Supporting Text

We present here the complete description of the networks shown in Fig. 3*C* and Fig. 5 as well as supplementary examples of networks that were created by our evolutionary procedure. Results of stochastic simulations of the switches of Fig. 3 *A* and *B* are also shown.

Examples of switches. As stated , the algorithm produced several bistable switches based on reciprocal inhibition. They provide working implementations of the idea sketched in Fig. 1 . Two examples are shown in Figs. 6 and 7.

The switches of Fig. 3 *A* and *B* were obtained with a variety of imposed conditions. Figs. 8 and 9 provide kinetic constants obtained for imposed high concentrations of several hundred proteins. Several switches fundamentally based on the principles of Fig. 3 *A* and *B* but with more complex interactions were also produced. Fig. 10 presents one such "complicated" version.

Fig. 11 is a switch with three genes, but gene *b* on which selection was based is simply a "reporter" gene of an actual two-gene switch between *a* and *c*. The two-gene switch is based on the same mechanism as that of Fig. 3*B* .

Finally, Fig. 12 gives the complete description of the switch shown as Fig. 3*C*, which is really based on the interaction of three genes.

Simulations with stochastic dynamics. To gain insight into the noise resistance of the selected circuits, we simulated the switch networks of Fig. 3 *A* and *B* (also displayed in Figs. 8 and 9) with a stochastic algorithm (1). For parameters corresponding to high concentration species with several hundred proteins (kinetic constants of Fig. 8), concentration fluctuations are clearly visible but the networks' switch function is not notably degraded, as shown in Fig. 13. For parameters corresponding to high concentrations species with only a few 10s of proteins, the concentration fluctuations are stronger, but

the networks still clearly perform as switches (Fig. 14). In these strong-fluctuation conditions, the switch of Fig. 3*A* displays spontaneous jumps between the two stable states with a typical jump time of several hours. Such an event is shown in Fig. 14 *A* after $\approx$ 400 min of free evolution. The switch of Fig.3*B* displays much rarer spontaneous events in the same conditions (Fig. 14*B*). This difference does not appear to be an intrinsic feature of the two networks' topologies because, for other kinetic constants, the noise resistance of the switch in Fig. 3*A* is quite comparable to that of switch in Fig. 3*B*.

Examples of oscillators. We provide here three examples of oscillating genetic circuits created by our evolutionary procedure. The first one (Fig. 15) is the complete description of the circuit of Fig. 5 . Fig. 16 is another example that also has similarities to circadian oscillators. Fig. 17 , on the contrary, is a biochemical oscillator with oscillations entirely at the protein level and no transcriptional regulation.

1. Gillepsie, D.T. (1977) *J. Phys. Chem.* **81**, 2340-2361.

Reactions			constants
a	$\rightarrow$	a+A	0.092
A	$\rightarrow$	Nothing	0.021
b	$\rightarrow$	b+B	1.5
B	$\rightarrow$	Nothing	0.11
a+A	$\rightarrow$	a:A	0.50
a:A	$\rightarrow$	a+A	0.56
a:A	$\rightarrow$	a:A+A	0.38
a+B	$\rightarrow$	a:B	0.59
a:B	$\rightarrow$	a+B	0.082
a:B	$\rightarrow$	a:B+A	0.0085
b+B	$\rightarrow$	b:B	0.47
b:B	$\rightarrow$	b+B	0.27
b:B	$\rightarrow$	b:B+B	3.0
b:B+A	$\rightarrow$	b:B:A	0.64
b:B:A	$\rightarrow$	b:B+A	0.67
b:B:A	$\rightarrow$	b:B:A+B	0.88
b:B:A+A	$\rightarrow$	b:B:A:A	0.38
b:B:A:A	$\rightarrow$	b:B:A+A	0.13
b:B:A:A	$\rightarrow$	b:B:A:A+B	0.014

