Thematic school on *Modelling Complex Biological Systems in the Context of Genomics*

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Logical approaches

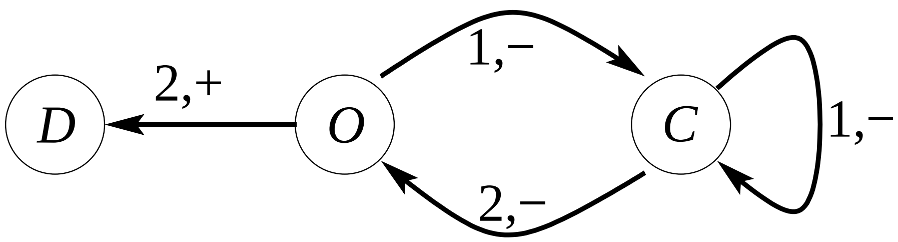
Gilles Bernot with the help of Christine Risso-de Faverney, Jean-Paul Comet, Janine Guespin, Marceline Kaufman, El Houssine Snoussi and Adrien Richard

The running example

We sketch the detoxification induced by hydrocarbons, such as Benzo[a]pyrene for instance. The oversimplified regulatory graph shown at the bottom of the page reflects the following general ideas:

- *Detoxification pathway 1*: when the hydrocarbons are accumulated in the cell at a medium level, a "medium" expression level of cytochromes in the cell (P450 as well as non-P450) allows to reduce the accumulated level of hydrocarbons and, in turn, it reduces the expression level of cytochromes. This is often called the *detoxification pathway 1*. In the figure, we leave hydrocarbon implicit, and this first general idea is represented by an inhibition arrow from C (=cytochrome) to itself. A "medium" level of expression for C being fixed at 1 in this model.
- *Detoxification pathway 2*: when the hydrocarbons are accumulated in the cell at a high level, an oxidative stress starts and a high expression level of cytochromes (non-P450) is favoured.
  - Cytochromes tend to inhibit the oxidative stress. In the figure, this inhibition is represented by an inhibition arrow from C to O. A "high" level of expression for C being fixed at 2 in this model.
  - Conversely, the hydrocarbon metabolites that start the oxidative stress, reduce the quantity of cytochromes (associated to cytochromes, they form water soluble metabolites that are easily excreted). In the figure, it is modelled by the inhibition arrow from O to C.

  The circuit $C \rightarrow O \rightarrow C$ is in fact an abstract view of the *detoxification pathway 2*.
- Lastly, if the detoxification pathway 2 is not powerful enough to reduce the oxidative stress, then DNA damages can appear, due to the high level of hydrocarbon metabolites. In the figure, it is modelled by the activation arrow from O to D at level 2.



Static analysis

According to the abstract description of interactions between C, O and D:

1. What are the possible discrete expression levels for each variable C, O and D according to the theory of René Thomas ?
2. How many discrete parameters are necessary to model this network ?
3. How to draw the table of ressources (i.e., the set of ressources of a variable for a given discrete state of the network) ?

   Remark that D never acts on other variables, so only 9 discrete states are relevant (instead of 18).

C	O	$ress.C$	$ress.O$	$ress.D$
0	0	$\cdots$	$\cdots$	$\cdots$
0	1	$\cdots$	$\cdots$	$\cdots$
0	2	$\cdots$	$\cdots$	$\cdots$
1	0	$\cdots$	$\cdots$	$\cdots$
1	1	$\cdots$	$\cdots$	$\cdots$
1	2	$\cdots$	$\cdots$	$\cdots$
2	0	$\cdots$	$\cdots$	$\cdots$
2	1	$\cdots$	$\cdots$	$\cdots$
2	2	$\cdots$	$\cdots$	$\cdots$

Hand made identification of parameters

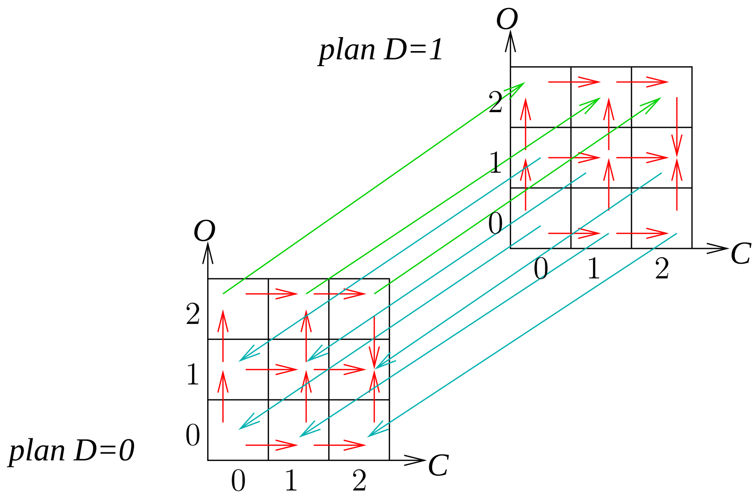
In a context of high level of hydrocarbon, the following has been observed:

1. $(C = 2, O = 1, D = 0)$ is an equilibrium state.
2. Snoussi conditions (monotonicity with respect to ressources) are satisfied.
3. Even when starting from an initial state with neither oxidative stress nor DNA damage, several cases of DNA damage have been observed.

Indeed, these three observations are sufficient to deduce the parameter values of the network when the level of hydrocarbon is high. Let's do it !

Parameters being identified, we can draw the discrete state graph:

$$K_C = 2, K_{C,C} = 2, K_{C,O} = 2, K_{C,CO} = 2, K_O = 1, K_{O,C} = 2, K_D = 0, K_{D,O} = 1$$



Thus, there is only one attraction basin: the one of the *stable* state $(C = 2, O = 1, D = 0)$. **This model predicts that the detoxification pathway 2 is efficient and that DNA damages are repaired.**

How to change this prediction ? It is sufficient to decide $K_O = 2$, which moves the stable state to $(C = 2, O = 2, D = 1)$. This modification does *not* modify the efficiency of the DNA damage repairing. It only says that the inhibition of the oxidative stress by cytochromes is less efficient.

CTL made identification of parameters

When observed properties are translated into formulas according to *temporal logic*, everything is automatically deduced by the computer.

1. $(C = 2, O = 1, D = 0)$ is an equilibrium state:

$$(C = 2 \wedge O = 1 \wedge D = 0) \Longrightarrow AG(C = 2 \wedge O = 1 \wedge D = 0)$$

2. Snoussi conditions (monotonicity with respect to ressources) are satisfied.

   is an option of SMBioNet, check the box [×]

3. Even when starting from an initial state with neither oxidative stress nor DNA damage, several cases of DNA damage have been observed.

$$(D = 0 \wedge O = 0) \Longrightarrow EF(D = 1)$$

... And then simply clic on [start SMBioNet] !