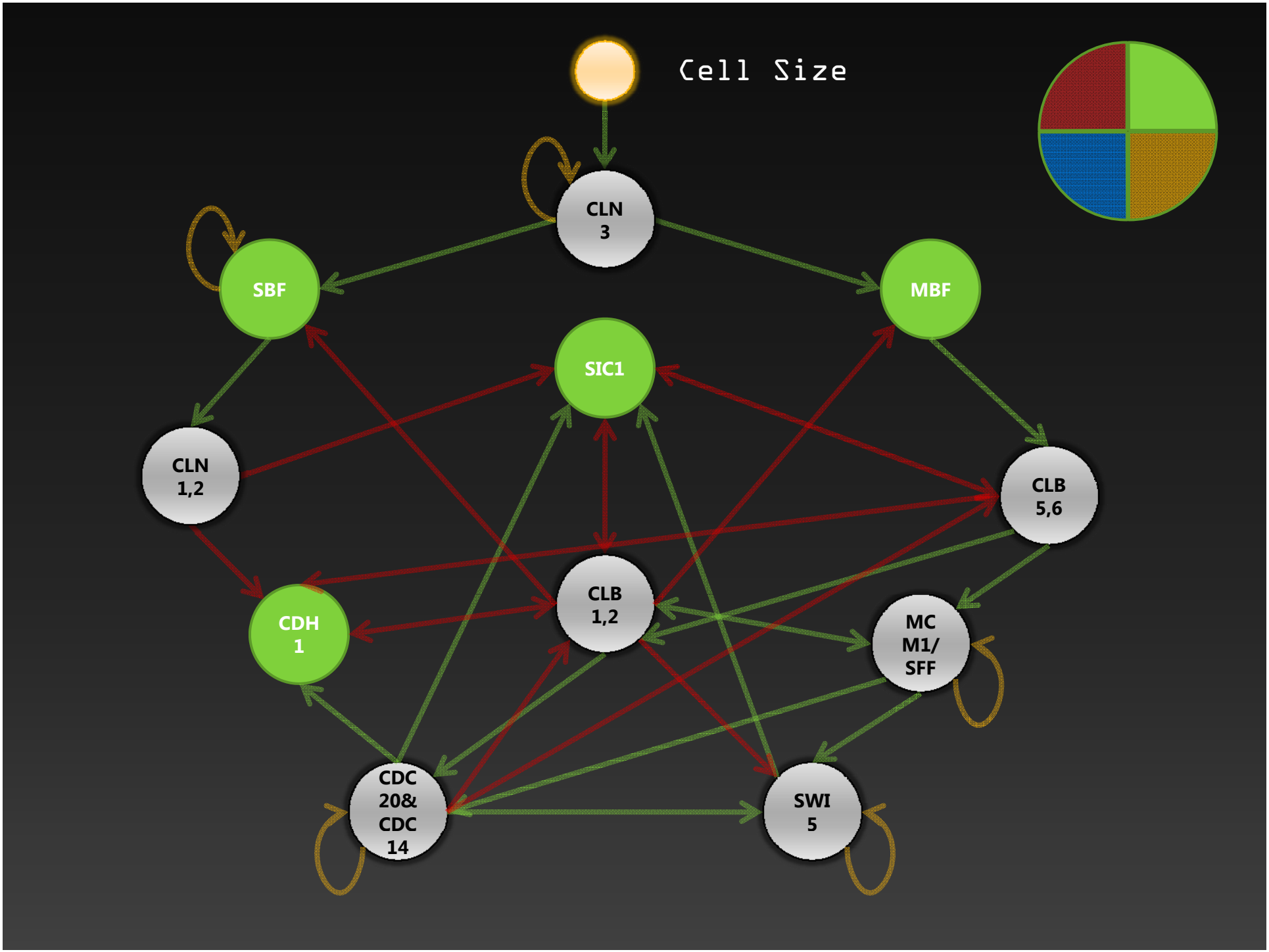
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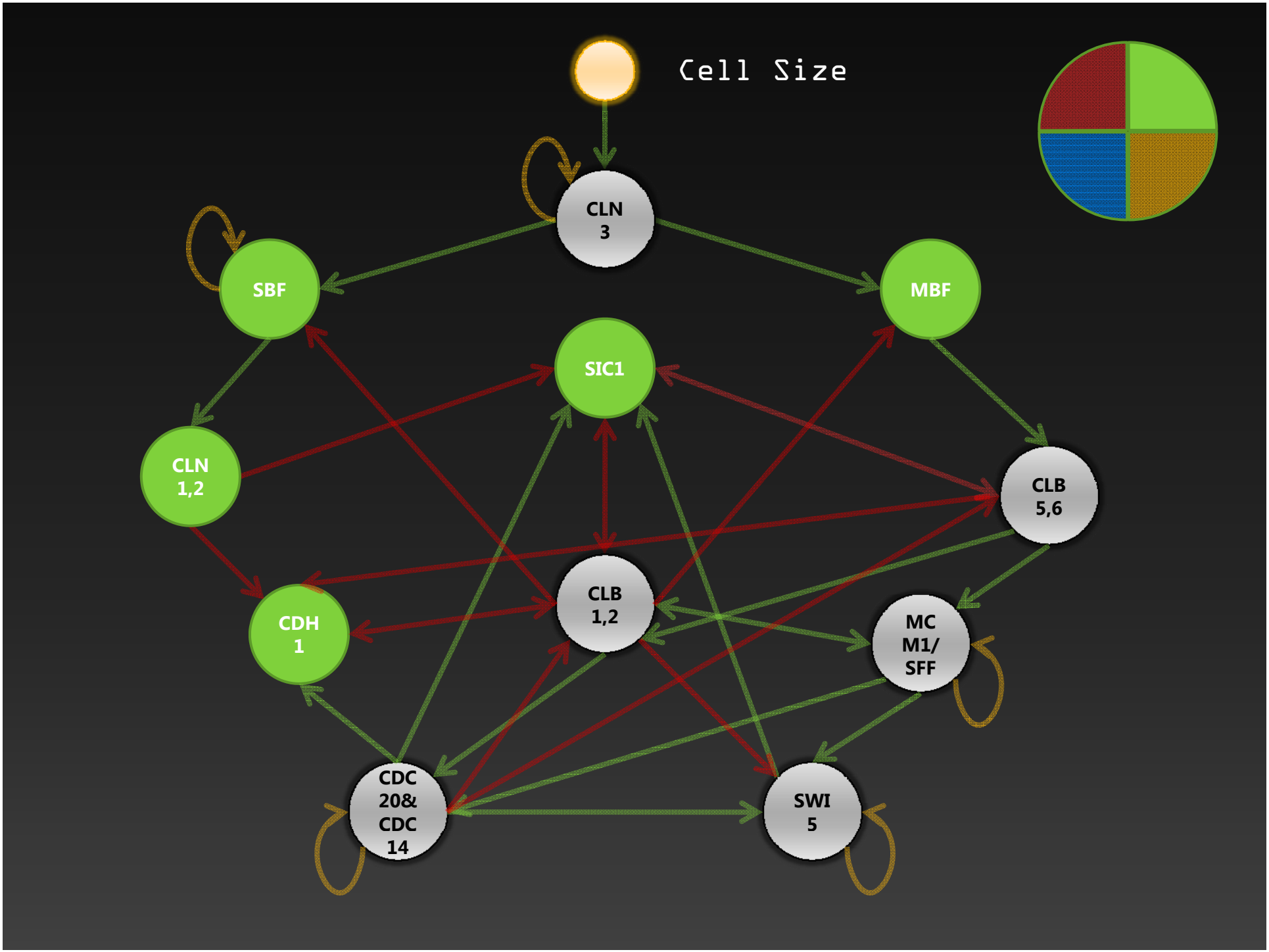
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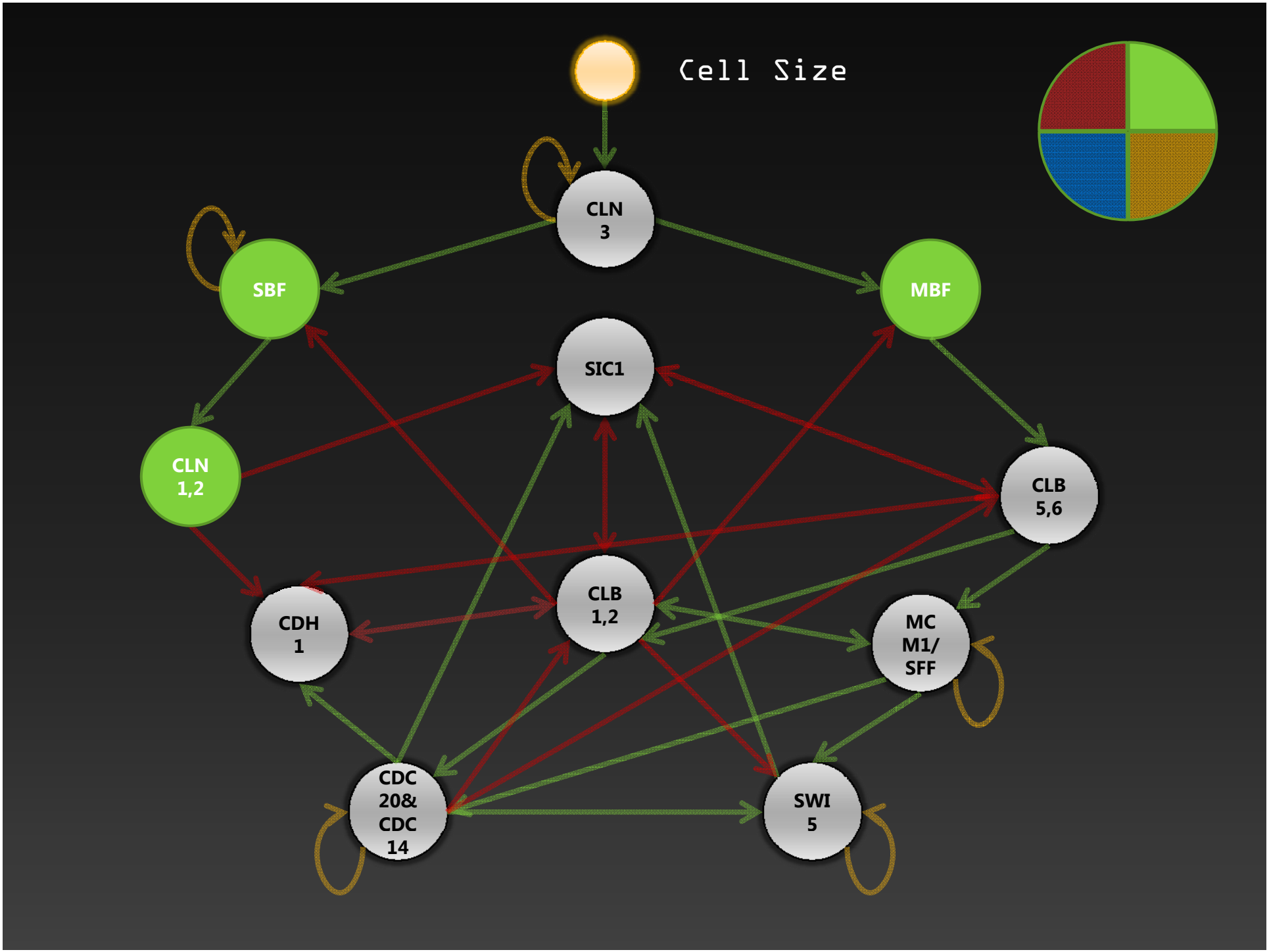
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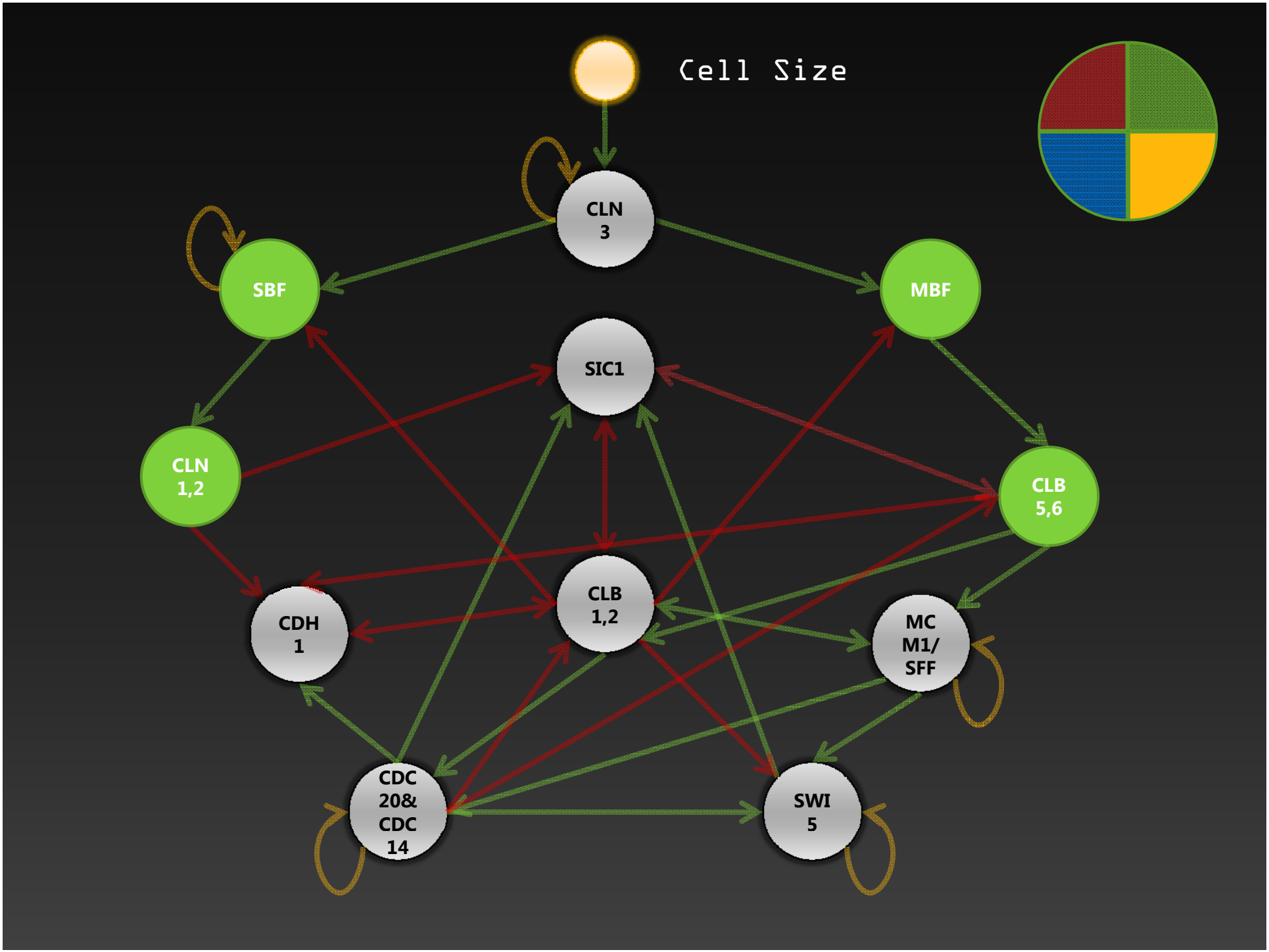
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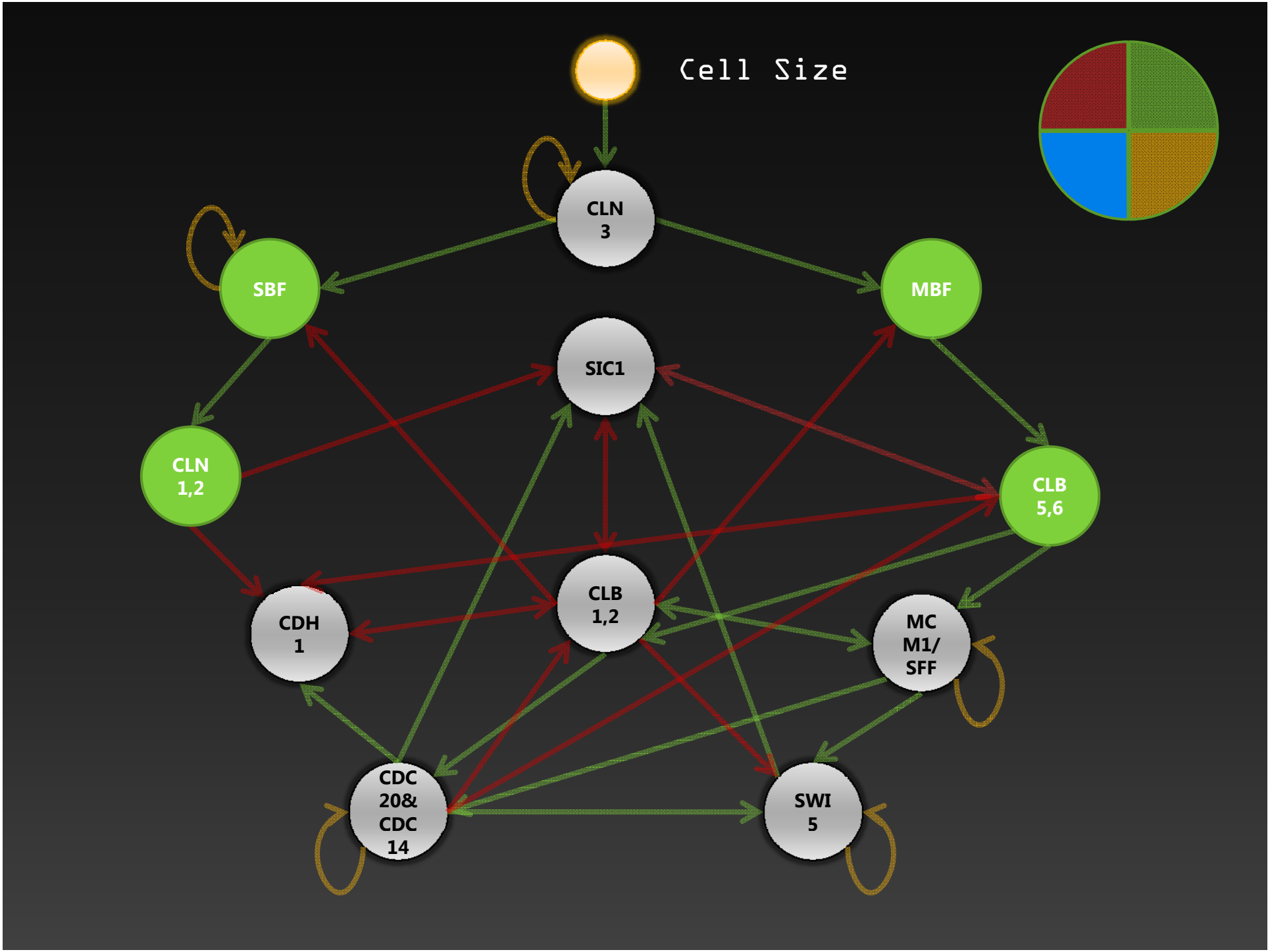
