The logical formalism for genetic networks

Réseaux d'interaction
fondements et applications à la biologie

5 janvier 2017

The logical modelling

(R.Thomas, *J. Theor. Biol.* 1973)

Simple enough

to derive analytical mathematical results, using e.g.

- Discrete dynamical systems
- Graph theory
- Combinatorics on finite sets
- Group actions
- Recurrent sequences
- Markov chains
- ...

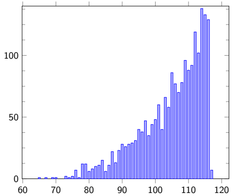
The logical modelling

(R.Thomas, *J. Theor. Biol.* 1973)

Simple enough

to derive analytical mathematical results, using e.g.

- Discrete dynamical systems
- Graph theory
- Combinatorics on finite sets
- Group actions
- Recurrent sequences
- Markov chains
- ...



Powerful enough

to capture main dynamical properties, derive biological results and predictions
$\Rightarrow$ More and more publications in pubmed with 'logical models'

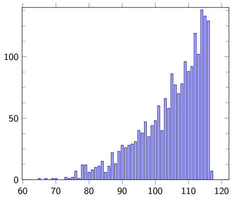
The logical modelling

(R.Thomas, *J. Theor. Biol.* 1973)

Simple enough

to derive analytical mathematical results, using e.g.

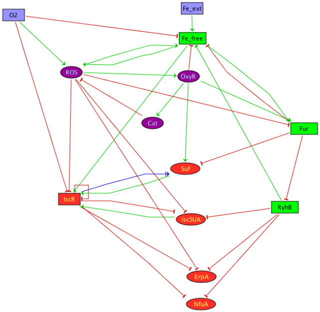
- Discrete dynamical systems
- Graph theory
- Combinatorics on finite sets
- Group actions
- Recurrent sequences
- Markov chains
- ...



Powerful enough

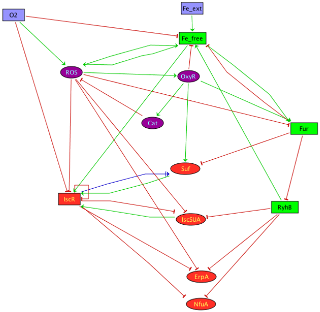
to capture main dynamical properties, derive biological results and predictions
$\Rightarrow$ More and more publications in pubmed with 'logical models'

- Drug synergy prediction in gastric cancer
- Give meaning to combinations of genetic alterations in bladder cancer

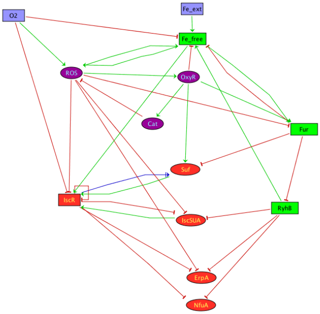


- directed signed graph

Logical modelling of genetic networks



- directed signed graph
- Introduce dynamics (logical parameters)
- Analysis: dynamical properties, asymptotical behaviour (stable states, cyclical attractors), reachability,...

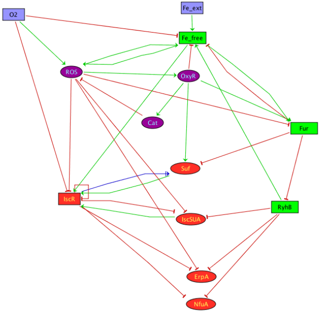


- directed signed graph
- Introduce dynamics (logical parameters)
- Analysis: dynamical properties, asymptotical behaviour (stable states, cyclical attractors), reachability,...

Mathematical model

- Explanatory and predictive
- Gives a mecanistic understanding of the biological process

Logical modelling of genetic networks



- directed signed graph
- Introduce dynamics (logical parameters)
- Analysis: dynamical properties, asymptotical behaviour (stable states, cyclical attractors), reachability,...

Mathematical model

- Explanatory and predictive
- Gives a mecanistic understanding of the biological process

Complex systems

Even simple cellular process

- involve many components
- display non-linear behaviour
- non-independent and non-additive interactions

1. Logical formalism: simple enough to derive mathematical results
2. Logical formalism: a predictive tool
   - Discovery of drug synergies
   - Give meaning to the combinations of genetic alterations

Notations

- $\{g_i,\ i = 1, ..., n\}$ set of n components in interaction
- (g_i, g_j, ε) interaction from g_i to g_j with sign $\varepsilon = \{-1, +1\}$
- $x_i \in \{0, 1\}$ boolean variable associated to each component g_i
- $x = (x_1, \dots x_n) \in \{0, 1\}^n$ **state** of the system

Notations

- $\{g_i,\ i = 1, ..., n\}$ set of n components in interaction
- (g_i, g_j, ε) interaction from g_i to g_j with sign $\varepsilon = \{-1, +1\}$
- $x_i \in \{0, 1\}$ boolean variable associated to each component g_i
- $x = (x_1, \ldots x_n) \in \{0, 1\}^n$ **state** of the system

boolean dynamics

$f : \{0, 1\}^n \rightarrow \{0, 1\}^n \qquad f(x) = (f_1(x), \ldots f_n(x))$

$f_i : \{0, 1\}^n \rightarrow \{0, 1\}$ function specifying the behaviour of g_i

Notations

- $\{g_i,\ i = 1, ..., n\}$ set of n components in interaction
- (g_i, g_j, ε) interaction from g_i to g_j with sign $\varepsilon = \{-1, +1\}$
- $x_i \in \{0, 1\}$ boolean variable associated to each component g_i
- $x = (x_1, \ldots x_n) \in \{0, 1\}^n$ **state** of the system

boolean dynamics

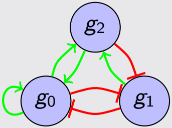
$f : \{0, 1\}^n \to \{0, 1\}^n \qquad f(x) = (f_1(x), \ldots f_n(x))$

$f_i : \{0, 1\}^n \to \{0, 1\}$ function specifying the behaviour of g_i

Updating set

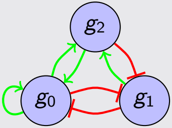
$Upd(x) = \{i \in \{1, \ldots, n\},\ f_i(x) \neq x_i\} \qquad x \in \{0, 1\}^n$

Example



$$
\begin{aligned}
f_0(x) &= 1 \quad \textit{if } (x_0 = 1) \vee (x_1 = 0) \vee (x_2 = 1) \\
f_1(x) &= 1 \quad \textit{if } (x_0 = 0) \vee (x_2 = 0) \\
f_2(x) &= 1 \quad \textit{if } (x_0 = 1) \wedge (x_1 = 1)
\end{aligned}
$$

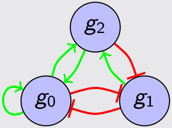
Example



$$
\begin{aligned}
f_0(x) = 1 &\quad \textit{if } (x_0 = 1) \vee (x_1 = 0) \vee (x_2 = 1) \\
f_1(x) = 1 &\quad \textit{if } (x_0 = 0) \vee (x_2 = 0) \\
f_2(x) = 1 &\quad \textit{if } (x_0 = 1) \wedge (x_1 = 1)
\end{aligned}
$$

x	$f(x)$
0 0 0	1 1 0
0 0 1	1 1 0
0 1 0	0 1 0
1 0 0	1 1 0
0 1 1	1 1 0
1 0 1	1 0 0
1 1 0	1 1 1
1 1 1	1 0 1

$$f(x) = (f_1(x),\ f_2(x),\ f_3(x))$$



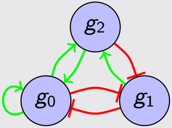
$$
\begin{aligned}
f_0(x) &= 1 \quad \textit{if } (x_0 = 1) \vee (x_1 = 0) \vee (x_2 = 1) \\
f_1(x) &= 1 \quad \textit{if } (x_0 = 0) \vee (x_2 = 0) \\
f_2(x) &= 1 \quad \textit{if } (x_0 = 1) \wedge (x_1 = 1)
\end{aligned}
$$