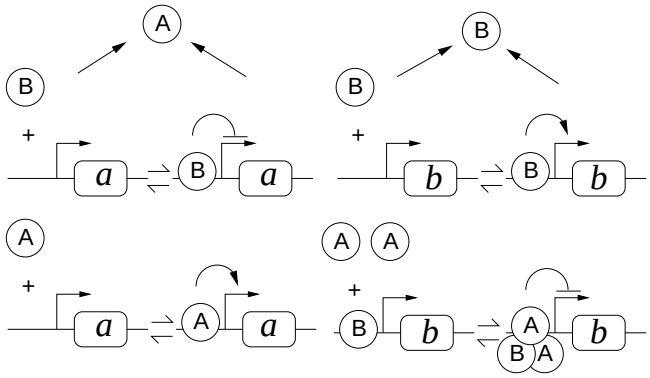

Fig. 6. One example of a bistable switch with reciprocal inhibition.

Reactions	Constants
$a \rightarrow a$+A	0.13
A $\rightarrow$Nothing	0.030
$b \rightarrow b$+B	0.16
B $\rightarrow$Nothing	0.080
a+A$\rightarrow$ a:A	1.4
a:A $\rightarrow$ a+A	0.65
a:A $\rightarrow$ a:A+A	0.70
a+B$\rightarrow$ a:B	0.89
a:B $\rightarrow$ a+B	0.076
a:B $\rightarrow$ a:B+A	0.033
b+B$\rightarrow$ b:B	0.19
b:B $\rightarrow$ b+B	0.30
b:B $\rightarrow$ b:B+B	2.6
b+A$\rightarrow$ b:A	0.95
b:A $\rightarrow$ b+A	0.26
b:A $\rightarrow$ b:A+B	0.0075

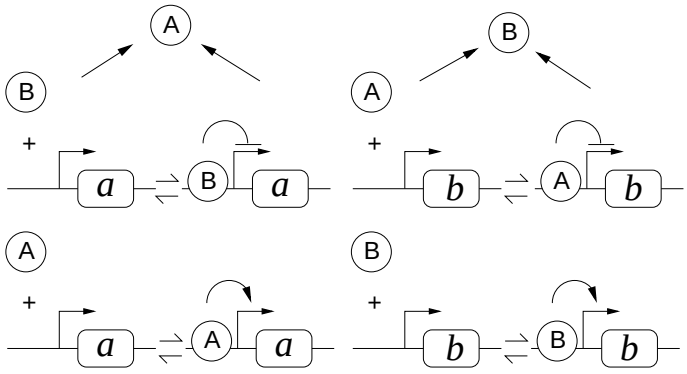

Fig. 7. Second example of a bistable switch with reciprocal inhibition.

Reactions	Constants
$a \rightarrow a$+A	0.52
A $\rightarrow$Nothing	0.00019
$b \rightarrow b$+B	0.79
B $\rightarrow$Nothing	0.0030
A+B$\rightarrow$ A:B	0.053
A:B $\rightarrow$Nothing	0.15
b+A$\rightarrow$ b:A	0.22
b:A $\rightarrow$ b+A	0.31
b:A $\rightarrow$ b:A+B	0.43

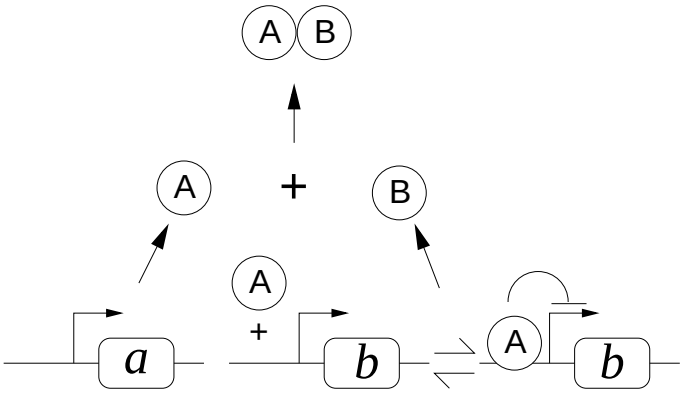

Fig. 8. Switch with the same design as in Fig. 3*A* but with high concentrations of several hundred proteins.