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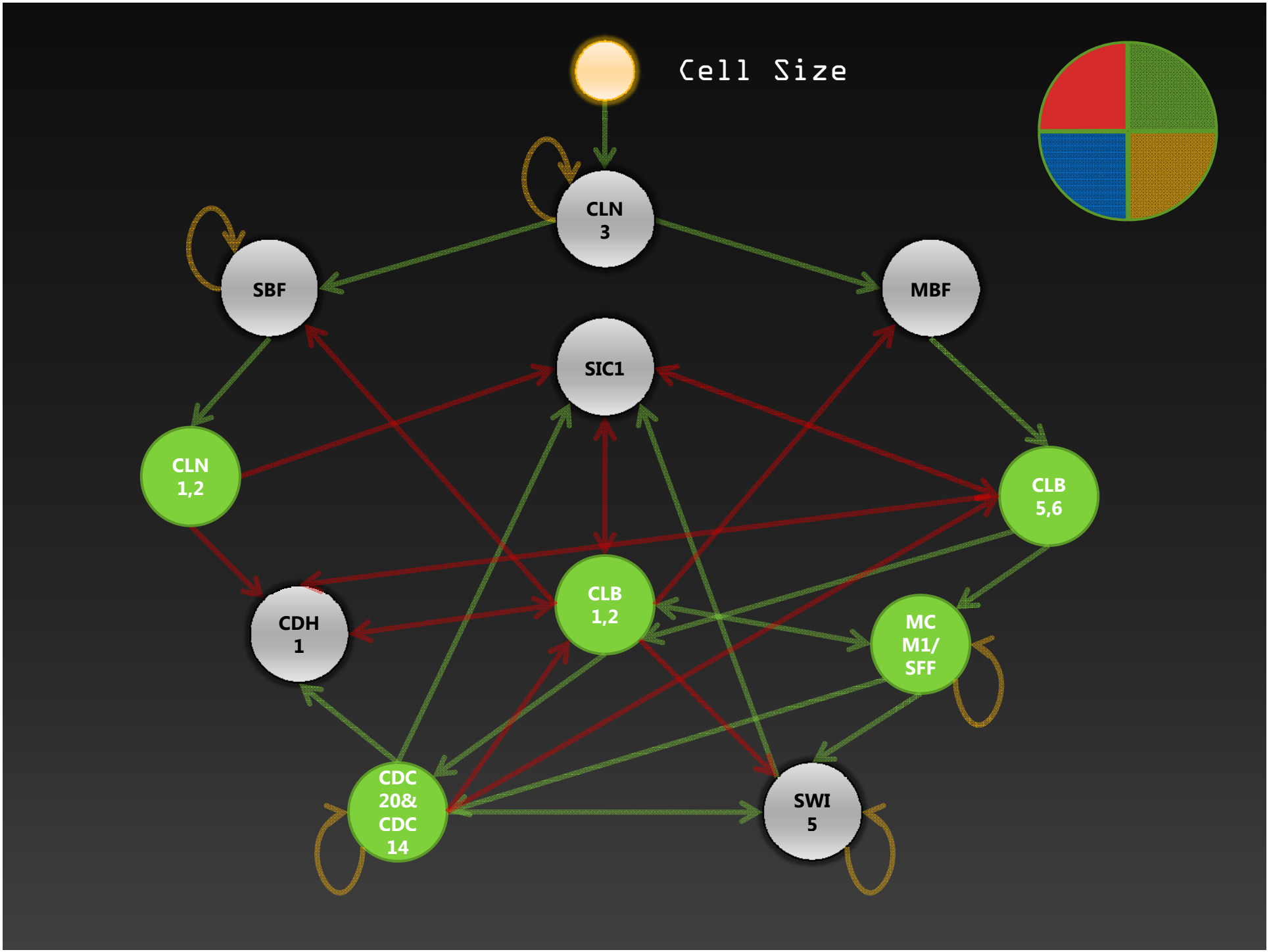
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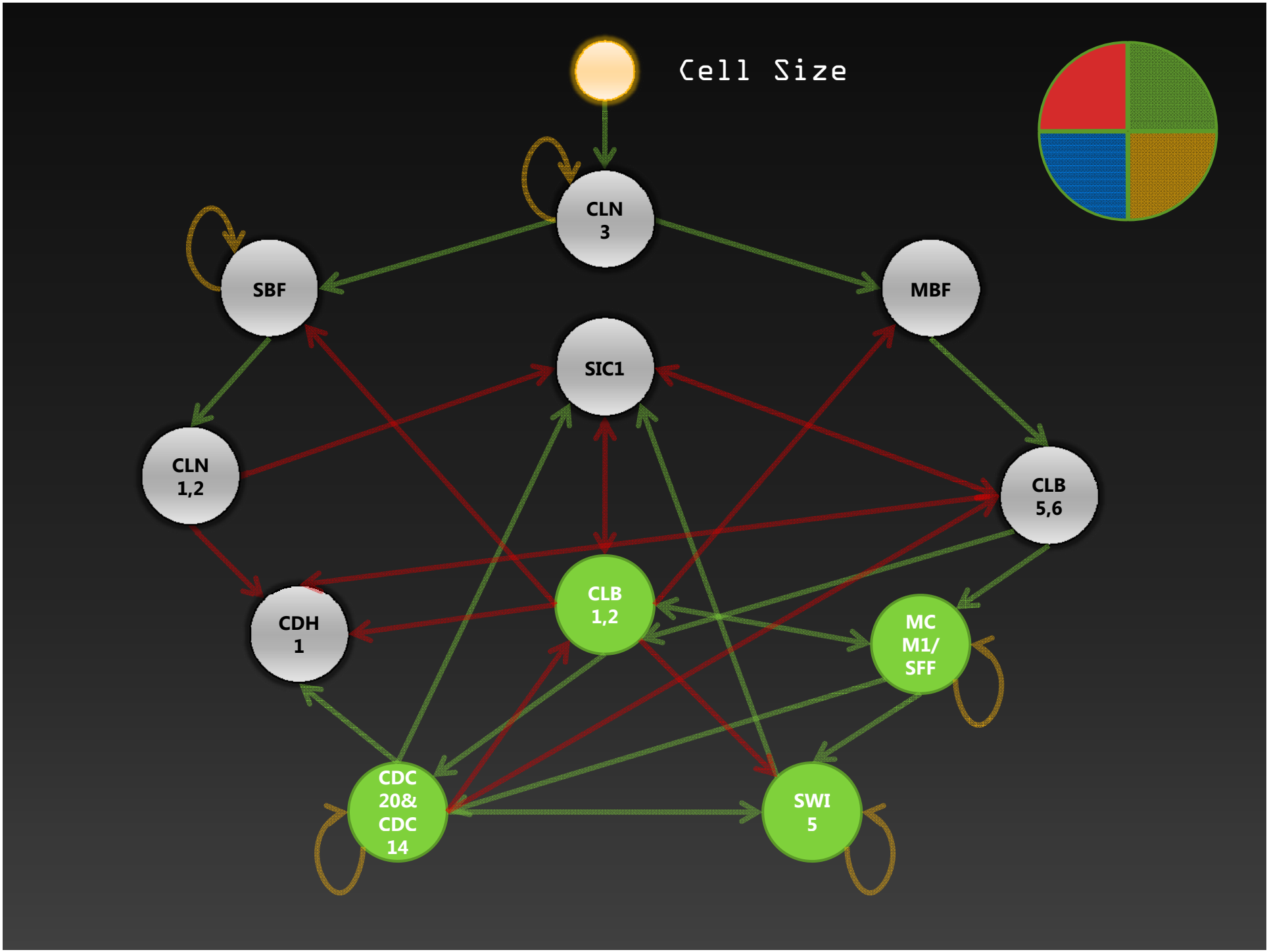
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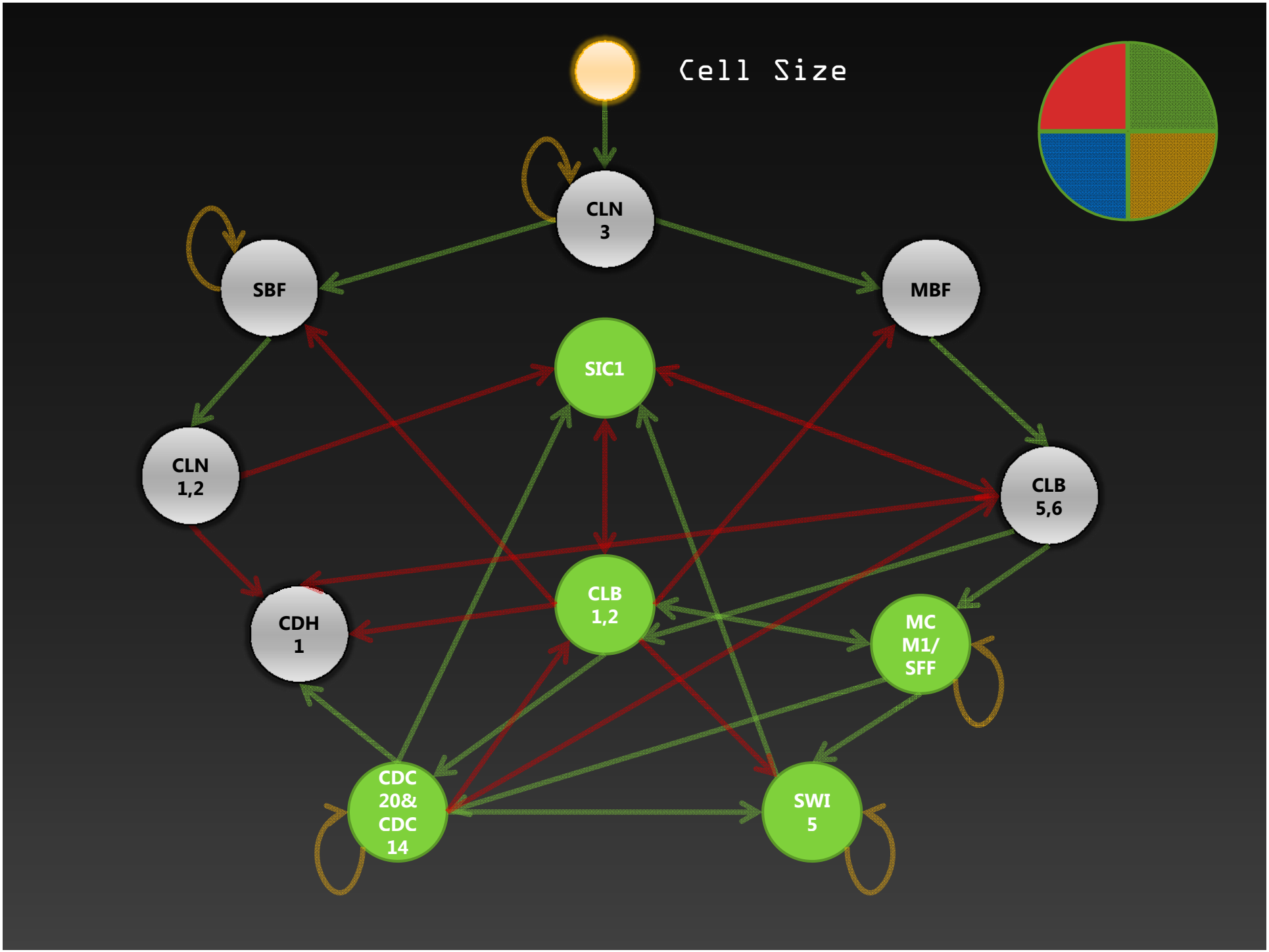
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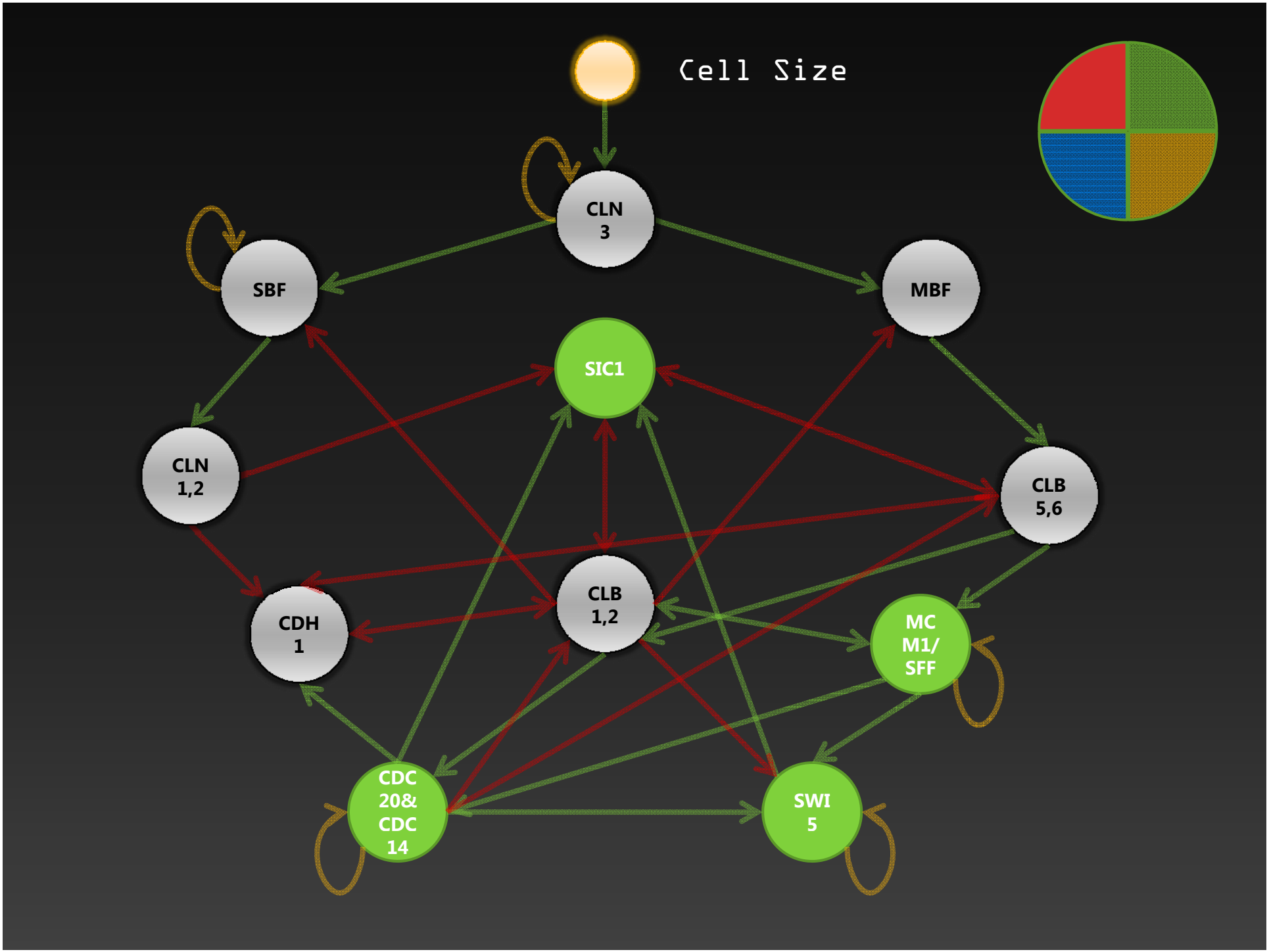