x	$f(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1

$$f(x) = (f_1(x),\ f_2(x),\ f_3(x))$$

$$Upd(000) = \{1, 2\} \ : \qquad \overset{+}{0}\ \overset{+}{0}\ 0$$

Example



$$
\begin{aligned}
f_0(x) &= 1 \quad \textit{if } (x_0 = 1) \lor (x_1 = 0) \lor (x_2 = 1)\\
f_1(x) &= 1 \quad \textit{if } (x_0 = 0) \lor (x_2 = 0)\\
f_2(x) &= 1 \quad \textit{if } (x_0 = 1) \land (x_1 = 1)
\end{aligned}
$$

x	$f(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1

$$f(x) = (f_1(x),\ f_2(x),\ f_3(x))$$

$$Upd(000) = \{1, 2\} \ : \quad \overset{+}{0}\ \overset{+}{0}\ 0$$

$$\overset{+}{0}\ \overset{+}{0}\ 0 \longrightarrow ?$$

Updating rules

Synchronous dynamics

The synchronous dynamics is described by the iterations of f

$$x \longrightarrow f(x) \longrightarrow f^2(x) \longrightarrow f^3(x) \longrightarrow \dots$$

Synchronous dynamics

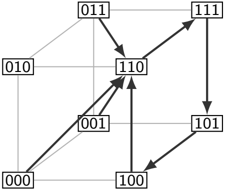
The synchronous dynamics is described by the iterations of f

$$x \longrightarrow f(x) \longrightarrow f^2(x) \longrightarrow f^3(x) \longrightarrow \dots$$

$$\overset{+}{0}\ \overset{+}{0}\ 0 \longrightarrow 1\ 1\ 0$$

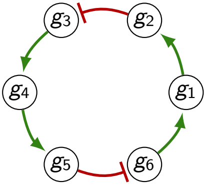
Example

x	$f(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1



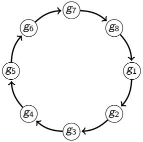
Synchronous update

Very simple structures: circuits



- Positive circuit: even nb of inhibitions
- Negative circuit: odd nb of inhibitions

Regulatory circuits



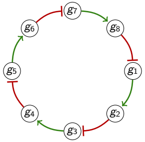
- Given an isolated circuit C, f is entirely defined :

$$f_{i+1}(x) = x_i^{\varepsilon_i}$$

- f is a one-to-one transformation (permutation)

Synchronous circuits

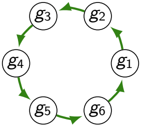
Synchronous case: composed of disconnected cycles

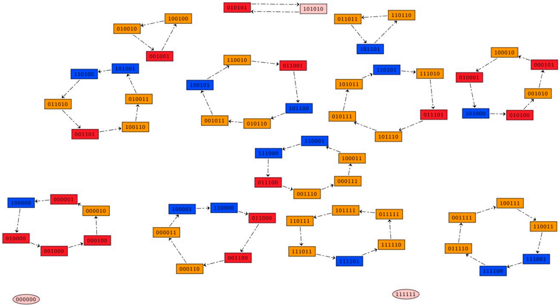


$\mathbf{x}$	01011101
$\mathbf{f}(\mathbf{x})$	00000100
$\mathbf{f}^2(\mathbf{x})$	10101000
	11111110
	11010101
	01000000
	10001010
	11101111
$\mathbf{f}^8(\mathbf{x}) = \mathbf{x}$	01011101
	$\vdots$

Regulatory circuits

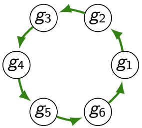
Synchronous case: composed of disconnected cycles

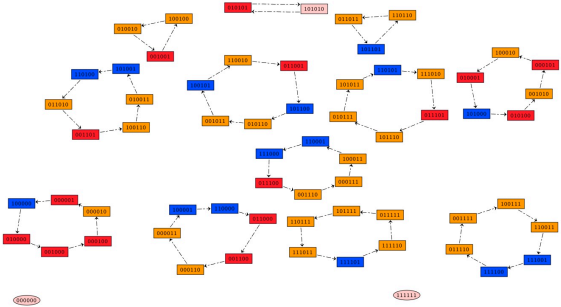




Regulatory circuits

Synchronous case: composed of disconnected cycles

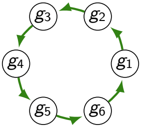


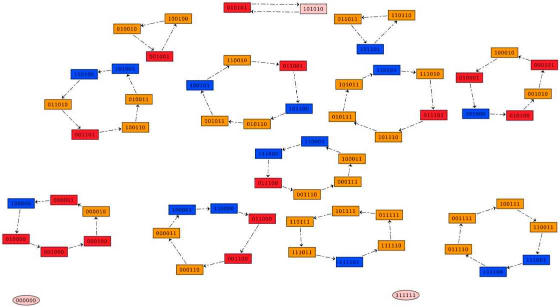


Questions

- How many attractors?
- Their periodicity?
- How this number depends on n?
- Detailled description of the trajectories

Synchronous case: composed of disconnected cycles





Questions

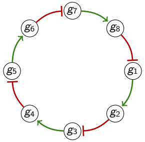
- How many attractors?
- Their periodicity?
- How this number depends on n?
- Detailled description of the trajectories

Mathematical tools

- Combinatorics
- Coding
- Orbit and group action

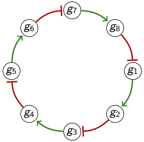
Synchronous circuits

Synchronous case: composed of disconnected cycles



$\mathbf{x}$	01011101
$\mathbf{f}(\mathbf{x})$	00000100
$\mathbf{f}^2(\mathbf{x})$	10101000
	11111110
	11010101
	01000000
	10001010
	11101111
$\mathbf{f}^8(\mathbf{x}) = \mathbf{x}$	01011101
	$\vdots$

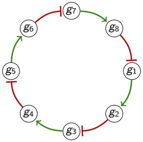
Synchronous case: composed of disconnected cycles



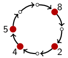
$\mathbf{x}$	01011101
$\mathbf{f}(\mathbf{x})$	00000100
$\mathbf{f}^2(\mathbf{x})$	10101000
	11111110
	11010101
	01000000
	10001010
	11101111
$\mathbf{f}^8(\mathbf{x}) = \mathbf{x}$	01011101
	⋮

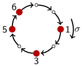
Synchronous circuits

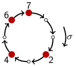
Synchronous case: composed of disconnected cycles



$\mathbf{x}$	01011101
$\mathbf{f}(\mathbf{x})$	00000100
$\mathbf{f}^2(\mathbf{x})$	10101000
	11111110
	11010101
	01000000
	10001010
	11101111
$\mathbf{f}^8(\mathbf{x}) = \mathbf{x}$	01011101
	⋮



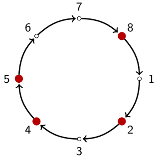




Geometrical representation

Definitions

P k-motif: subset of $\{1, \dots n\}$ of size k

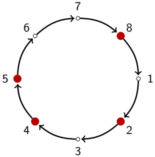


$n = 8,\ k = 4$
$P = \{2, 4, 5, 8\}$

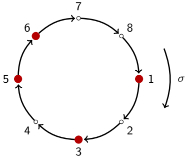
Definitions

P k-motif: subset of $\{1, \ldots n\}$ of size k

σ: increment of 1 in $\mathbb{Z}/n\mathbb{Z}$



$n = 8,\ k = 4$
$P = \{2, 4, 5, 8\}$

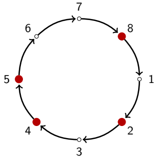


$\sigma(P) = \{1, 3, 5, 6\}$

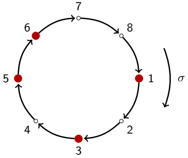
Definitions

P k-motif: subset of $\{1, \dots n\}$ of size k

σ: increment of 1 in $\mathbb{Z}/n\mathbb{Z}$



$n = 8$, $k = 4$
$P = \{2, 4, 5, 8\}$

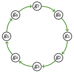


$\sigma(P) = \{1, 3, 5, 6\}$

Configuration of P: orbit of P under σ

Synchronous circuit

Let P a k-motif ($0 \leq k \leq n$)