Reactions	Constants
$a \rightarrow a$+A	0.39
A $\rightarrow$Nothing	0.00039
$b \rightarrow b$+B	0.26
B $\rightarrow$Nothing	0.0033
A+B$\rightarrow$ A:B	0.015
A:B $\rightarrow$Nothing	0.34
b+B$\rightarrow$ b:B	0.30
b:B $\rightarrow$ b+B	1.0
b:B $\rightarrow$ b:B+B	0.71

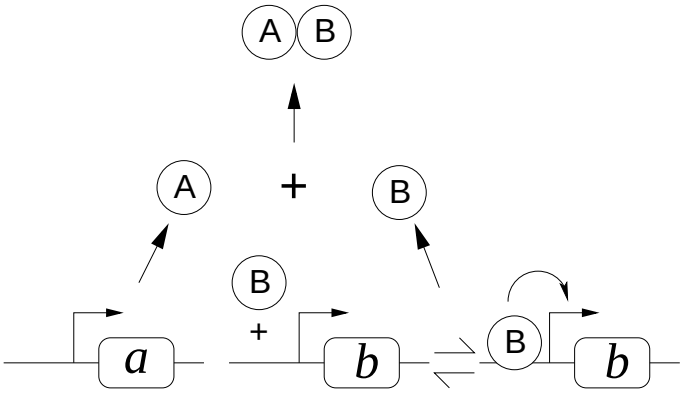

Fig. 9. Switch with the same design as in Fig. 3*B* but with high concentrations of several hundred proteins.

Reactions	constants
$a \rightarrow a$+A	0.79
A $\rightarrow$ Nothing	0.046
$b \rightarrow b$+B	0.070
B $\rightarrow$ Nothing	0.0039
A+B $\rightarrow$ A:B	0.28
A:B $\rightarrow$ Nothing	0.027
a+A $\rightarrow$ a:A	0.78
a:A $\rightarrow$ a+A	0.020
a:A $\rightarrow$ a:A+A	0.75
b+B $\rightarrow$ b:B	0.26
b:B $\rightarrow$ b+B	0.95
b:B $\rightarrow$ b:B+B	0.56
a:A+B$\rightarrow$ a:A:B	0.087
a:A:B $\rightarrow$ a:A+B	0.11
a:A:B $\rightarrow$$a$:A:B+A	0.30

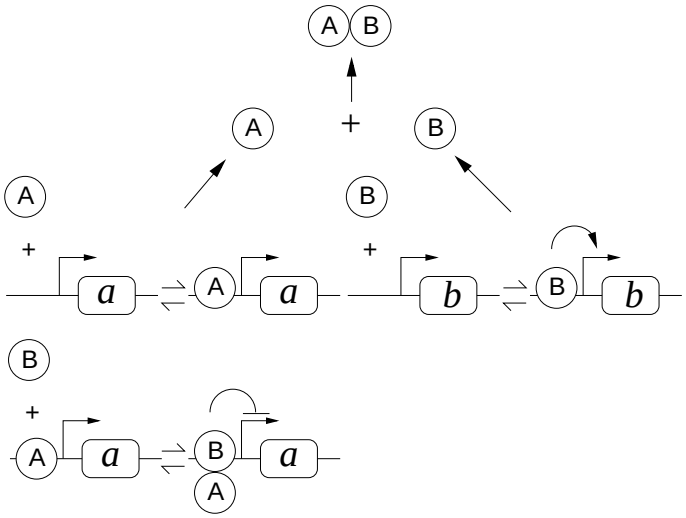

Fig. 10. A switch based on the principle of Fig. 3*B* with a slightly more complex design.