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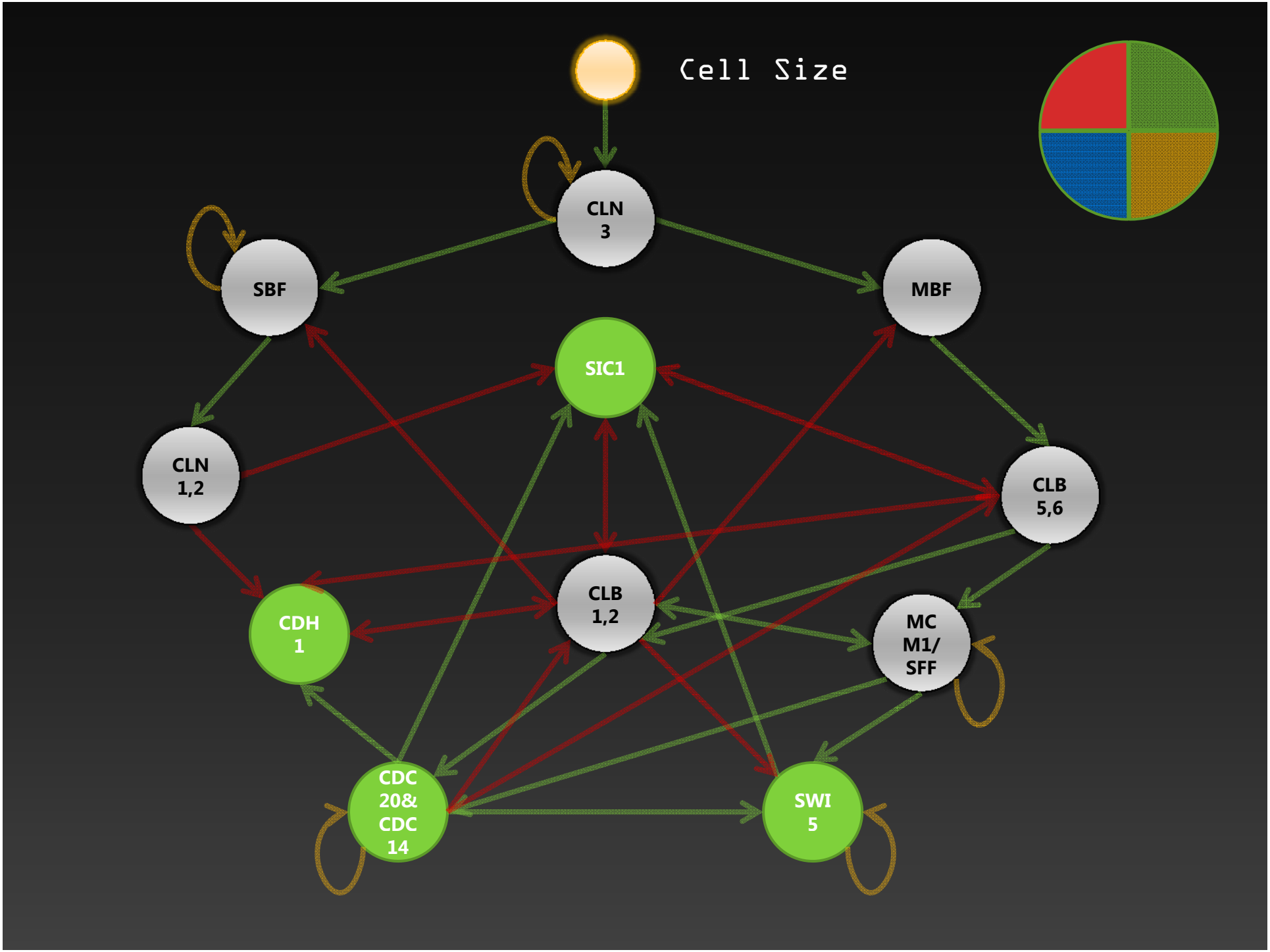
Cell Size
CLN 3
SBF
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SIC1
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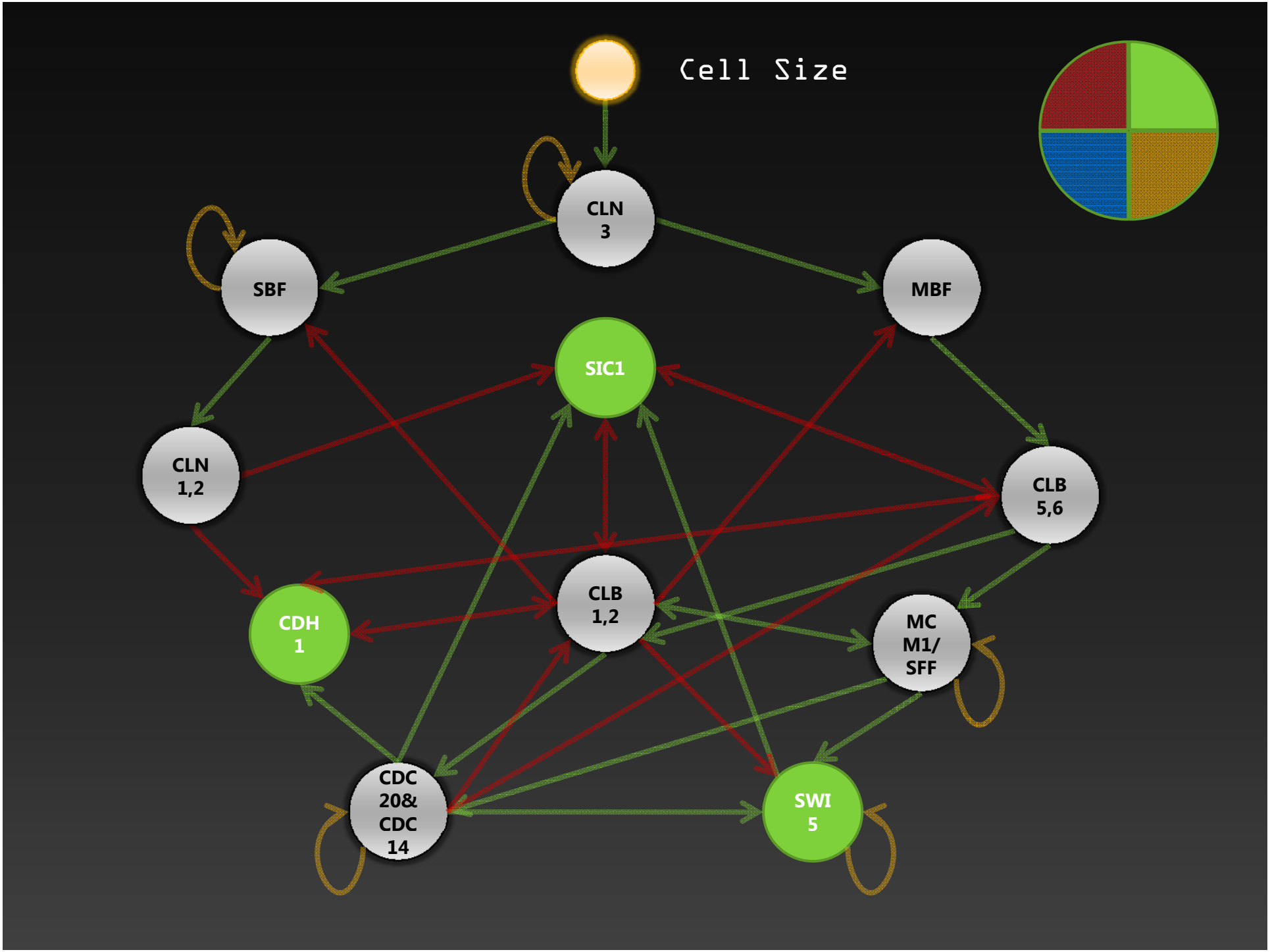
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CLN 3
SBF
MBF
SIC1
CLN 1,2
CLB 5,6
CDH 1
CLB 1,2