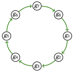


$P = \bullet - \bullet - \bullet \bullet - -$

$x = 0\ 0\ 1\ 1\ 0\ 1\ 1\ 1$

$y = 1\ 1\ 0\ 0\ 1\ 0\ 0\ 0$

Let P a k-motif $(0 \leq k \leq n)$

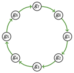


$P = \bullet - \bullet - \bullet\bullet - -$
$x = 0\,0\,1\,1\,0\,1\,1\,1$
$y = 1\,1\,0\,0\,1\,0\,0\,0$

- If C is positive and k is even, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$
- If C is negative and k is odd, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$

Synchronous circuit

Let P a k-motif ($0 \leq k \leq n$)



$$P = \bullet - \bullet - \bullet \bullet - -$$
$$x = 0\ 0\ 1\ 1\ 0\ 1\ 1\ 1$$
$$y = 1\ 1\ 0\ 0\ 1\ 0\ 0\ 0$$

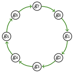
- If C is positive and k is even, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$
- If C is negative and k is odd, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$

$$Upd(f(x)) = \sigma(Upd(x)) = \sigma(P)$$

all the successors of x have their updating set in Conf(P)

Synchronous circuit

Let P a k-motif ($0 \leq k \leq n$)



$P = \bullet - \bullet - \bullet\bullet - -$

$x = 0\ 0\ 1\ 1\ 0\ 1\ 1\ 1$

$y = 1\ 1\ 0\ 0\ 1\ 0\ 0\ 0$

- If C is positive and k is even, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$
- If C is negative and k is odd, there exists exactly two states x and y such that $Upd(x) = Upd(y) = P$

$$Upd(f(x)) = \sigma(Upd(x)) = \sigma(P)$$

all the successors of x have their updating set in Conf(P)

- $A(n, k)$ number of configurations of k-motifs
- Let m the smallest strictly positif integer s.t. $\sigma^m(P) = P$ $\#\{x/Upd(x) \in Conf(P)\} = 2\,m$, spread in 1 or 2 cycles depending on arithmetical properties of m

$p \backslash n$	1	2	3	4	5	6	7	8	9	10	11	12	…	21	22
1	2	2	2	2	2	2	2	2	2	2	2	2		2	2
2	–	1	–	1	–	1	–	1	–	1	–	1		–	1
3	–	–	2	–	–	2	–	–	2	–	–	2		2	–
4	–	–	–	3	–	–	–	3	–	–	–	3		–	–
5	–	–	–	–	6	–	–	–	–	6	–	–		–	–
6	–	–	–	–	–	9	–	–	–	–	–	9		–	–
7	–	–	–	–	–	–	18	–	–	–	–	–		18	–
8	–	–	–	–	–	–	–	30	–	–	–	–		–	–
9	–	–	–	–	–	–	–	–	56	–	–	–		–	–
10	–	–	–	–	–	–	–	–	–	99	–	–		–	–
11	–	–	–	–	–	–	–	–	–	–	186	–		–	186
12	–	–	–	–	–	–	–	–	–	–	–	335		–	–
…															
21	–	–	–	–	–	–	–	–	–	–	–	–		99858	–
22	–	–	–	–	–	–	–	–	–	–	–	–		–	190557
T_n^+	2	3	4	6	8	14	20	36	60	108	188	352		99880	190746

a.

$p \backslash n$	1	2	3	4	5	6	7	8	…	15	16	17	18	…	21	22
2	1	–	1	–	1	–	1	–		1	–	1	–		1	–
4	–	1	–	–	–	1	–	–		–	–	–	1		–	1
6	–	–	1	–	–	–	–	–		1	–	–	–		1	–
8	–	–	–	2	–	–	–	–		–	–	–	–		–	–
10	–	–	–	–	3	–	–	–		3	–	–	–		–	–
12	–	–	–	–	–	5	–	–		–	–	–	5		–	–
14	–	–	–	–	–	–	9	–		–	–	–	–		9	–
16	–	–	–	–	–	–	–	16		–	–	–	–		–	–
…																
30	–	–	–	–	–	–	–	–		1091	–	–	–		–	–
32	–	–	–	–	–	–	–	–		–	2048	–	–		–	–
34	–	–	–	–	–	–	–	–		–	–	3855	–		–	–
36	–	–	–	–	–	–	–	–		–	–	–	7280		–	–
…																
42	–	–	–	–	–	–	–	–		–	–	–	–		49929	–
44	–	–	–	–	–	–	–	–		–	–	–	–		–	95325
T_n^-	1	1	2	2	4	6	10	16		1096	2048	3856	7286		49940	95326

b.

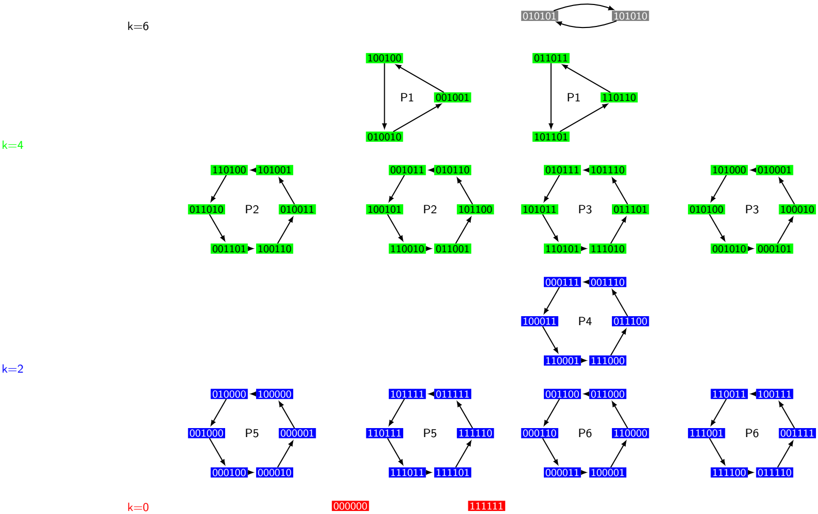
Table 1: Number of p-attractors of positive ($a.$) and negative ($b.$) Boolean automata circuits of size n (the number in cell (p, n) is $A_p(C)$ where C is a Boolean automata circuit of size n).

ELSEVIER
Discrete Applied Mathematics
Volume 160, Issues 4–5, March 2012, Pages 398–415

Combinatorics of Boolean automata circuits dynamics

Jacques Demongeot[a, d], Mathilde Noual[b, d], Sylvain Sené[c, d]

Synchronous circuits

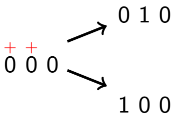


Asynchronous updating rule

Asynchronous state transition graph

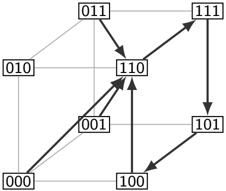
The asynchronous STG is the directed graph on $\{0,1\}^n$ with the following set of arcs:

$$\{x \longrightarrow \overline{x}^i \mid x \in \{0,1\}^n, i \in Upd(x)\}$$

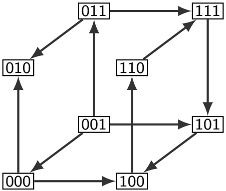


Example

x	$f(x)$
$\overset{+}{0}\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ \overset{+}{0}\ \overset{-}{1}$	1 1 0
0 1 0	0 1 0
$1\ \overset{+}{0}\ 0$	1 1 0
$\overset{+}{0}\ 1\ \overset{-}{1}$	1 1 0
$1\ 0\ \overset{-}{1}$	1 0 0
$1\ 1\ \overset{+}{0}$	1 1 1
$1\ \overset{-}{1}\ 1$	1 0 1