Reactions	Constants
$a \rightarrow a$+A	0.17
A $\rightarrow$ Nothing	0.038
$b \rightarrow b$+B	0.88
B $\rightarrow$ Nothing	0.060
$c \rightarrow c$+C	0.42
C $\rightarrow$ Nothing	0.041
a+A $\rightarrow$ a:A	0.62
a:A $\rightarrow$ a+A	0.70
a:A $\rightarrow$ a:A+A	0.58
b+C $\rightarrow$ b:C	0.98
b:C $\rightarrow$ b+C	0.15
b:C $\rightarrow$ b:C+B	0.95
a:A+A $\rightarrow$ a:A:A	0.70
a:A:A $\rightarrow$ a:A+A	0.83
a:A:A $\rightarrow$ a:A:A+A	0.93
b:C+A $\rightarrow$ b:C:A	0.94
b:C:A $\rightarrow$ b:C+A	0.59
b:C:A $\rightarrow$ b:C:A+B	0.15
A+C $\rightarrow$ A:C	0.61

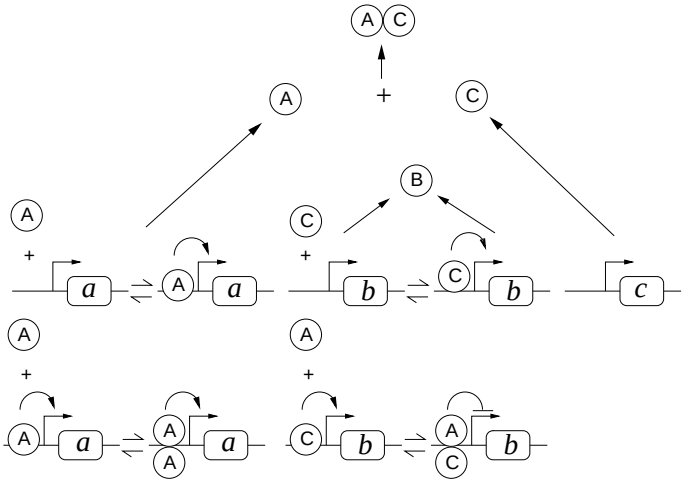

Fig. 11. Switch with three genes where b is simply a "reporter" gene (note that protein B reacts neither with genes a and c nor with other proteins).

Reactions			Constants
a	→	a+A	0.0048
A	→	Nothing	0.0093
b	→	b+B	1.3
B	→	Nothing	0.058
c	→	c+C	0.75
C	→	Nothing	0.091
B+C	→	B	0.81
a+C	→	a:C	0.22
a:C	→	a+C	0.95
a:C	→	a:C+A	0.57
b+B	→	b:B	0.39
b:B	→	b+B	0.40
b:B	→	b:B+B	1.6
b+A	→	b:A	1.2
b:A	→	b+A	0.6
b:A	→	b:A+B	0.45
b:A+A	→	b:A:A	0.25
b:A:A	→	b:A+A	1.1
b:A:A	→	b:A:A+B	0.060
b:A:A+A	→	b:A:A:A	0.32
b:A:A:A	→	b:A:A+A	0.10
b:A:A:A	→	b:A:A:A+B	0.032

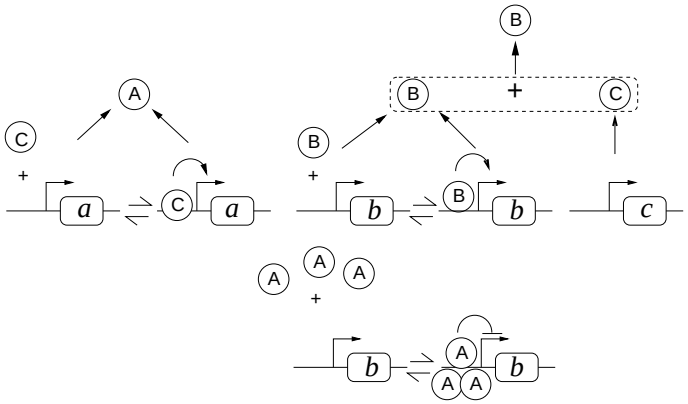

Fig. 12. Switch involving the interaction of three genes (shown as Fig. 3*C*).