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CDC 20& CDC 14
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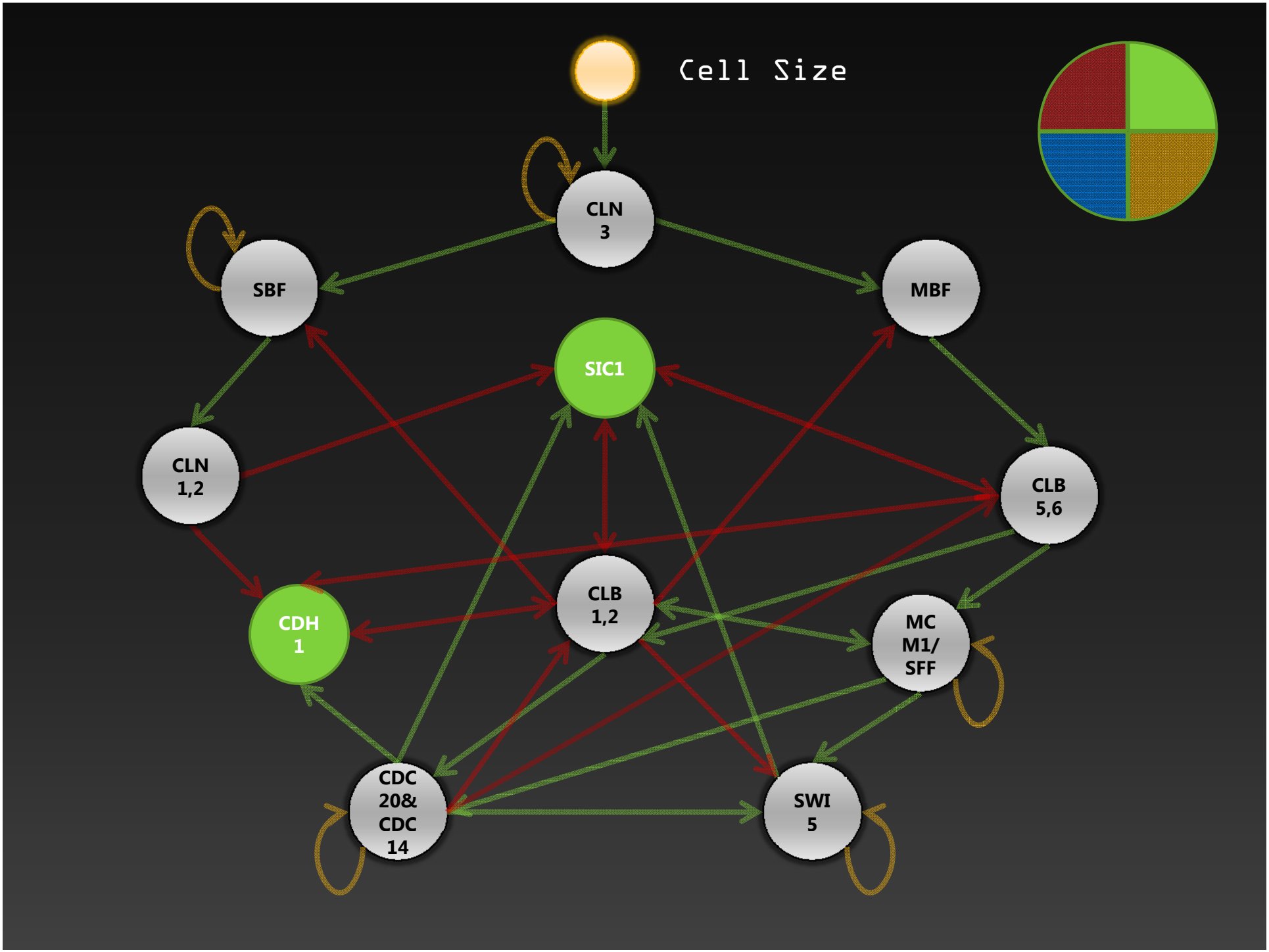
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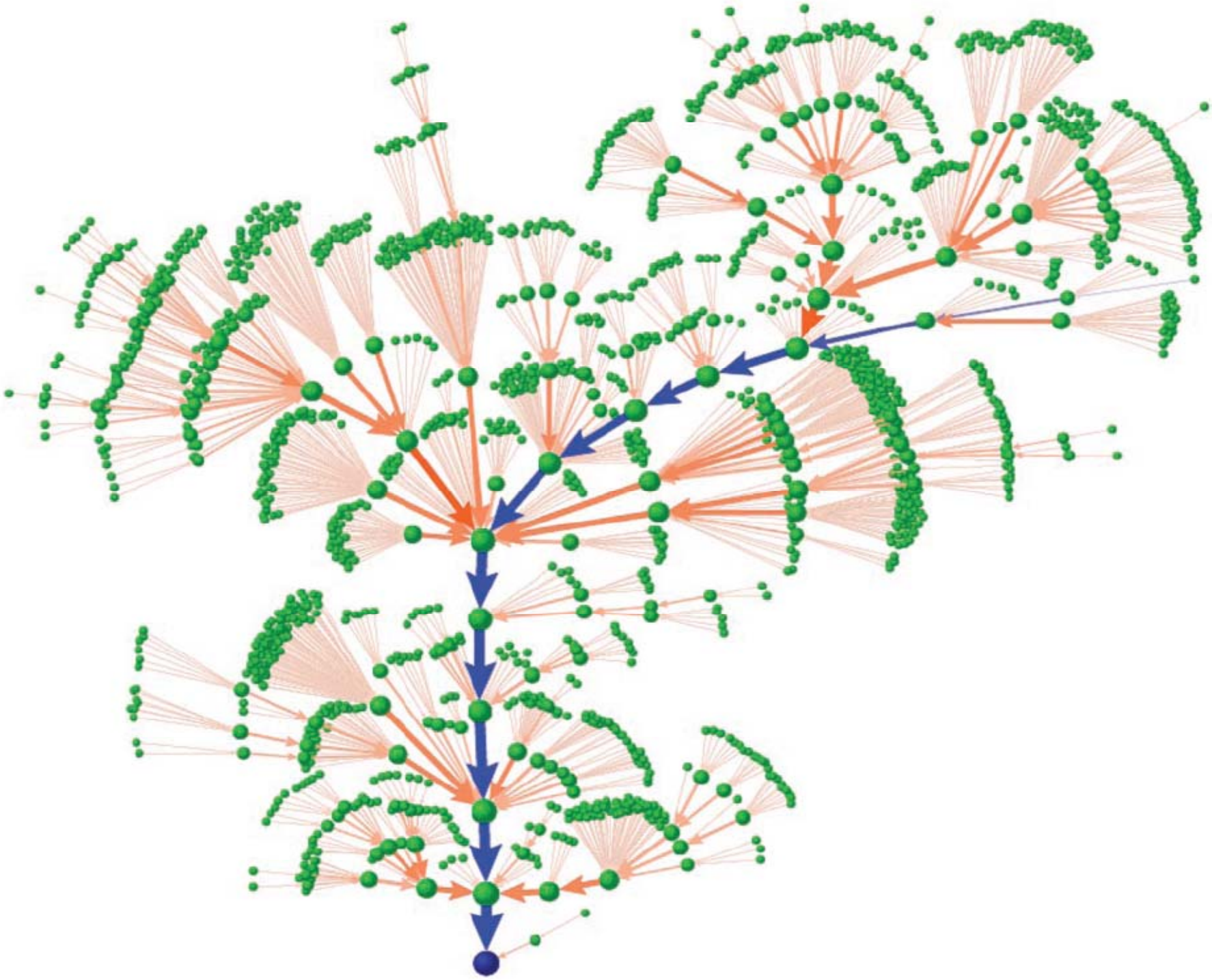
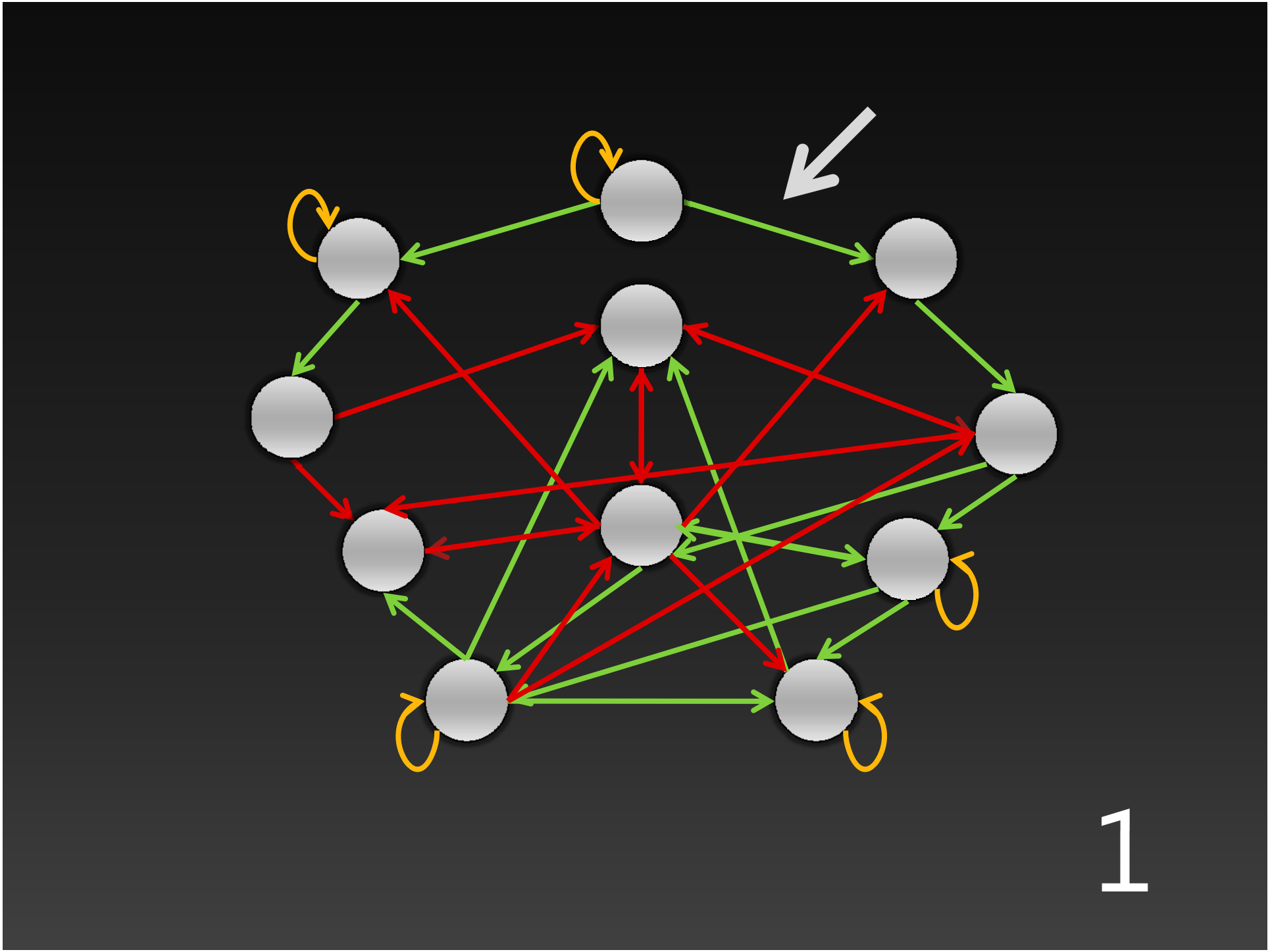
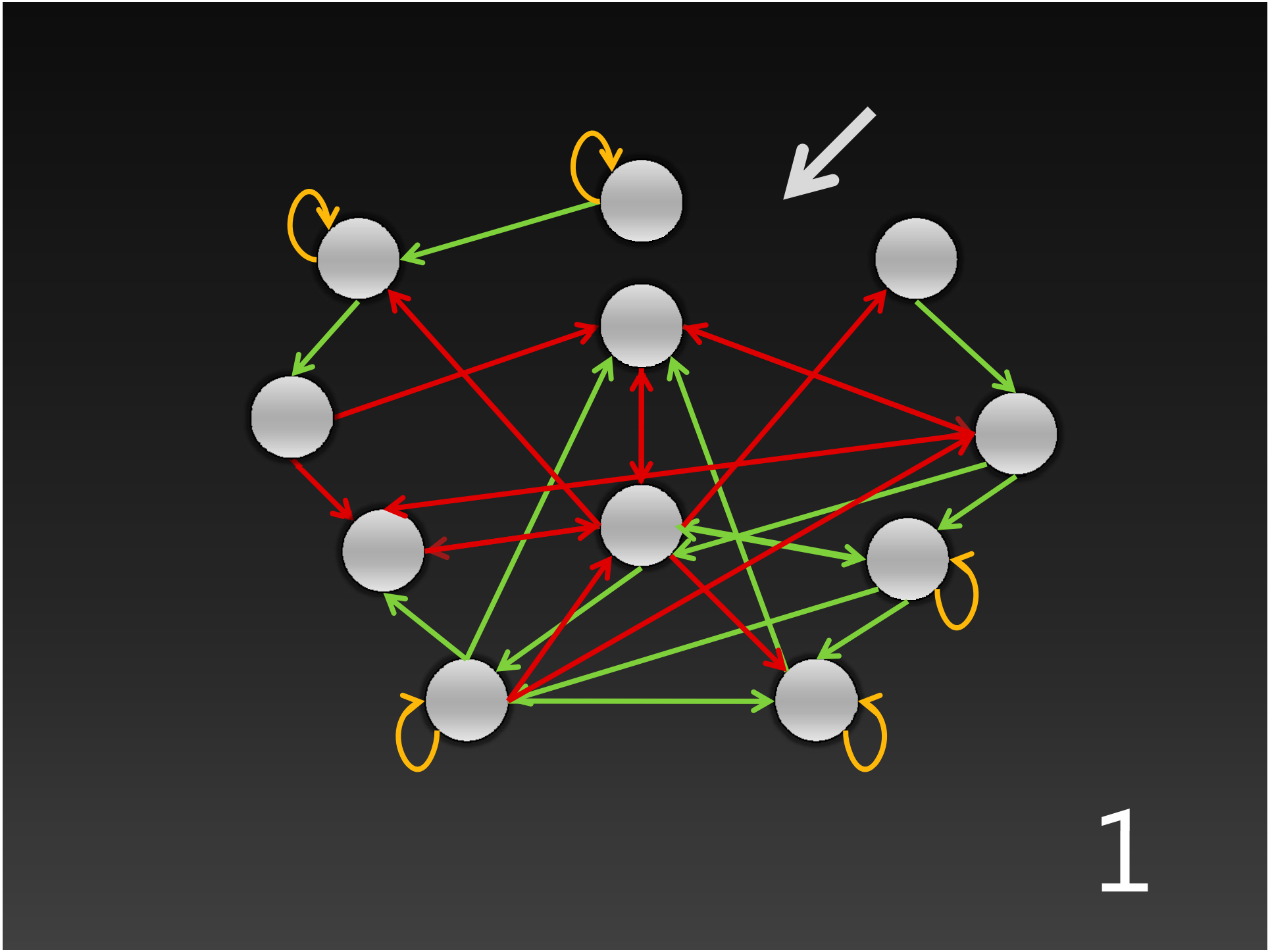
CLN 3
SBF
MBF
SIC1
CLN 1,2
CLB 5,6
CDH 1
CLB 1,2
MC M1/ SFF
CDC 20& CDC 14
SWI 5