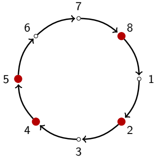


Synchronous update



Asynchronous update

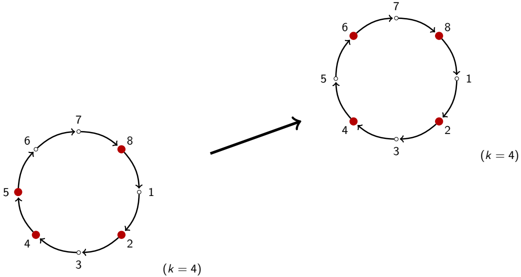
Let P a k-motif, and x a state s.t. $Upd(x) = P$
Commutation of node i: $x \longrightarrow \overline{x}^i$
2 situations :



$(k = 4)$

Let P a k-motif, and x a state s.t. $Upd(x) = P$
Commutation of node i: $x \longrightarrow \overline{x}^i$
2 situations :

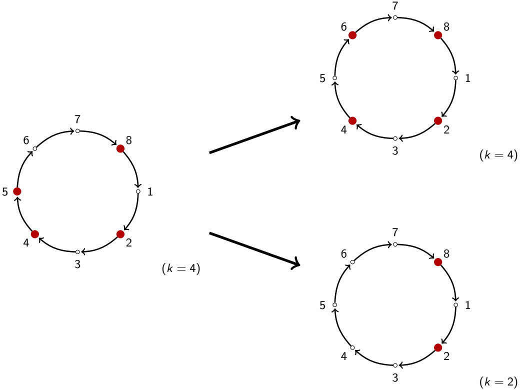
- $i + 1 \notin Upd(x) \Rightarrow Upd(\overline{x}^i)$ k-motif



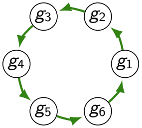
Geometrical representation

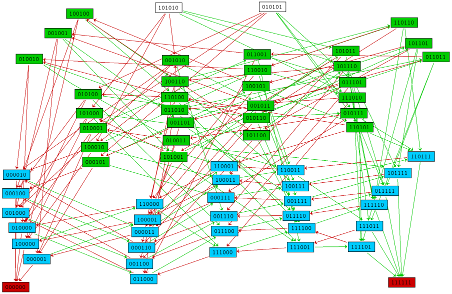
Let P a k-motif, and x a state s.t. $Upd(x) = P$
Commutation of node i: $x \longrightarrow \overline{x}^i$
2 situations :

- $i + 1 \notin Upd(x) \Rightarrow Upd(\overline{x}^i)$ k-motif
- $i + 1 \in Upd(x) \Rightarrow Upd(\overline{x}^i)$ $(k - 2)$-motif

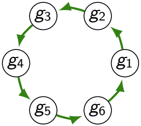


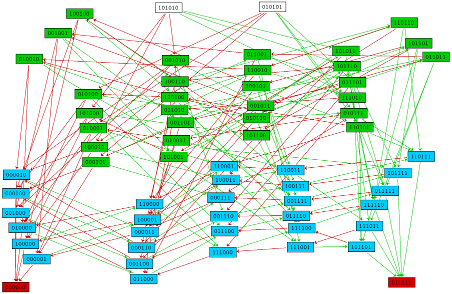
Asynchronous circuits





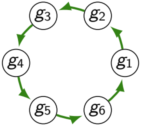
Asynchronous circuits

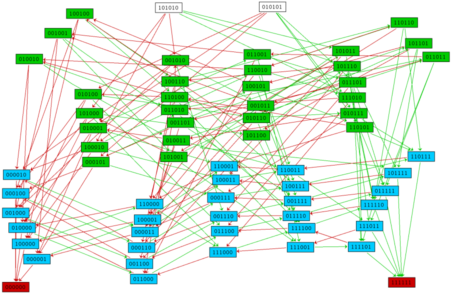




- Connected graph
- Leveled structure of the STG
- Detailed description of the trajectories
- Each level is a strongly connected component

Asynchronous circuits



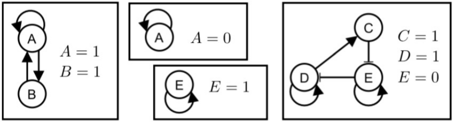


- Connected graph
- Leveled structure of the STG
- Detailed description of the trajectories
- Each level is a strongly connected component

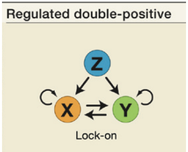
The topology of the dynamical graph of a circuit depends only on the length and the sign of the circuit

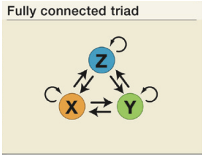
Network Motifs

↪ Motifs of interest in the litterature: small strongly connected components



J. Zanudo, R. Albert (2015) *PLOS Comp. Bio.*



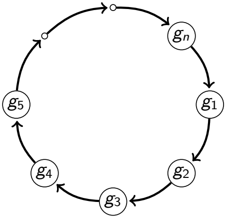


O. Shoval, U. Alon (2010) *Cell* 143

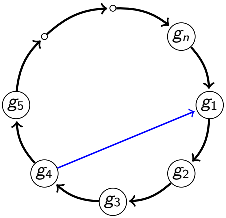
Circuit *vs* chorded-circuit

Question

How does the addition of a short-cut affect the dynamics of the isolated circuit?



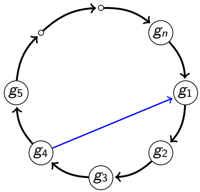
$f_1(x) = x_n$



$f_1(x) = x_n \perp x_4$

$\perp \in \{\text{AND}, \text{OR}, \text{XOR}\}$

Circuits *vs* chorded-circuits

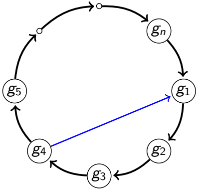


$f_1(x) = x_n \perp x_4$
$\perp \in \{\text{AND}, \text{OR}, \text{XOR}\}$

Definitions

- ς sign long circuit
- $\varsigma^{(s)}$ sign short circuit
- The chorded-circuit is coherent if $\varsigma = \varsigma^{(s)}$
- The chorded-circuit is incoherent if $\varsigma \neq \varsigma^{(s)}$

Circuits *vs* chorded-circuits



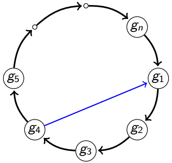
$f_1(x) = x_n \perp x_4$
$\perp \in \{\text{AND}, \text{OR}, \text{XOR}\}$

Definitions

- ς sign long circuit
- $\varsigma^{(s)}$ sign short circuit
- The chorded-circuit is coherent if $\varsigma = \varsigma^{(s)}$
- The chorded-circuit is incoherent if $\varsigma \neq \varsigma^{(s)}$

- Description of synchronous dynamics using recurrence sequences
- Asynchronous dynamics obtained from the asynchronous isolated circuits

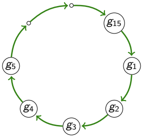
Chorded-circuits



Short-circuit sensitive states

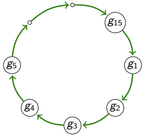
scs-state : its dynamics is different from the isolated circuit

- In AND case, $x = (*, *, *, 0, *, *, \ldots, 1)$ are scs-states
- In OR case, $x = (*, *, *, 1, *, *, \ldots, 0)$ are scs-states
- In XOR case, $x = (*, *, *, 1, *, *, \ldots, 0)$ and $x = (*, *, *, 0, *, *, \ldots, 1)$ are scs-states