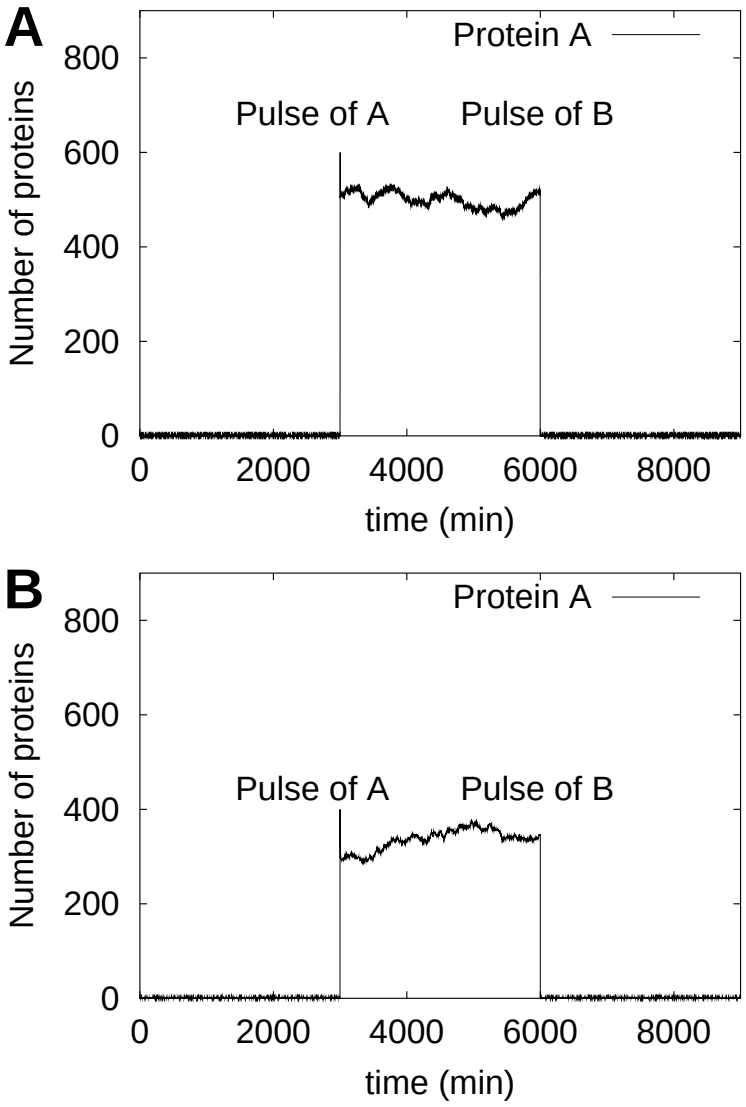

Fig. 13. (A) Stochastic evolution for the switch of Fig. 3A with the parameters of Fig. 8. For these parameter values with several hundred proteins in the high concentration species, fluctuations do not significantly affect the switch function. The low A concentration state evolves freely and is stable for 3,000 min. Rapid switching to the high A concentration state is induced by a pulse of protein A at time 3,000. This new state persists for 3,000 min when a pulse of B switches back the network to the low A state. (B) Similar evolution for the switch of Fig. 3B with the parameters of Fig. 9.

