Model of a Chemical Reaction Flip-flop with one Unique Switching Input

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Flip-flop, (in)stability, steady state, monoflop

The model of a flip-flop consisting of an interacting pair of completely equivalent chemical reaction systems (branches) is displayed. Beyond a critical threshold value of the influx to the apex substance of both branches the symmetric state (both branches active to an equal extent) is unstable; so essentially only one will be active. A negative pulse in the influx beneath the threshold brings the total system back towards the symmetric state. Introducing additional short reaction chains into both branches that cause a time delay in the rate of destruction of the end products generate an overshoot, so the opposite branch is active, when the pulse is over. Thus the same pulse can switch over the system in either direction opposite to the former state.

In previous papers 1, 2 we introduced a model for the spontaneous formation of optical antipodes (here designated A* and A0) in strongly asymmetric yield whose goal it just was to get an irreversible flipping in one direction. The minimal circuitry of this system is shown in Fig. 1. Even if the influx to the common substance S becomes smaller than the critical threshold value jth, where the system strives towards the symmetric state, there will be a small excess of that substance A* or A0, respectively, that had the majority in the overcritical asymmetric domain of j, because the symmetric state is approached — roughly speaking — in an exponential way. But the smallest excess suffices to bring the system back in the same direction, if j is again raised above jth, or in other words: to make the former monoflop become a flipflop.

To our knowledge, no model of a chemical flip-flop with one unique switching input in terms of explicit dynamical equations has yet been developed. A model in terms of binary logic is due to Sugita 3, another qualitative discussion is due to Monod and Jacob 7. In either case it is not the same pulse that flips the system into the opposite direction, but these influences are assumed to be specific for the two branches and thus different. The same is true for Kacser's model.

Qualitative Design

Investigating the reasons for the monoflop behaviour of the former model revealed that it is the fact that the efflux from A* or A0 respectively is proportional to the concentrations of these substances that has the main effect.

Let us assume that the concentration of A* is high and that of A0 is low. The idea was to hold in case of a sudden lowering of j the efflux of A* high and that of A0 low although the concentrations of both are striving for equality. This would mean that A* is destroyed too strongly and A0 too weakly so that the equalling of both concentrations would...
be accelerated and exaggerated in such a way that the sign of preponderance would be reversed. If now the pulse ceases not too late it could be expected that the new preponderance would be preserved and even enforced, because now \( j \) is again in the overcritical region. This is equivalent to make in the symmetric state at \( j < j_{th} \) the formerly stable node become a stable focus.

Searching for a means that could cause the effect of reversing, it was thought of additional components causing a time delay, especially short reaction chains. So, if the destruction of \( A^* \) would be no longer proportional to its own concentration, but to that of \( C^* \), where \( C^* \) is generated by the pseudo-first order reaction chain \( A^* \rightarrow B^* \rightarrow C^* \), a sudden decrease of \( A^* \) would effectuate a decrease of the destruction of \( A^* \) after a certain time. The same but with reverse sign is true in the chain \( A^0 \rightarrow B^0 \rightarrow C^0 \).

This circuitry was tested on an analog computer (Dornier 240) and showed that the concentration of \( A^* \) turned negative indicating that the linear idealization is not correct for small concentrations although at long everything should be alright. So the explicit quasi-linear formulation was chosen as treated in the context of sinusoidal oscillations\(^8,9\), although here the special complications in that circuitry are certainly not necessary. Indeed, the desired flip-flop behaviour could be realized.

Finally a circuitry was investigated which seems to be the minimal design for this purpose. This model is shown in Fig. 2 and shall be studied in greater detail in the next sections. The apparent difference between the monoflop and flip-flop models as displayed in Figs. 1 and 2 is that in the latter in each branch the efflux of A is no longer proportional to A, but to A and B, which is generated from A and destroyed linearly in an additional reaction.

### Quantitative Formulation

The differential equations governing the system of Fig. 2 are (with \( X = \frac{dX}{dt} \))

\[
S = j - k_1 S (A^* + A^0) \quad (1)
\]

\[
\dot{A}^* = (k_1 S - k_4 B^*) A^* - k_2 A^* A^0 + k_3 R \quad (2)
\]

\[
A^0 = (k_1 S - k_4 B^0 - k_3) A^0 - k_2 A^* A^0 + k_3 R \quad (3)
\]

\[
\dot{B}^* = k_5 A^* - (k_4 A^* + k_6) B^* \quad (4)
\]

\[
\dot{B}^0 = k_5 A^0 - (k_4 A^0 + k_6) B^0 \quad (5)
\]

As in previous discussions of the properties of the parent system as displayed in Fig. 1 the symmetry of the system allows for a transformation of the state variables according to

\[
X_+ = \frac{1}{V^2} (X^* + X^0) \quad (6)
\]

\[
X = A, B
\]

\[
X_- = \frac{1}{V^2} (X^* - X^0) \quad (7)
\]

with \( A_+ = B_- = 0 \) in the symmetric steady state.

The flip-flop character of the system is manifested by a reversal of sign in the variables of the \( X_- \)-subspace on reentrance from the monostable \((j < j_{th})\) to the bistable region \((j > j_{th})\), where \( j_{th} \) is the threshold value of \( j \) separating both regions.

It is apparent that the quantitative prerequisite for the overshoot mentioned in the preceding section is that the two eigenvalues of the Jacobian in the \( X_- \)-subspace on reentrance from the monostable \((j < j_{th})\) to the bistable region form a pair of conjugate complex numbers so that this critical point is a stable focus. However, if \( j \) is suddenly raised above \( j_{th} \), for which situation the former point is no longer a critical point, the trajectory must remain on the same side.