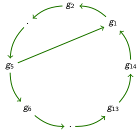


$\mathbf{x}$	111011111111111
$\mathbf{f}(\mathbf{x})$	111101111111111
$\mathbf{f}^2(\mathbf{x})$	111110111111111
	111111011111111
	111111101111111
	111111110111111
	111111111011111
	111111111101111
	111111111110111
	111111111111011
	111111111111101
	111111111111110
	011111111111111
	101111111111111
	110111111111111
$\mathbf{f}^{15}(\mathbf{x}) = \mathbf{x}$	111011111111111
	⋮

Synchronous chorded-circuits through recurrent sequences



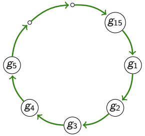
$\mathbf{x}$	111011111111111
$\mathbf{f(x)}$	111101111111111
$\mathbf{f^2(x)}$	111110111111111
	111111011111111
	111111101111111
	111111110111111
	111111111011111
	111111111101111
	111111111110111
	111111111111011
	111111111111101
	111111111111110
	011111111111111
	101111111111111
	110111111111111
$\mathbf{f^{15}(x) = x}$	111011111111111
	⋮



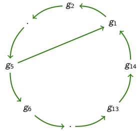
u
↓

$\mathbf{x} \rightarrow$	11101111111111
(*scs*)	11110111111111
	01111011111111
	10111101111111
	11011110111111
	11101111011111
(*scs*)	11110111101111
	01111011110111
	10111101111011
	11011110111101
	11101111011110
(*scs*)	01110111101111
	00111011110111
	10011101111011
	11001110111101
	11100111011110
	01110011101111
	00111001110111
	10011100111011
	11001110011101
	11100111001110
	01110011100111
	00111001110011
	10011100111001
	11001110011100
	01100111001110
	00110011100111
	00011001110011
	10001100111001
	11000110011100
	01100011001110
	00110001100111
	00011000110011
	10001100011001
	11000110001100
	01100011000110
	00110001100011
	00011000110001
	⋮
$\mathbf{ss} \rightarrow$	00000000000000

Synchronous chorded-circuits through recurrent sequences



x	111011111111111
f(x)	111101111111111
$\mathbf{f^2(x)}$	111110111111111
	111111011111111
	111111101111111
	111111110111111
	111111111011111
	111111111101111
	111111111110111
	111111111111011
	111111111111101
	111111111111110
	011111111111111
	101111111111111
	110111111111111
$\mathbf{f^{15}(x) = x}$	111011111111111
	⋮



	u ↓
x →	11101111111111
(*scs*)	11110111111111
	01111011111111
	10111101111111
	11011110111111
	11101111011111
(*scs*)	11110111101111
	01111011110111
	10111101111011
	11011110111101
	11101111011110
(*scs*)	01110111101111
	00111011110111
	10011101111011
	11001110111101
	11100111011110
	01110011101111
	00111001110111
	10011100111011
	11001110011101
	11100111001110
	01110011100111
	00111001110011
	10011100111001
	11001110011100
	01100111001110
	00110011100111
	00011001110011
	10001100111001
	11000110011100
	01100011001110
	00110001100111
	00011000110011
	10001100011001
	11000110001100
	01100011000110
	00110001100011
	00011000110001
	⋮
ss →	00000000000000

x (*scs*)	**1**	**1**	**1**	**0**	**1**
(*scs*)	0	1	1	1	0
(*scs*)	1	0	1	1	1
	0	1	0	1	1
(*scs*)	1	0	1	0	1
	0	1	0	1	0
(*scs*)	0	0	1	0	1
	0	0	0	1	0
	0	0	0	0	1
	1	0	0	0	0
	0	1	0	0	0
(*scs*)	0	0	1	0	0
	1	0	0	1	0
	0	1	0	0	1
(*scs*)	1	0	1	0	0
	1	1	0	1	0
(*scs*)	0	1	1	0	1
(*scs*)	0	0	1	1	0
	1	0	0	1	1
	1	1	0	0	1
(*scs*)	1	1	1	0	0
(*scs*)	1	1	1	1	0
(*scs*)	1	1	1	1	1
(*scs*)	0	1	1	1	1
(*scs*)	0	0	1	1	1
	0	0	0	1	1
	1	0	0	0	1
	1	1	0	0	0
(*scs*)	0	1	1	0	0
(*scs*)	1	0	1	1	0
	1	1	0	1	1
x (*scs*)	**1**	**1**	**1**	**0**	**1**

$$u_i = u^{\varsigma}_{i-n} \perp u^{\varsigma^{(s)}}_{i-n+q}$$

$$u_i = (f^{(i)}(x))_1$$

(ς sign long circuit; $\varsigma^{(s)}$ sign short circuit)

Case $\perp \in \{\textsc{and}, \textsc{or}\}$

Stable states

- incoherent chorded-circuits: 1 stable state
- positive coherent chorded-circuits: 2 stable states
- negative coherent chorded-circuits: no stable states

Case $\bot \in \{\text{AND}, \text{OR}\}$

Stable states

- incoherent chorded-circuits: 1 stable state
- positive coherent chorded-circuits: 2 stable states
- negative coherent chorded-circuits: no stable states

$\varsigma = +1$: Attractors

$\{$attractors of chorded circuit$\} \subset \{$attractors of the long circuit$\}$

Synchronous chorded-circuits through recurrent sequences

Case $\perp \in \{\textsc{and},\ \textsc{or}\}$

Stable states

- incoherent chorded-circuits: 1 stable state
- positive coherent chorded-circuits: 2 stable states
- negative coherent chorded-circuits: no stable states

$\varsigma = +1$: Attractors

$\{$attractors of chorded circuit$\} \subset \{$attractors of the long circuit$\}$

$\varsigma = -1$: Attractors

$\{$attractors of chorded circuit$\} \cap \{$attractors of the long circuit$\} = \emptyset$
for some arithmetical conditions

Case $\perp \in \{\textsc{and}, \textsc{or}\}$

Stable states

- incoherent chorded-circuits: 1 stable state
- positive coherent chorded-circuits: 2 stable states
- negative coherent chorded-circuits: no stable states

$\varsigma = +1$: Attractors

{attractors of chorded circuit} $\subset$ {attractors of the long circuit}

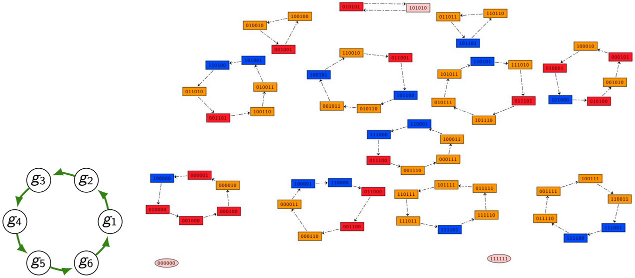
$\varsigma = -1$: Attractors

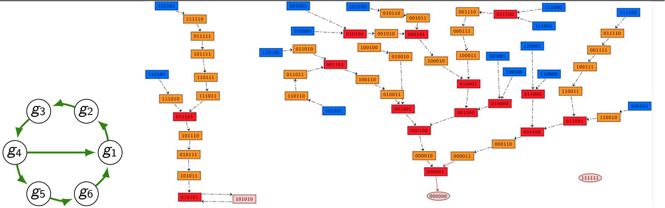
{attractors of chorded circuit} $\cap$ {attractors of the long circuit} $= \emptyset$
for some arithmetical conditions

The topology of the (a)synchronous dynamical graph of chorded-circuits depends only on the length of the circuits and their sign