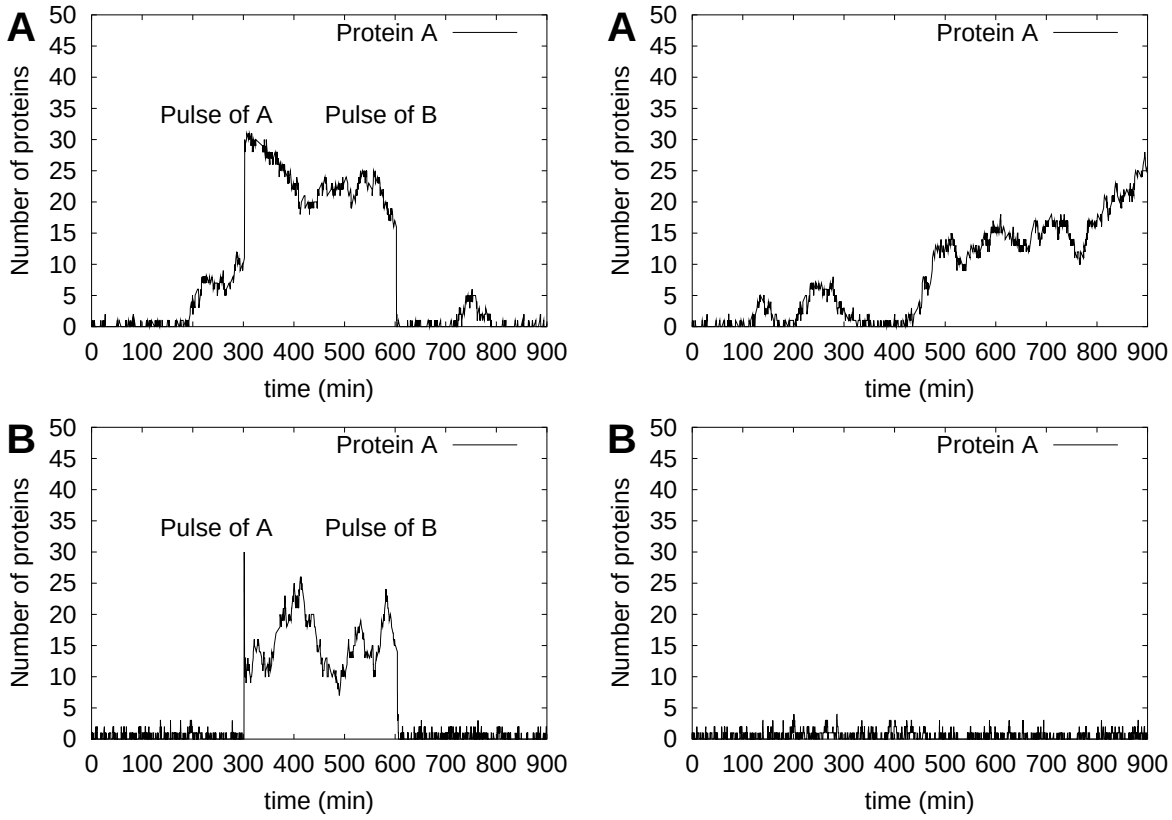

Fig. 14. (*A*) Stochastic evolution for the switch of Fig. 3*A* with the parameters given in the main text. For these parameter values, the high concentration species have only a few 10s of proteins, and fluctuations are strong. Nonetheless, the bistable character of the network is still clearly visible. (*Left*) Rapid switching to the high A concentration state is induced by a pulse of protein A at time 300. A pulse of B switches back the network to the low A state at time 600. Note that at the time of the first pulse, the network is already undergoing spontaneous switching. (*Right*) Free evolution during 900 min showing a spontaneous switch around t = 450 min from the low to the high A state.(*B*) Similar evolution for the switch of Fig. 3*B* with the parameters of the main text. (*Left*) Switching between the two states induced by pulses of protein A and B. (*Right*) Free evolution during 900 min showing that, in spite of strong fluctuations, for these parameters switch B is much less prone to spontaneous switching than switch A.

Reactions			Constants
a	→	a+A	0
A	→	Nothing	0.00019
b	→	b+B	0.43
B	→	Nothing	0.077
c	→	c+C	0.57
C	→	Nothing	0.023
A+B	→	A:B	0.066
A:B	→	Nothing	0.057
C+C	→	C:C	0.14
C:C	→	Nothing	0.0014
C:C + B	→	C:C	0.21
C:C +C:C	→	C:C:C:C	0.37
C:C:C:C	→	Nothing	0.24
C+A:B	→	A:B	1.5
a+ C:C:C:C	→	a:C:C:C:C	0.5
a:C:C:C:C	→	a+ C:C:C:C	0.33
a:C:C:C:C	→	a:C:C:C:C+A	0.56
A:B+C:C	→	A:B:C:C	0.74