Time	Cln3	MBF	SBF	Cln1,2	Clb5,6	Clb1,2	Mcm1	Cdc20	Swi5	Sic1	Cdh1	Phase
1	1	0	0	0	0	0	0	0	0	1	1	**„Excited“ G1**
2	0	1	1	0	0	0	0	0	0	1	1	**G_1**
3	0	1	1	1	0	0	0	0	0	1	1	**G_1**
4	0	1	1	1	0	0	0	0	0	0	0	**G_1**
5	0	1	1	1	1	0	0	0	0	0	0	**S**
6	0	1	1	1	1	1	1	0	0	0	0	**G_2**
7	0	0	0	1	1	1	1	1	0	0	0	**M**
8	0	0	0	0	0	1	1	1	1	0	0	**M**
9	0	0	0	0	0	1	1	1	1	1	0	**M**
10	0	0	0	0	0	0	1	1	1	1	0	**M**
11	0	0	0	0	0	0	0	1	1	1	1	**M**
12	0	0	0	0	0	0	0	0	1	1	1	**G_1**
13	0	0	0	0	0	0	0	0	0	1	1	**Stationary G_1**




1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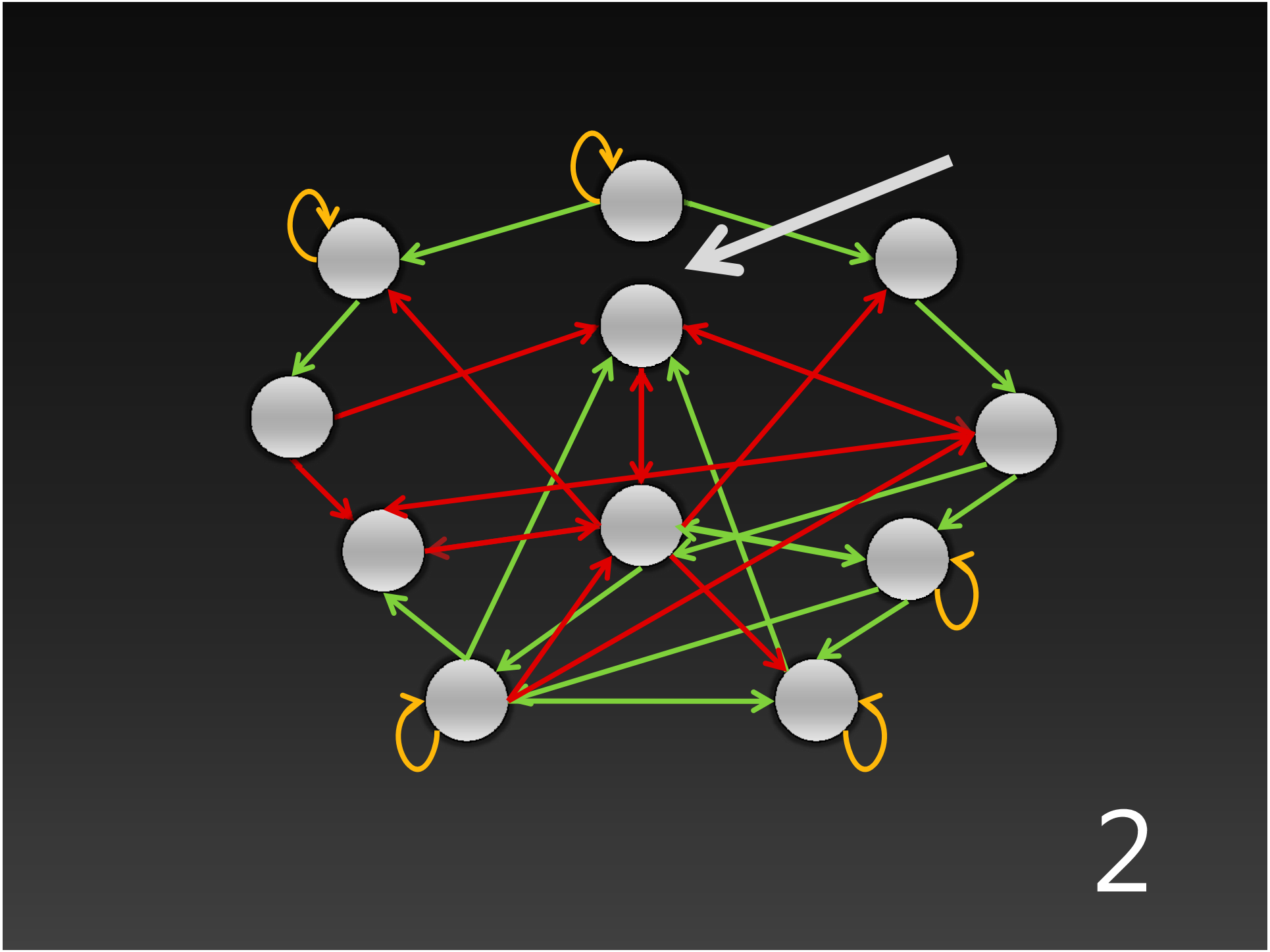
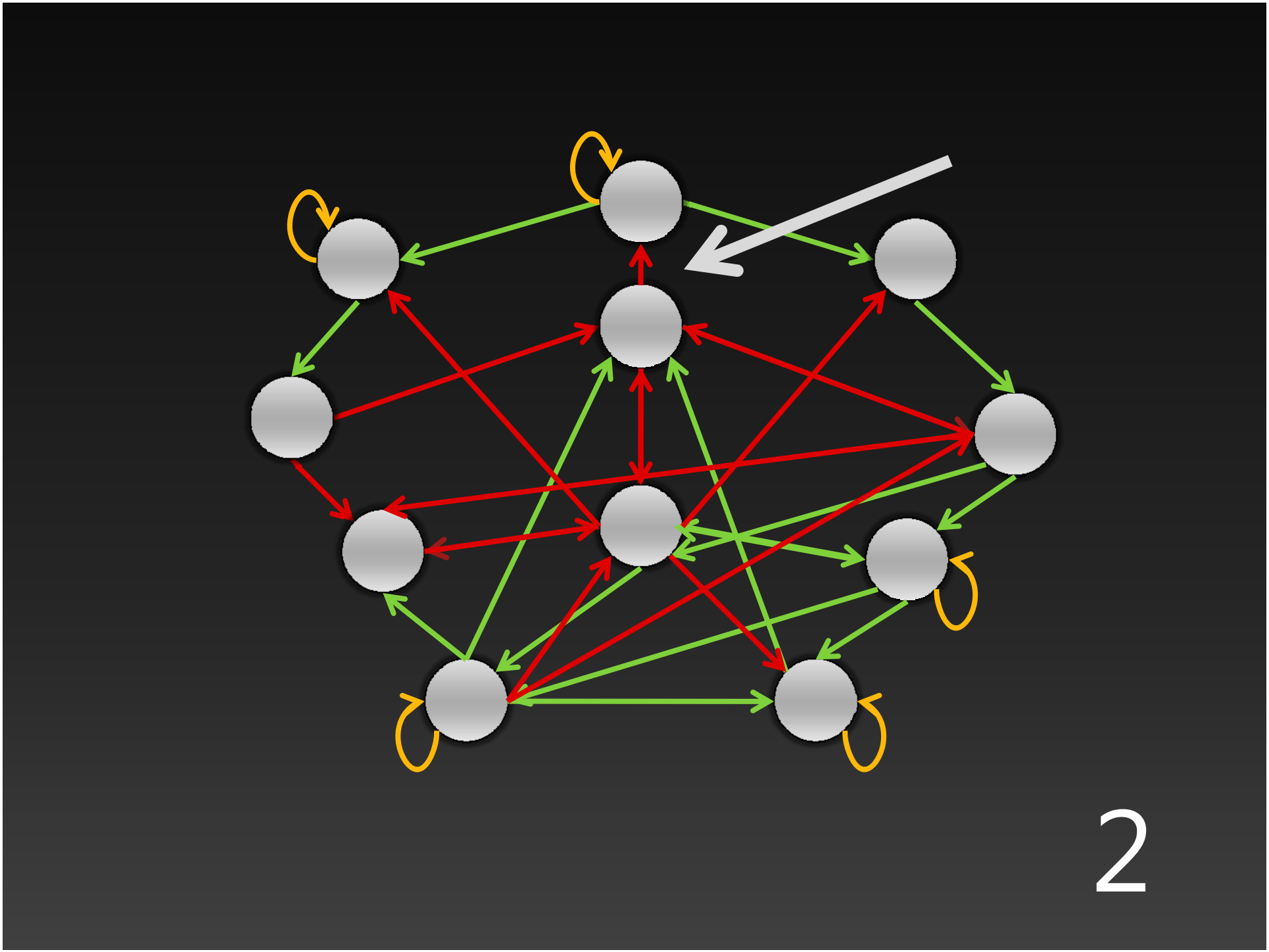
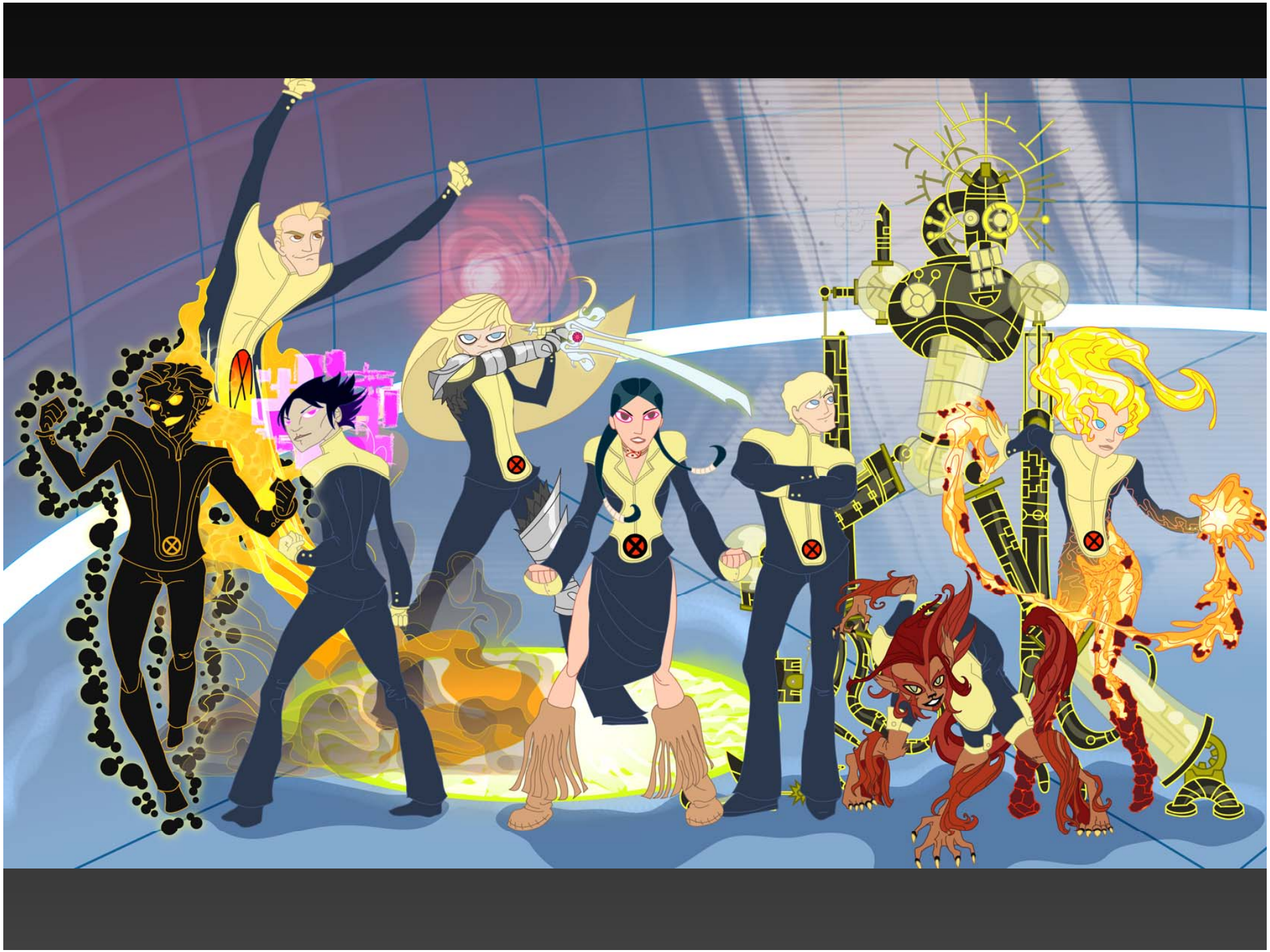
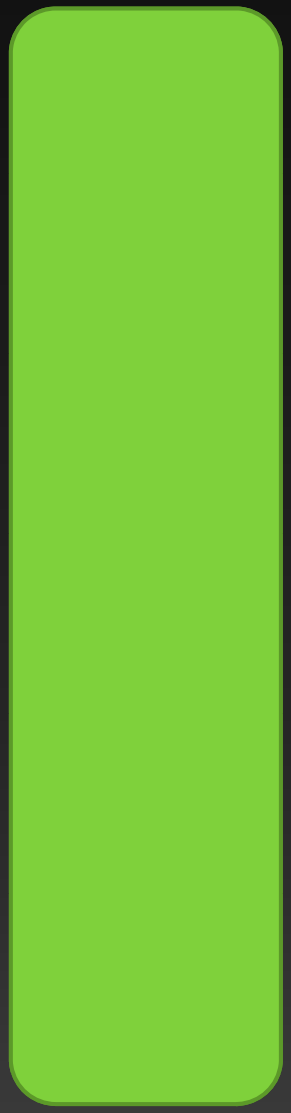