Case $\bot \in \{\text{AND}, \text{OR}\}$

Synchronous graphs more connected





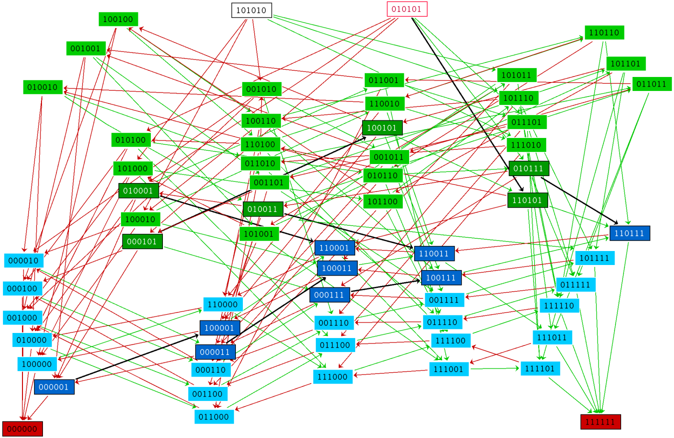
Case $\perp = \{\text{XOR}\}$

The topology of the (a)synchronous dynamical graph of the XOR-chorded-circuit depends only on the length of the two circuits

- There is a unique stable state

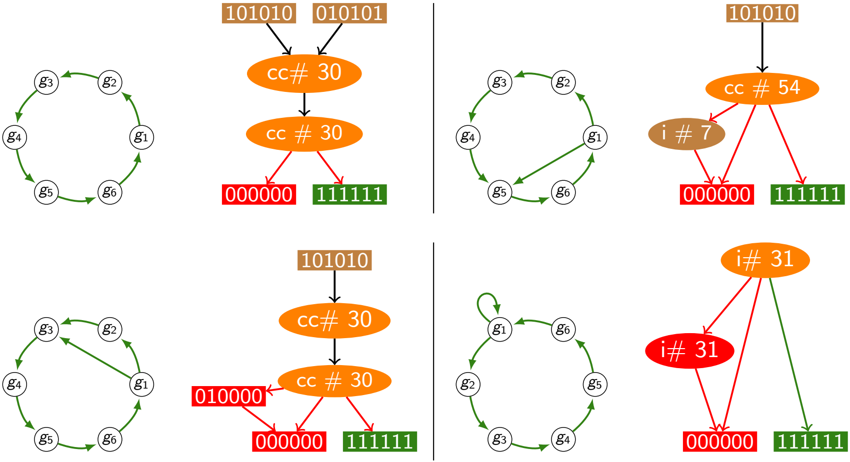
Asynchronous chorded-circuits

↪ inversion or deletion of edges in the STG



Basins of attraction

+/+ chorded-circuits



E.R., B. Mossé, D. Thieffry (2016)

Outline

1. Logical formalism: simple enough to derive mathematical results
2. Logical formalism: a predictive tool
   - Discovery of drug synergies
   - Give meaning to the combinations of genetic alterations

Outline

1. Logical formalism: simple enough to derive mathematical results

2. Logical formalism: a predictive tool
   - Discovery of drug synergies
   - Give meaning to the combinations of genetic alterations

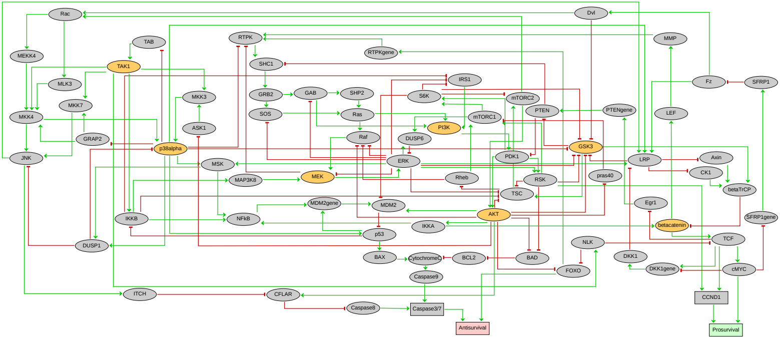
Cancer therapies: combination of drugs

- Increase treatment efficacity (target multiple robustness features of tumours)
- Allow for significant dosage reduction
- Lower drug-induced toxic effect
- Restrain the evolution of drug resistance

Aim

Prediction of drug synergies

Discovery of drug synergies in Gastric cancer



Model centered on molecular mechanisms controlling cellular growth of AGS cell line

75 components, including 7 for which chemical inhibitors are available

Discovery of drug synergies in Gastric cancer

Growth=Prosurvival-Antisurvival

Synergy prediction

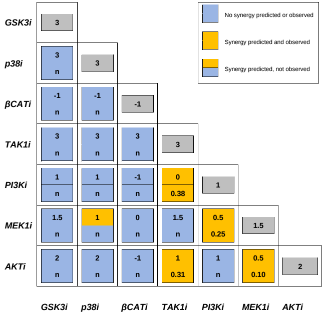
Growth (KO(A, B)) < min(Growth(KO(A)), Growth KO(B))

Discovery of drug synergies in Gastric cancer

Growth=Prosurvival-Antisurvival

Synergy prediction

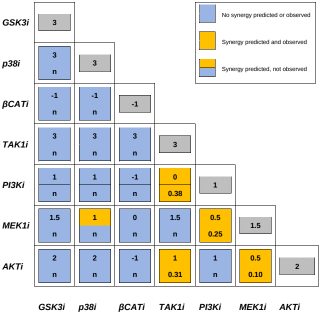
Growth (KO(A, B)) < min(Growth(KO(A)), Growth KO(B))



Growth=Prosurvival-Antisurvival

Synergy prediction

Growth (KO(A, B)) < min(Growth(KO(A)), Growth KO(B))



- 5 predicted synergies, 4 validated
- no false negative prediction

1. Logical formalism: simple enough to derive mathematical results

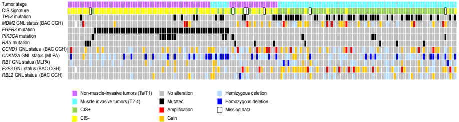
2. Logical formalism: a predictive tool
   - Discovery of drug synergies
   - Give meaning to the combinations of genetic alterations

Bladder Tumorigenesis model

Coll. with Curie institute (F. Radvanyi, L. Calzone, S. Rebouissou) and Instituto Gulbenkian de Cienca (C. Chaouiya)

Patients data (copy nb and mutations)

- Tumour samples: 163
- Invasive samples: 89
- Non-invasive samples: 74



Public datasets

Lindgren, Iyer, TCGA

Alterations in bladder tumours

	Associations	Reported in literature	Observed in data								
			CIT	CIT sup	CIT inv	Lindgren	Lindgren sup	Lindgren inv	Iyer	TCGA	Invasive (public data)
FGFR3 mutations + oncogene alteration	Exclusivity RAS mutation	yes	0.009	0.002	1	0.235	0.088	NA	1	0.604	0.22
	Exclusivity E2F3 amplification	no	0.017	0.078	1	0.041	0.035	0.159	0.067	0.195	0.001
	Exclusivity CCND1 amplification	no	0.009	0.005	1	1	0.592	0.23	0.21	1	0.619
	Co-occurrence PIK3CA mutation	yes	0.0231	0.177	0.11	0.035	0.379	0.131	1	0.764	1
FGFR3 mutations + tumour suppressor alteration	Co-occurrence CDKN2A homozygous deletion	yes	0.039	0.569	0.0013	1	0.495	0.126	0.011	0.009	0.0002
	Exclusivity TP53 mutation	yes	0.0006	0.226	1	0.005	0.114	0.41	0.033	0.32	0.039
TP53 mutations + oncogene alteration	Co-occurrence E2F3 amplification	no	0.0007	0.059	0.058	0.099	0.005	0.677	1E-05	0.493	0.0026
CDKN2A homozygous deletions + oncogene alteration (≠FGFR3)	Co-occurrence CCND1 amplification	no (found in head & neck tumours)	0.043	0.006	1	0.3	0.39	0.56	0.072	0.78	0.7
	Co-occurrence PIK3CA mutation	no	0.044	0.67	0.011	0.033	0.68	0.003	1	0.243	0.7

Question

Can we understand the role of co-occurence/mutual exclusivity of genetic alterations?