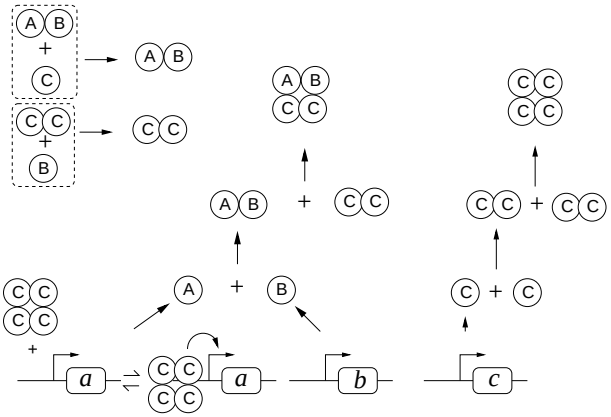

Fig. 15. Complete description of the oscillating circuit shown as Fig. 5.

Reactions	Constants
$a \rightarrow a$+A	1.2
A $\rightarrow$Nothing	0.000075
$b \rightarrow b$+B	2.0
B $\rightarrow$Nothing	0.23
$c \rightarrow c$+C	1.2
C $\rightarrow$Nothing	0.0045
A+B $\rightarrow$ A:B	2.7
A:B $\rightarrow$Nothing	0
a+B $\rightarrow$ a:B	0.50
a:B $\rightarrow$ a+B	0.11
a:B $\rightarrow$ a:B+A	21
c+B $\rightarrow$ c:B	2.9
c:B $\rightarrow$ c+B	0.56
c:B $\rightarrow$ c:B+C	11
c+A $\rightarrow$ c:A	0.62
c:A $\rightarrow$ c+A	0.90
c:A $\rightarrow$ c:A+C	0.85
A:B+C$\rightarrow$ C	0.47
A:B+C$\rightarrow$ B	0.99
A:B $\rightarrow$ B	0.20

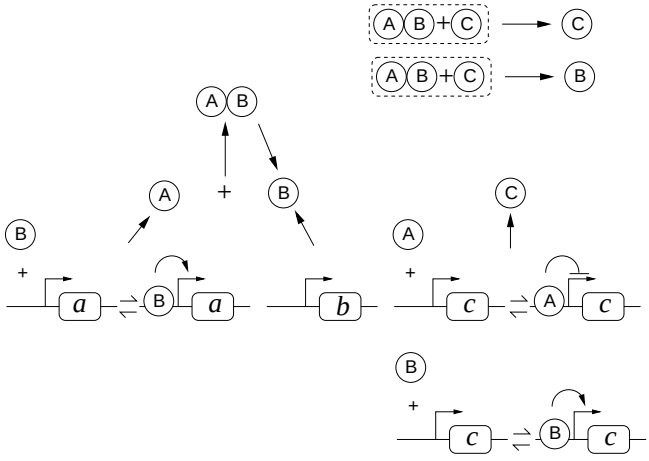

Fig. 16. Another oscillating network that features a negative feedback loop reminiscent of circadian gene networks.

Reactions	Constants
$a \rightarrow a$+A	1.3
A $\rightarrow$Nothing	0
$b \rightarrow b$+B	0.17
B $\rightarrow$Nothing	0.00017
A+A $\rightarrow$ A:A	0.012
A:A $\rightarrow$Nothing	0.000047
A:A+B $\rightarrow$ A:A:B	8.3
A:A+A:A $\rightarrow$A:A:A:A	0.23
A:A:A:A $\rightarrow$Nothing	0.00018
A:A:A:A+A$\rightarrow$A:A:A:A	15
A:A:A:A+B$\rightarrow$ A	0.39

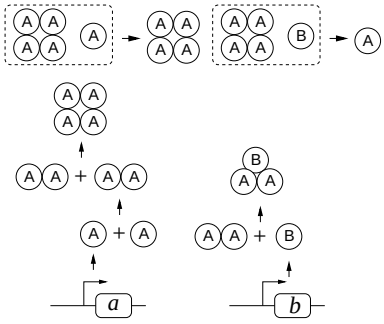

Fig. 17. A purely biochemical oscillator.