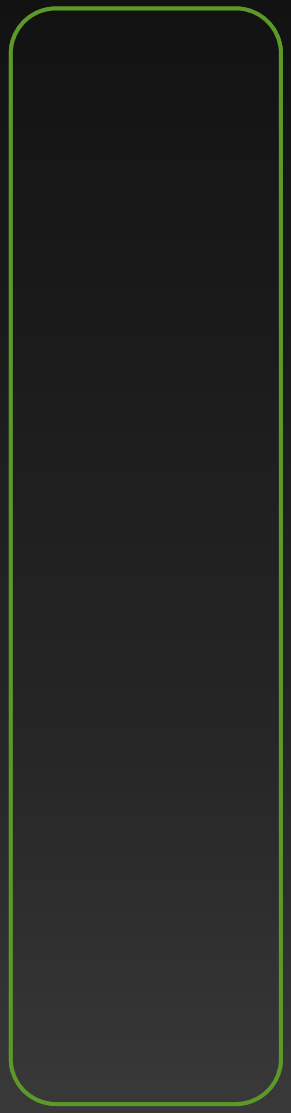


How many functional mutants of the yeast network exist?



$$311^2 \sim 5.39 * 10^{57}$$

539000000000000000000000000000000000000000000000000000



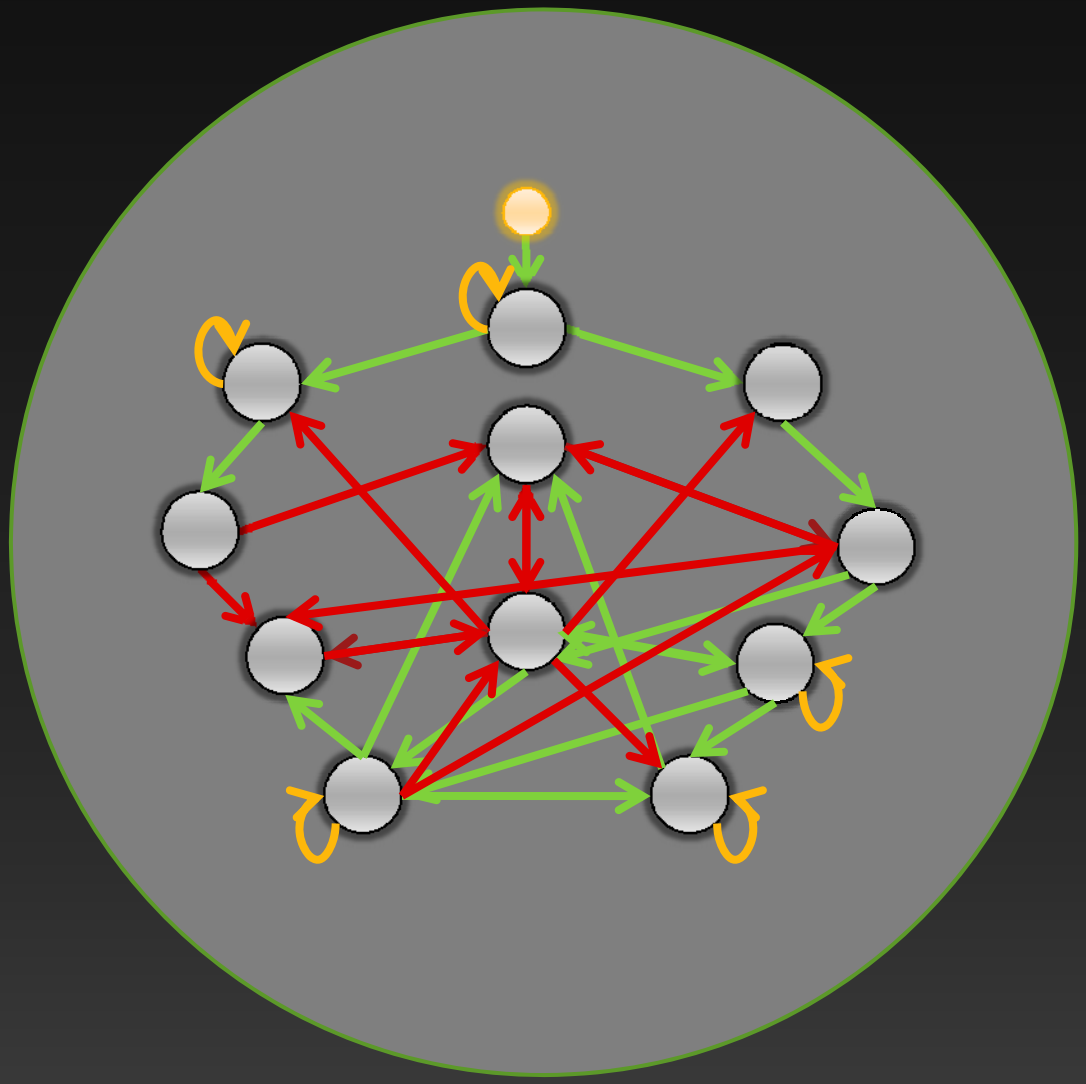
$$311^2 \sim 5.39 * 10^{57}$$

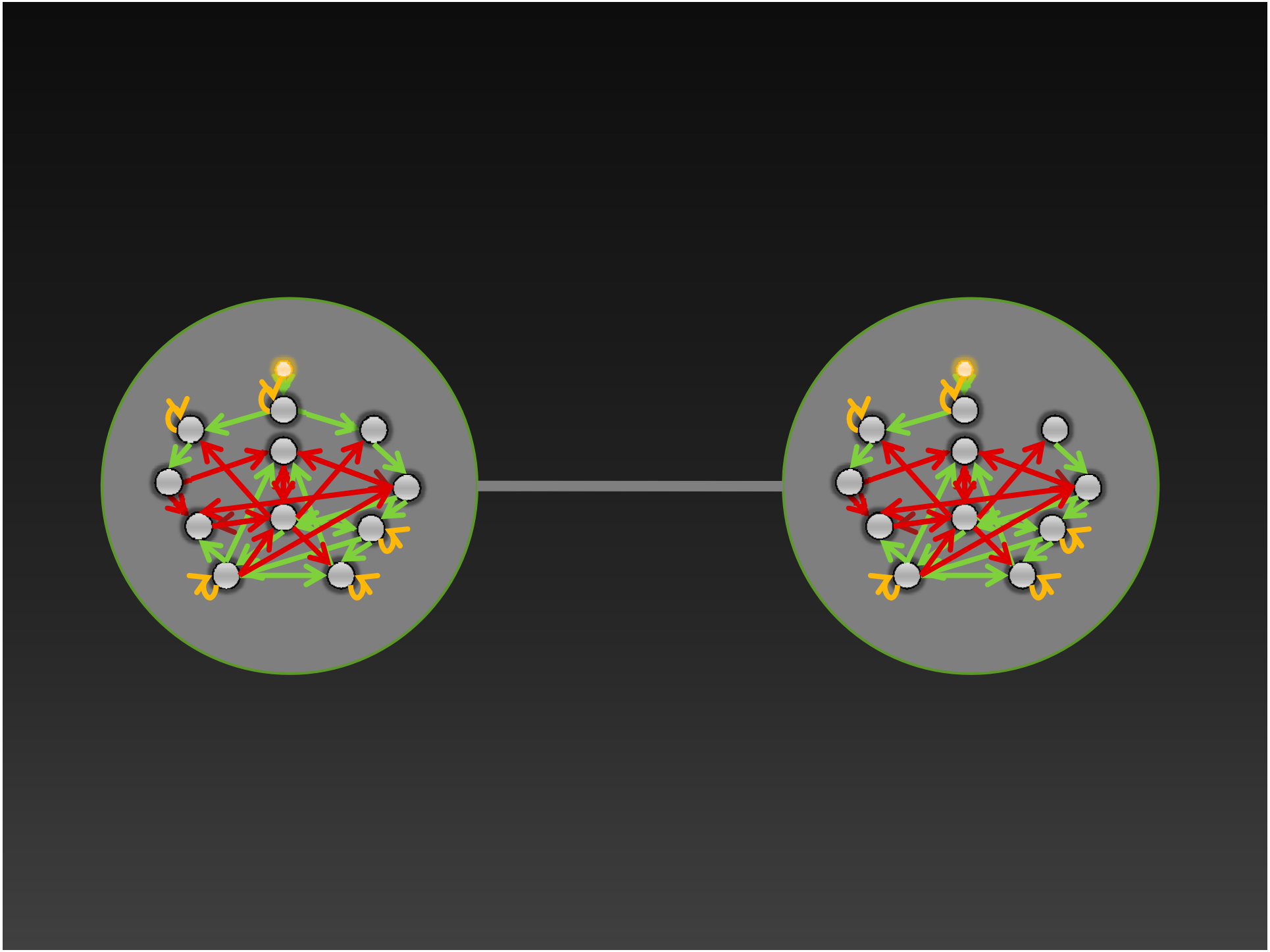
100000000000000000000000000000000000000000000000000