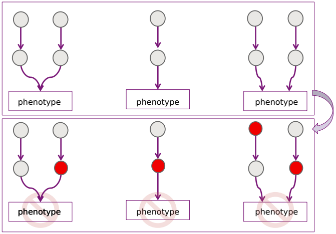
Bladder Tumorigenesis model

Question

Can we understand the role of co-occurence/mutual exclusivity of genetic alterations?

Topological analysis

- co-occurring gene alterations ⟶ belong to parallel pathway
- mutually exclusive gene alterations ⟶ from redundant pathways



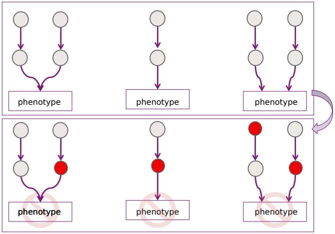
Bladder Tumorigenesis model

Question

Can we understand the role of co-occurence/mutual exclusivity of genetic alterations?

Topological analysis

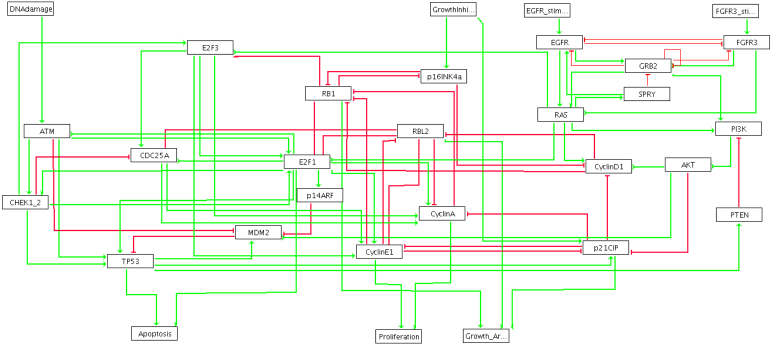
- co-occurring gene alterations $\longrightarrow$ belong to parallel pathway
- mutually exclusive gene alterations $\longrightarrow$ from redundant pathways



Use of the mathematical modeling

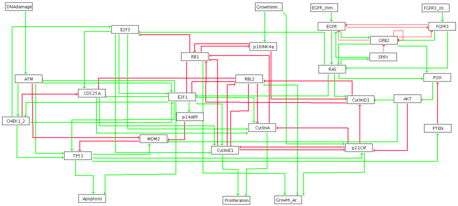
to provide insight on possible mechanisms by which cells become invasive

A mathematical model



23 internal components, 4 inputs, 3 outputs

A mathematical model



Node	Value	Logical function
DNAdamage	0/1	Constant (input)
GrowthInhibitors	0/1	Constant (input)
EGFR_stimulus	0/1	Constant (input)
FGFR3_stimulus	0/1	Constant (input)
EGFR	1	(EGFR_stimulus | SPRY) & !FGFR3 & !GRB2
FGFR3	1	FGFR3_stimulus &!EGFR &!GRB2
GRB2	1	(FGFR3 & !GRB2 & !SPRY) | EGFR
SPRY	1	RAS
RAS	1	EGFR | FGFR3 | GRB2
PI3K	1	GRB2 & RAS & !PTEN
AKT	1	PI3K
PTEN	1	TP53
CyclinD1	1	(RAS | AKT) & !p16INK4a & !p21CIP
p16INK4a	1	GrowthInhibitors & !RB1
p14ARF	1	E2F1
RB1	1	!CyclinD1 & !CyclinE1 & !p16INK4a & !CyclinA
RBL2	1	!CyclinD1 & !CyclinE1
p21CIP	1	(GrowthInhibitors | TP53) & !CyclinE1 & !AKT
CDC25A	1	(E2F1 | E2F3) & !CHEK1_2 & !RBL2:1
CyclinE1	1	CDC25A & (E2F1 | E2F3) & !RBL2 & !p21CIP
CyclinA	1	(E2F1 | E2F3) & CDC25A & !p21CIP & !RBL2
E2F1	1	((!(CHEK1_2:2 & ATM:2) & (RAS | E2F3:1 | E2F3:2)) | (CHEK1_2:2 & ATM:2 & !RAS & E2F3:1)) & !RB1 & !RBL2
	2	(RAS | E2F3:2) & CHEK1_2:2 & ATM:2 & !RB1 & !RBL2
E2F3	1	RAS&!RB1 & !CHEK1_2:2
	2	RAS & !RB1 & CHEK1_2:2
ATM	1	DNAdamage & !E2F1
	2	DNAdamage & E2F1
CHEK1_2	1	ATM & !E2F1
	2	ATM & E2F1
MDM2	1	(TP53 | AKT) & !p14ARF & !ATM
TP53	1	((ATM & CHEK1_2) | E2F1:2) & !MDM2
Apoptosis	1	!E2F1 & TP53
	2	E2F1:1|E2F1:2
Proliferation	1	CyclinE1 | CyclinA
GrowthArrest	1	p21CIP | RB1 | RBL2

R. *et al* (2015) *Cancer Res.* 75(19):4042-52

Attractors of the Bladder cancer model

EGFR_stimulus	FGFR3_stimulus	DNA_damage	Growth_inhibitor	Proliferation	Apoptosis	Growth_arrest	EGFR	FGRF3	HRAS	E2F1	E2F3	CyclinD1	CylinE1	CylcinA	CDC25A	P16INK4a	RB1	RBL2	p21CIP	ATM	CHEK1	MDM2	TP53	p14ARF	PTEN	PI3K	AKT	GRB2	SRPY	Number of states
0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1
0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1
				0	0	1	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1
0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0	0	1
0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0	0	1
				0	1	1	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	0	1	0	1	0	0	0	0	1
0	1	0	0	1	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1
0	1	0	1	0	0	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1
				0	0	1	0	1	1	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	1	1
				1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	1	1
0	1	1	0	0	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0	1	1
0	1	1	1	0	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0	1	1
				0	1	1	0	1	1	0	1	0	0	0	0	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1
1	0	0	0	*	0	*	*	0	*	*	0/1	*	0	*	*	0	*	*	0	0	0	*	0	*	0	*	*	*	*	184320
				*	0	*	*	0	*	0	0	*	*	*	*	0	*	0	0	0	0	*	0	*	0	*	*	*	*	
				*	0	*	*	0	*	*	0/1	*	*	*	*	0	0	0	0	0	0	*	0	*	0	*	*	*	*	
				*	0	*	*	0	*	*	0/1	*	*	*	1	0	*	0	0	0	0	*	0	*	0	*	*	*	*	
1	0	0	1	0	0	1	*	0	*	0	0/1	0	0	0	0	1	0	1	*	0	0	*	0	0	0	*	*	*	*	512
1	0	1	0	0	1	1	*	0	*	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	*	*	16
1	0	1	1	0	1	1	*	0	*	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	*	*	16
							*	0	*	0	0/1	0	0	0	0	1	0	1	1	1	1	0	1	0	1	0	0	*	*	32
1	1	0	0	1	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1
1	1	0	1	0	0	1	0	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1
				0	0	1	0	1	1	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	1	1
				1	0	0	0	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	1	1
1	1	1	0	0	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	1	1	0	1	0	1	0	0	0	1	1
1	1	1	1	0	1	1	0	1	1	0	1	0	0	0	0	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1
				0	1	1	0	1	1	0	1	0	0	0	0	1	0	1	1	1	1	0	1	0	1	0	0	0	1	1

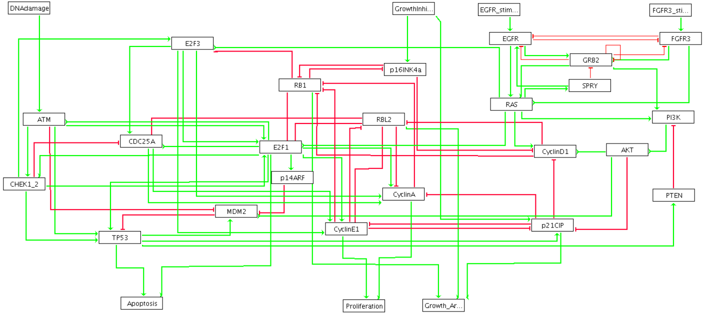
Significative co-occurence PIK3CA/FGFR3 alterations