A full analytical investigation of the question which constraints this necessity imposes on the parameters is unwieldy because of the nonlinearities and the many parameters involved. Besides, the full dynamical behaviour is not only a question of the stability of the s.s. alone.

It is hoped that this question can be settled more easily in similar systems with the aid of some mathematical tricks later.

Here and now we shall postpone this problem.

![Fig. 2. Minimal circuitry of the flip-flop system.](image)
Numerical Results

The problem was tackled empirically instead, by integrating (1) through (5) for a relatively arbitrarily chosen set of parameters.

The general procedure was to start from one asymmetric s.s. in the bistable region \( j > j_{th} \), then to lower \( j \) well beneath \( j_{th} \) in a step function where only the one symmetric s.s. is stable, and to go back again with \( j \) in one step to the former high value as soon as the polarity of \( A^- = \frac{1}{\sqrt{2}} (A^* - A^0) \) had changed.

One question was how critical the right moment of switching back was. If the system really spirals to the symmetric s.s. in a strongly damped oscillation the switching time should not be critical as long as the trajectory is on the side opposite to the former state. This prediction could be verified as is seen in Fig. 3. The parameter set was \( k_1 = k_2 = k_4 = 1, \ k_3 = 0.5, \ k_3 R = 0.01; \ j = 1, \) if the negative pulse in \( j \) is “off”, and \( j = 0, \) if it is “on”; all values are given in arbitrary units. The pulse was always turned on at \( t = 30. \) In the first curve (from left) the pulse was turned off as soon as the sign of \( \Delta A = \sqrt{2} A \) changed from positive to negative, which was the case at \( t_0 \approx 50. \) The system swings in a S-shaped curve into the opposite asymmetric s.s. In the second case the pulse was turned off 5 units later, then 10, 15, 20, 25.

The corresponding curves are shifted to the right by more than 5 time units each (at last nearly 15), because the deviation from the symmetric state from which they start when the pulse is shut off gets smaller and smaller and consequently they need more and more time to grow up. The seventh curve (for a delay of 30 time units) returns to the old asymmetric state because now the system had swung back again. The duration of the negative pulse in \( j \) could consequently be varied by at least 25 time units to give the same result.

In another numerical experiment (Fig. 4, note the tenfold contracted time scale!) negative pulses in \( j \) which reduced this parameter from 1 to 0 at the arbitrary times (Fig. 4 a) \( t' = 30, 300, 500, 900, 1500 \) and 1800 for 20 time units switched the same system to and fro in double-S-shaped curves with a shoulder in the symmetric state (\( \Delta A = 0 \)).

![Fig. 3. Response \( \Delta A = A^* - A^0 \) to negative pulses (\( j = 1 \) to \( j = 0 \)) lasting 20, 25, 30, 35, 40, 45, and 50 time units. Beginning of each pulse is at \( t_0 = 30. \) ]

![Fig. 4. Response to several switching pulses (\( j = 1 \) to \( j = 0, \) back to \( j = 1 \) after 20 time units) at arbitrary times, a) \( j \) over time \( t, \) b) \( \Delta A = A^* - A^0 \) over \( t. \) ]

All simulations were done with the MIMIC program already used in previous work on the IBM 7094 of the Deutsches Rechenzentrum at Darmstadt, Germany. Since the critical deviations from the symmetric s.s. were very small (down to \( 10^{-12} \)), the ordinary precision of that 36-bit computer was not sufficient. Instead the program was rewritten for double precision.
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A Rashevsky-Turing System as a Two-cellular Flip-flop

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In a simple two-compartment system, the behaviour of a flip-flop can be obtained by reversible reduction of selective membrane permeability. The behaviour corresponds to a triggerable reversal of "differentiation" of the two-cellular system. The model is identical with the simplest Rashevsky-Turing system, that is a two-compartment system showing spontaneous differentiation if the selective permeability for one constituent is raised above a critical value. The identity is not accidental and can be interpreted as an example of Rosen's principle of function change. The phenomenon may be used for an empirical test of the Rashevsky-Turing theory of morphogenesis.

In a preceding communication 1 it has been demonstrated that in a symmetrically-built, homogeneous reaction system in which instability of the symmetrical steady state arises beyond a threshold value of a certain parameter, flip-flop behaviour can be elicited by a short-lived reduction of this parameter beyond the instability threshold, supposed that the meanwhile occurring stable steady state is a focal point. This latter condition could be fulfilled by incorporating delayed self-inhibition into each half-system.

Now the presupposed symmetry-breaking behaviour, namely evocation of instability of the symmetrical steady state under a parametric change, is long known as the essential behavioral characteristic of Rashevsky-Turing (RT) systems. Rashevsky 2 was the first to observe this sort of bifurcation behaviour, how it can also be named 3, in an abstract model cell. Later on, Turing 4 based his theory of morphogenesis on the same, independently detected principle.

The general structure of any RT system can be derived with the aid of a simple rule determining the occurrence of "evocation behaviour" (ref. 4) of the described sort in any symmetrically-built reaction system possessing one main variable on either side 5. The rule says that "evocation" occurs whenever, in the symmetrical state, the numerical value of cross-inhibition between the two main variables exceeds the numerical value of self-inhibition of either main variable, i.e.

\[ -\frac{\partial A}{\partial A'} < -\frac{\partial A}{\partial A} \]

where the prime refers to the contralateral side.

In systems made up of two identical compartments coupled by a symmetrically permeable membrane, as considered by Turing, evocation behaviour can only occur if (1) either side contains at least two constituents and if (2) the permeability coefficients for these substances are different 6. This follows immediately from the above stated constraint which says that there has to be some self-activation on each side which is not mediated to the other side.

The derived, double-component structure implies the existence of a certain delay in the inner dy-