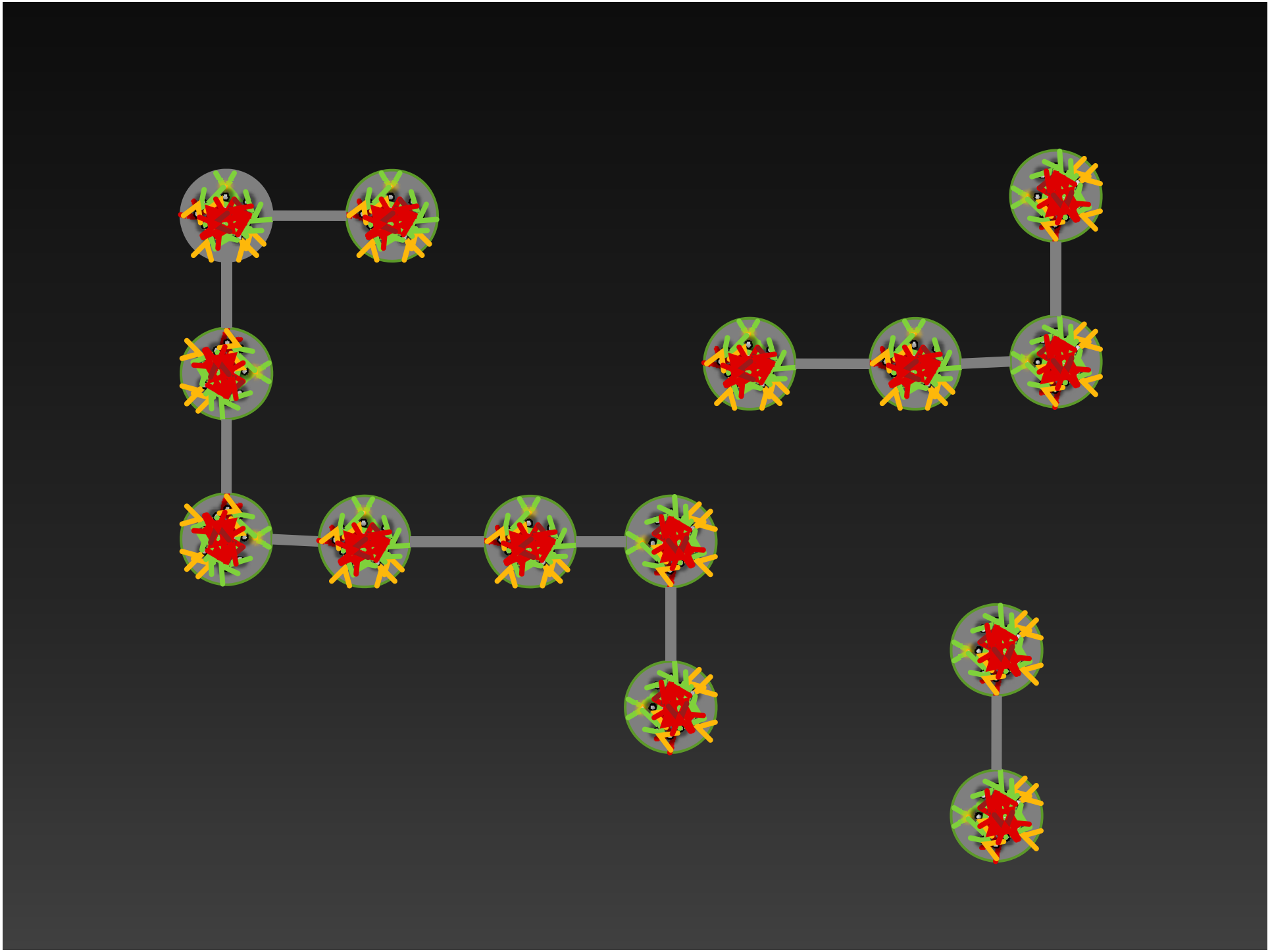
$$5.11 * 10^{34}$$

511000000000000000000000000000000

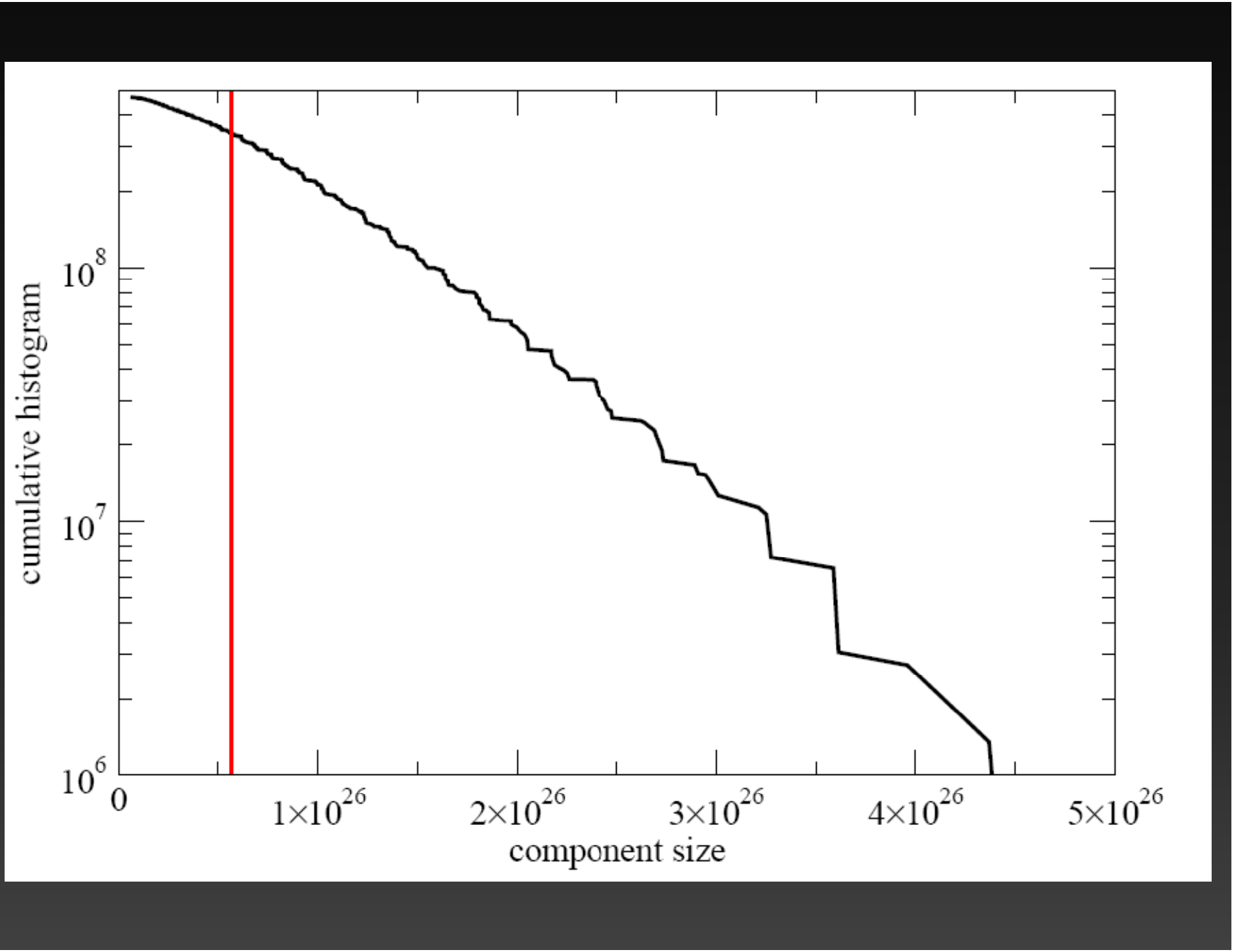
0.00000000000000000001 %



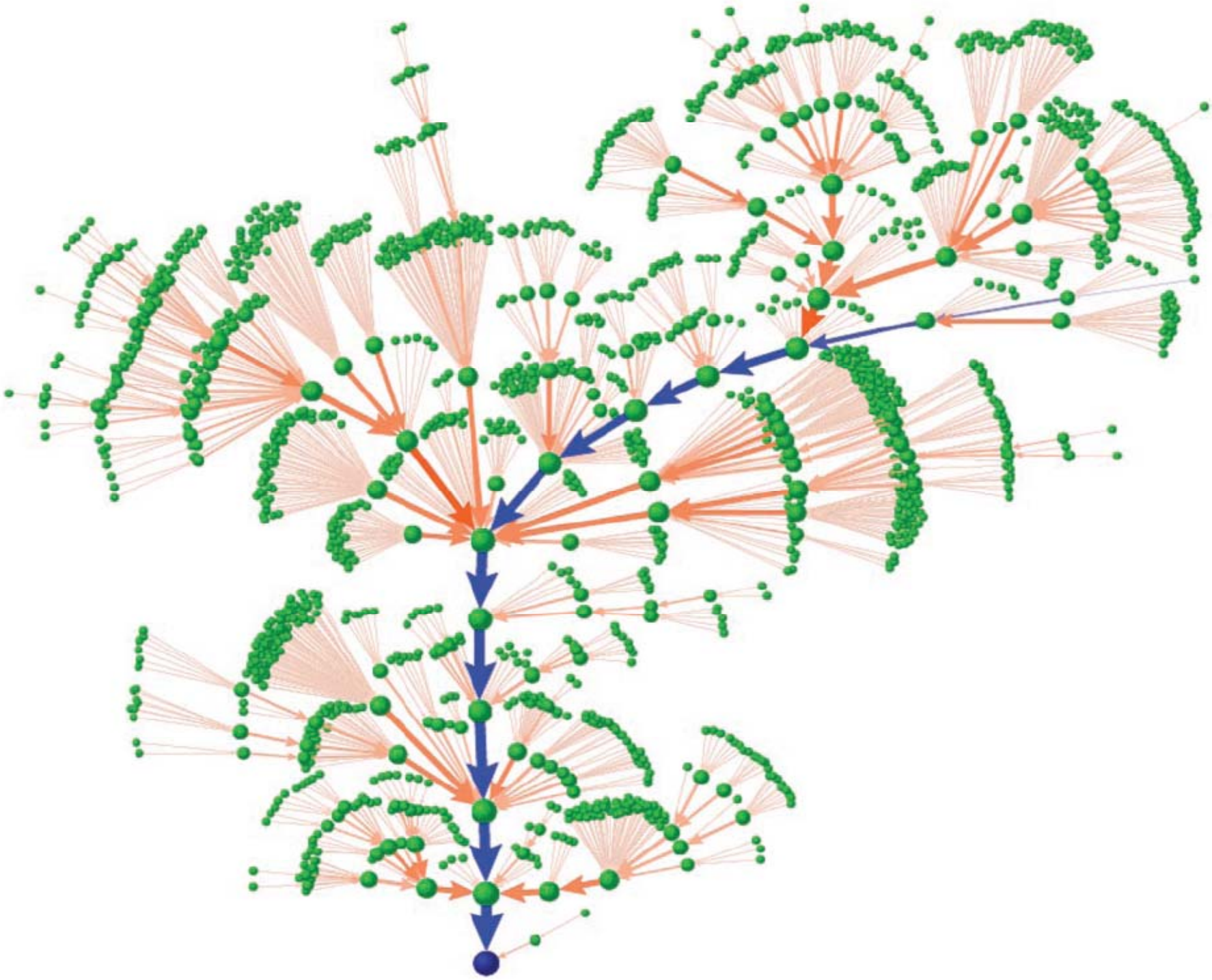


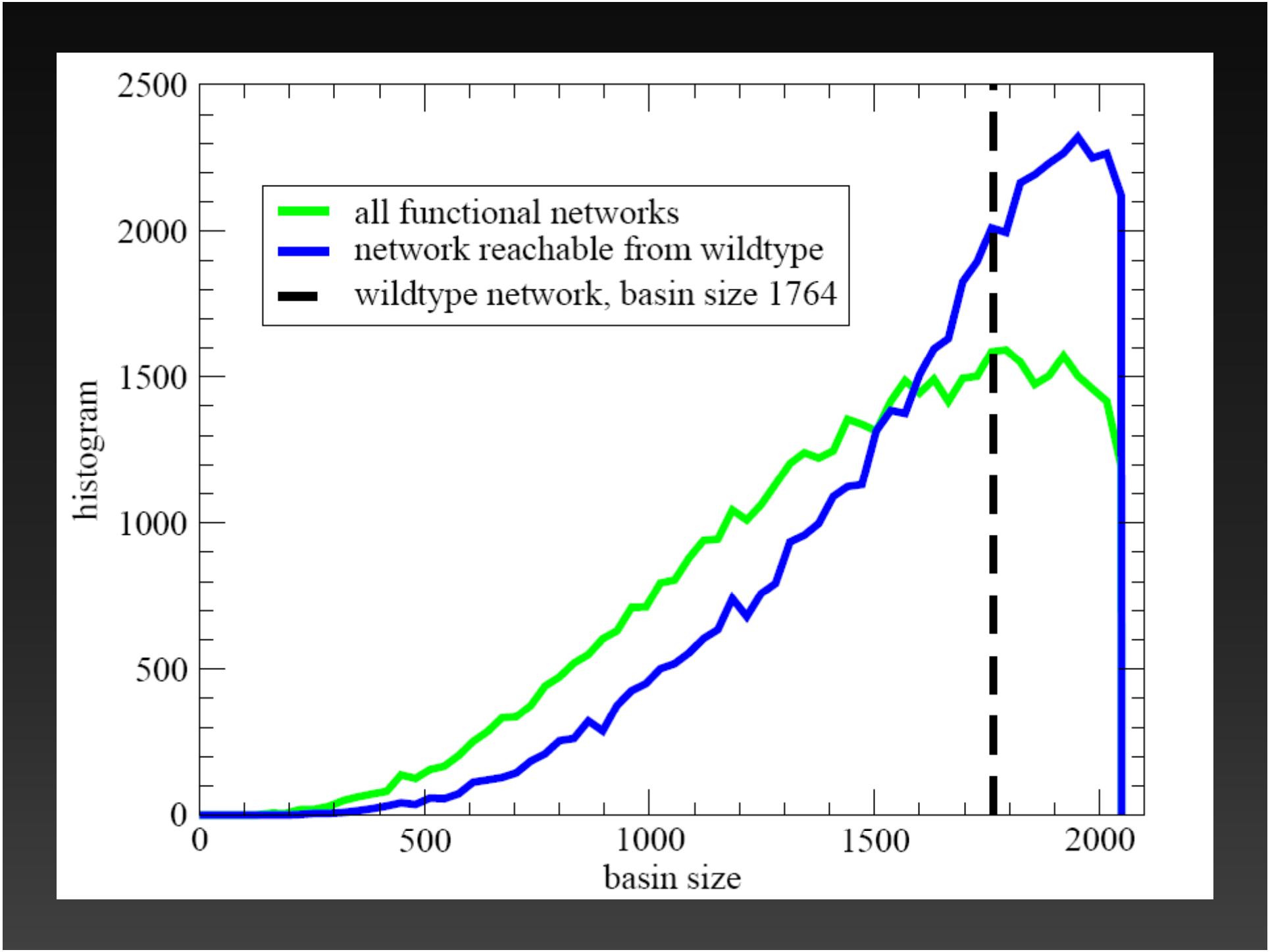


Is the wildtype network in the biggest connected component?

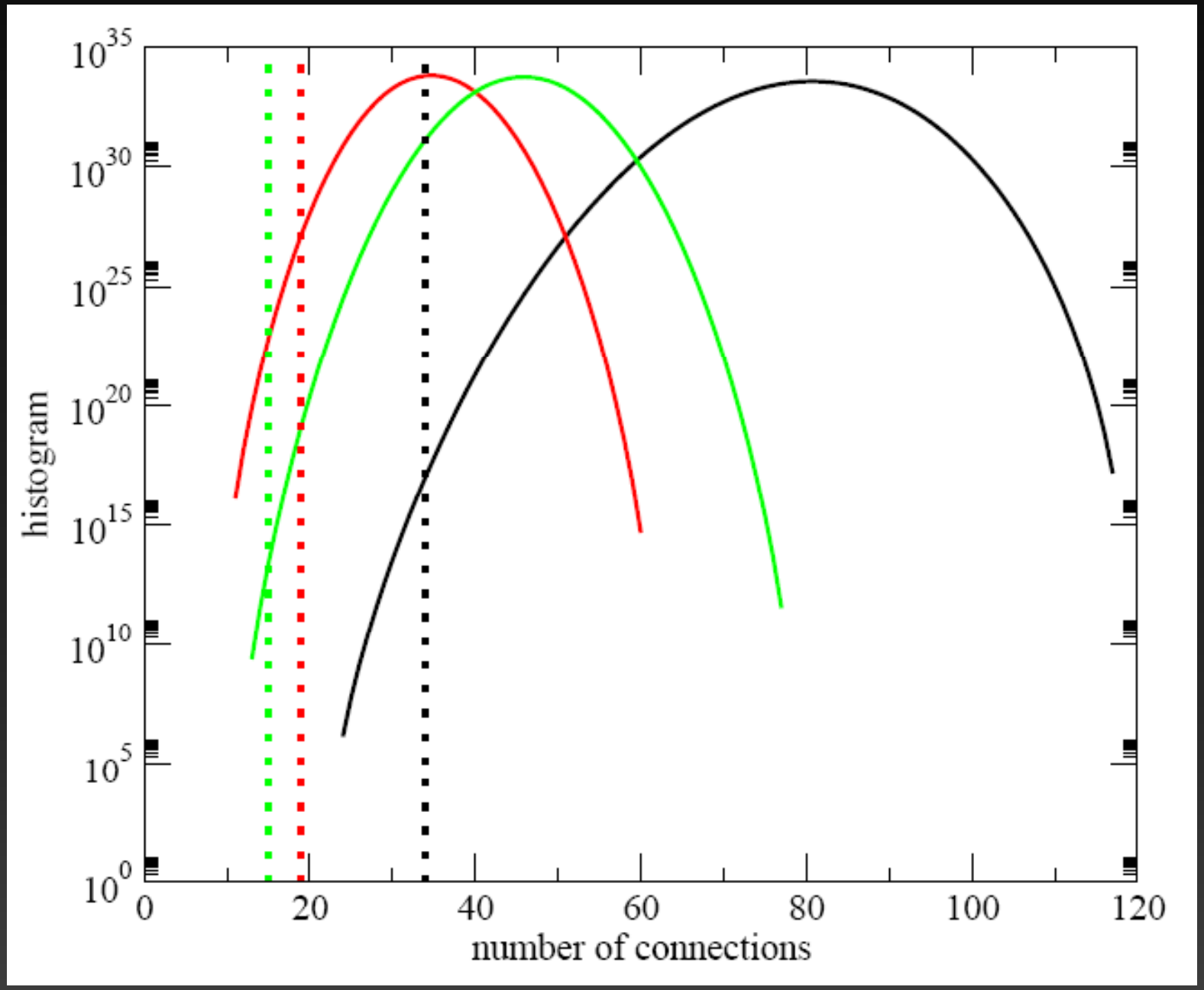

cumulative histogram
10^8
10^7
10^6
0
1×10^{26}
2×10^{26}
3×10^{26}
4×10^{26}
5×10^{26}
component size

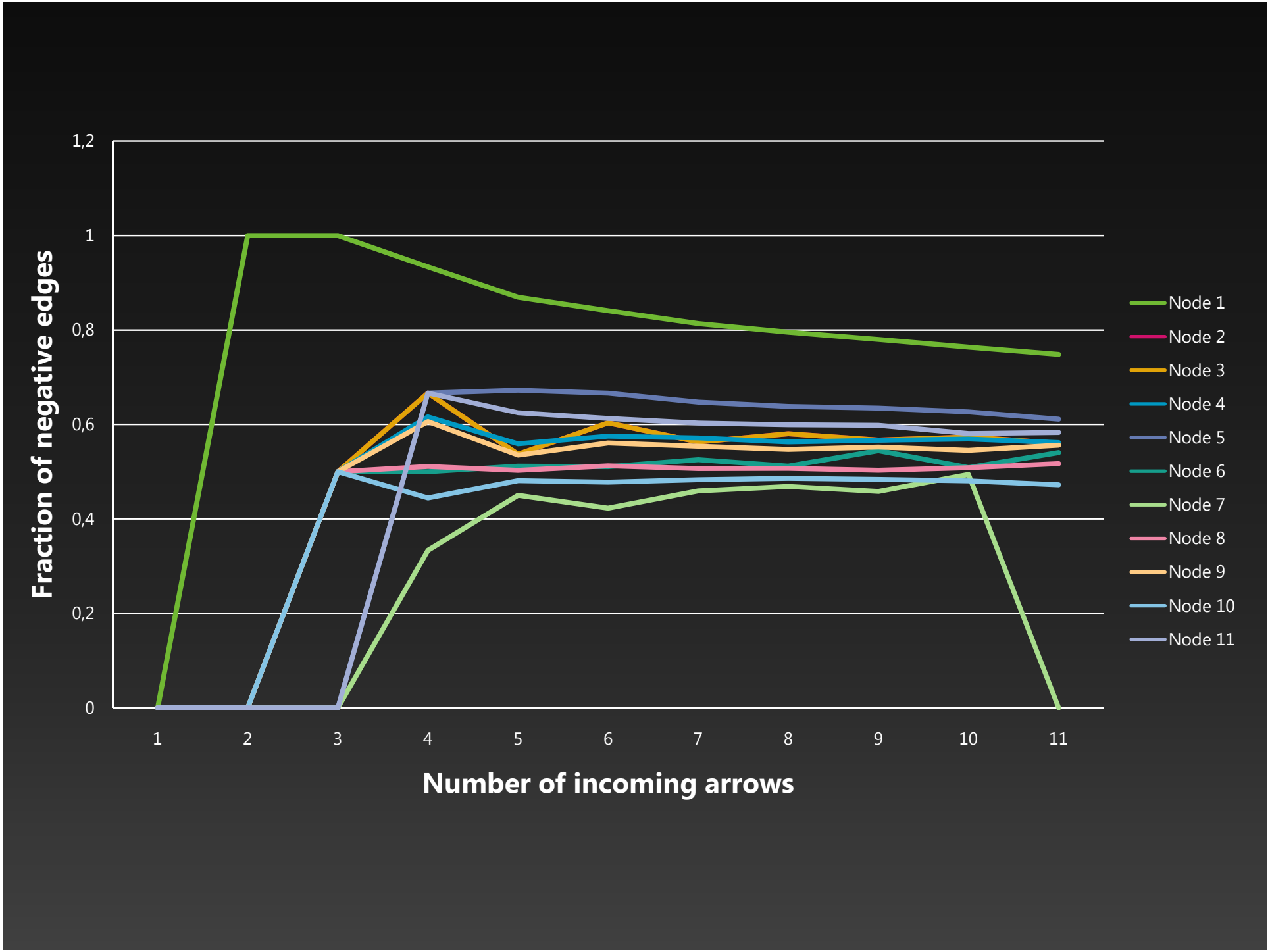
What about the attractor basin?




2500
2000
1500
1000
500
0
histogram
0
500
1000
1500
2000
basin size
all functional networks
network reachable from wildtype
wildtype network, basin size 1764

What about the distribution of edges?


histogram
number of connections
10^{35}
10^{30}
10^{25}
10^{20}
10^{15}
10^{10}
10^{5}
10^{0}
0
20
40
60
80
100
120


Fraction of negative edges
1,2
1
0,8
0,6
0,4
0,2
0
1
2
3
4
5
6
7
8
9
10
11
Number of incoming arrows
Node 1
Node 2
Node 3
Node 4
Node 5
Node 6
Node 7
Node 8
Node 9
Node 10
Node 11

Outlook

bigger network size

study further yeast species

other robustness measures

Nothing clarifies ideas in one's mind so much as explaining them to other people.

Vernon Booth

Questions?