Give meaning to genetic alterations

Significative co-occurence PIK3CA/FGFR3 alterations

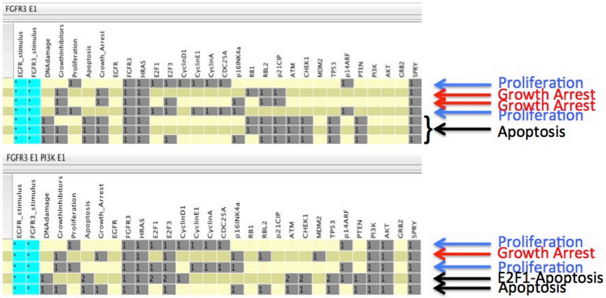
Network topology

PI3K is downstream of FGFR3 $\longrightarrow$ not enough to explain



Simulations of mutants (simple, double)

Appearance of the E2F1-dependent apoptosis (when DNAdam is ON, and p16 OFF)

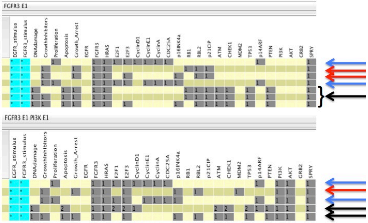


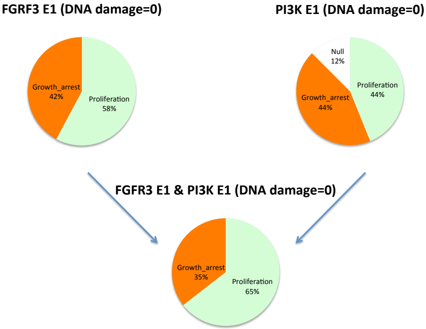
Same phenotypes are reaches ⇒ no striking difference...

Co-occurence PIK3CA/FGFR3 alterations: Prediction of the model

Avatar

Quantification of the basins of attraction (exploration of dynamics using Markov Chains)





It seems advantageous to mutate FGFR3 in PI3K-mutated tumours (in terms of proliferation)

Co-occurence PIK3CA/FGFR3 alterations: Prediction of the model

Systematic analysis of mutants (single, double, triple, ...)

A third deletion of CDKN2A (p16INK4a + p14ARF) eliminates growth arrest in absence of DNA damage

Triple mutant FGFR3 E1 & PIK3 E1 & p16 KO

EGFR_stimulus	FGFR3_stimulus	DNAdamage	GrowthInhibitors	Proliferation	Apoptosis	Growth_Arrest	EGFR	FGFR3	HRAS	E2F1	E2F3	CyclinD1	CyclinE1	CyclinA	CDC25A	p16INK4a	RB1	RBL2	p21CIP	ATM	CHEK1	MDM2	TP53	p14ARF	PTEN	PI3K	AKT	GRB2	SPRY
*	*			1			1		1	1	1	1	1	1	1									1		1	1	1	1
*	*		1	1			1		1	1	1		1	1	1	1								1		1	1	1	1
*	*	1			1	1	1		1								1		1	1	1		1		1			1	1
*	*	1	1		1	1	1		1								1		1	1	1		1		1			1	1
*	*	1	1		2	1	1		1	2	2					1			1	2	2		2	1	1			1	1

- DNA damage ON : only apoptosis (both types)
- DNA damage OFF : only proliferation $\rightarrow$ Uncontrolled growth, Very invasive tumours

Co-occurence PIK3CA/FGFR3 alterations: Prediction of the model

Systematic analysis of mutants (single, double, triple, ...)

A third deletion of CDKN2A (p16INK4a + p14ARF) eliminates growth arrest in absence of DNA damage

Triple mutant FGFR3 E1 & PIK3 E1 & p16 KO

EGFR_stimulus	FGFR3_stimulus	DNAdamage	GrowthInhibitors	Proliferation	Apoptosis	Growth_Arrest	EGFR	FGFR3	HRAS	E2F1	E2F3	CyclinD1	CyclinE1	CyclinA	CDC25A
*	*			1			1		1	1	1	1	1	1	1
*	*		1	1			1		1	1	1		1	1	1
*	*	1			1	1	1		1						
*	*	1	1		1	1	1		1						
*	*	1	1		2	1	1		1	2	2				

p16INK4a	RB1	RBL2	p21CIP	ATM	CHEK1	MDM2	TP53	p14ARF	PTEN	PI3K	AKT	GRB2	SPRY
								1		1	1	1	1
1								1		1	1	1	1
	1		1	1	1		1		1			1	1
	1		1	1	1		1		1			1	1
1			1	2	2		2	1	1			1	1

- DNA damage ON : only apoptosis (both types)
- DNA damage OFF : only proliferation → Uncontrolled growth, Very invasive tumours

Conclusion

To fully lead to uncontrolled proliferation, other checkpoints need to be deleted

Co-occurence PIK3CA/FGFR3 alterations: Prediction of the model

Systematic analysis of mutants (single, double, triple, ...)

A third deletion of CDKN2A (p16INK4a + p14ARF) eliminates growth arrest in absence of DNA damage

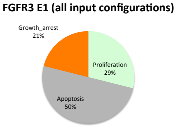
Verification in the data

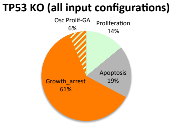
- 162 tumours
- 12 tumors are FGFR3 & PIK3CA-mutated: 4 of them have an homozygote deletion of CDKN2A
- the 2 invasive tumours among the 12 are CDKN2A deleted

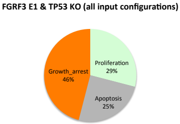
Give meaning to genetic alterations

Significative mutual exclusivity between TP53 and FGFR3 alterations

Significative mutual exclusivity between TP53 and FGFR3 alterations

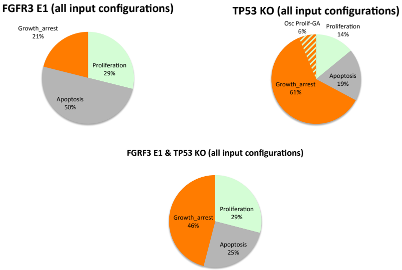






- TP53 mutation in a FGFR3-mutated context has very little impact on Proliferation ($\Rightarrow$ mutual exclusivity)
- Mutating FGFR3 in a TP53-mutated context increase the Proliferation probability ($\Rightarrow$ advantage)

Significative mutual exclusivity between TP53 and FGFR3 alterations

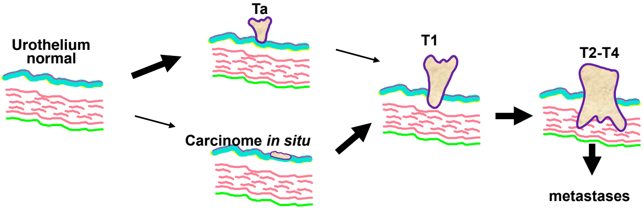


- TP53 mutation in a FGFR3-mutated context has very little impact on Proliferation ($\Rightarrow$ mutual exclusivity)
- Mutating FGFR3 in a TP53-mutated context increase the Proliferation probability ($\Rightarrow$ advantage)

This mutual exclusivity may concern FGFR3-mutated tumors

Bladder cancer pathway

Bladder cancer pathway



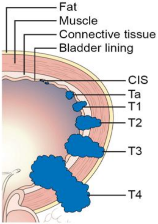


Diagram showing the T stages of bladder cancer
© CancerHelp UK

Two types of tumours

Ta : low grade – recur – low probability invasivness
Cis : high grade – muscle invasive

Coll. L. Calzone, F. radvanyi (Curie); C. Chaouiya (IGC)

Thank you for your attention !!