Attractor identification and quantification in asynchronous discrete dynamics

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FUNDAÇÃO CALOUSTE GULBENKIAN
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Outline

Discrete modelling: logical formalism (Thomas and d'Ari, *Biological Feedback* 1989)

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Logical regulatory graph (LRG) $\mathcal{R}= (\mathcal{G}, K)$

- $\mathcal{G} = \{g_i\}_{i=0,\dots,n}$ is a set of regulatory components
- $Max : \mathcal{G} \rightarrow \mathbb{N}^*$ associates a maximum level M_i to each component g_i
- $\mathcal{S} = \prod_{g_i \in \mathcal{G}} D_i$: is the state space, where $D_i = \{0, \dots, Max(g_i)\}$
- $\forall g_i : K_i : \mathcal{S} \rightarrow D_i$ is the regulatory function specifying the behaviour of g_i

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State transition graph (STG)

The dynamic behaviour of an LRG, is represented by an STG where:

- nodes are states in $\mathcal{S}$
- and arcs $(v, w) \in \mathcal{S}^2$ denote transitions between states

Background: Toy example (Boolean)

$$
\begin{aligned}
K_0(v) &= 1 \quad \textit{if } v_0 = 1 \lor v_1 = 0 \lor v_2 = 1 \\
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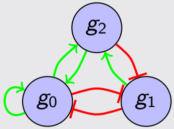

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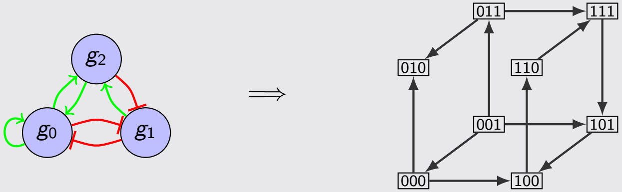
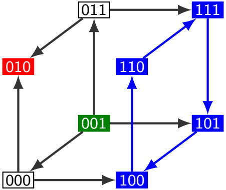


Problem

Attractors

Correspond to asymptotic behaviours where:

- all gene levels are maintained — Stable state
- long-lasting oscillating behaviour — Complex attractor



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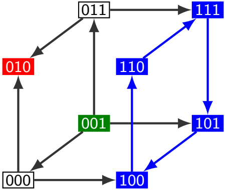
Trajectories quantification

- The weighted number of trajectories towards an attractor represents the structural biases of the STG
- Hidden assumption: successor states are **equiprobable**
- This assumption can easily be modified introducing **weights**



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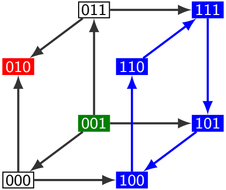
Central question

What is the likelihood of reaching an attractor from a given portion of the state space?



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Objective

- Given a (set of) initial condition(s) and, optionally, a (set of) attractor(s), quantify the trajectories towards the attractor(s)
- Identify/characterize unknown attractor(s)

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Size of the State Transition Graphs

# Components	# States	
	Boolean	**3-valued**
3	8	27
10	1 024	59 049
20	1 048 576	3 486 784 401
30	1 073 741 824	205 891 132 094 649
40	1 099 511 627 776	12 157 665 459 056 928 801

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Challenge

Combinatorial explosion!

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Attractor characterization approaches

Without STG exploration

- Using OMDDs (Naldi *et al.*, *CMSB* 2007)
- Using SAT (de Jong and Page, *IEEE/ACM Trans. Comp. Biol. Bioinf.* 2008)
- Using reduction techniques and network motifs (Zañudo and Albert, *PLoS One* 2013)

With full (reachable) STG exploration

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Trajectory characterization approach:

- MaBoSS (Stoll *et al.*, *BMC Syst Biol* 2012)

Approach: Quasi-exact (FIREFRONT algorithm)

Intuition

- Explore the STG from an **initial condition**
- **Divide** and **carry** probability to successor states
- Accumulate probability in states with no successors – **stable states**
- Do not explore states with probability below α

The algorithm maintains 3 state sets:

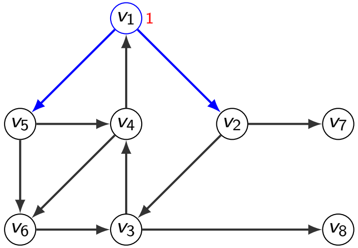
- F – the current firefront
- N – the set of neglected states
- A – the set of attractors

Approach: Quasi-exact (FireFront algorithm)

$\alpha = \frac{1}{16}$ max iterations $= 10$

Start exploration from given initial condition v_1, with unitary probability

Iteration $= 1$
$F = \{v_1\}$
$N = \emptyset$
$A = \emptyset$



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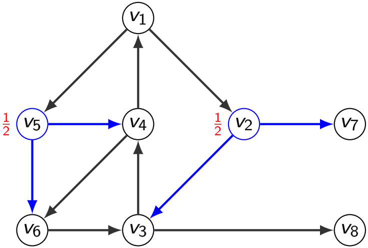
Carry probability to successors dividing it by the number of successors – current firefront

Iteration $= 2$
$F = \{v_2, v_5\}$
$N = \emptyset$
$A = \emptyset$

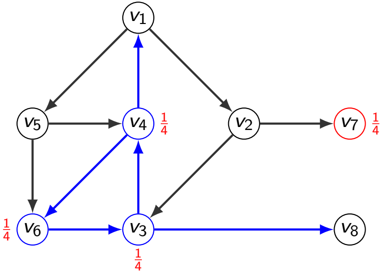


Approach: Quasi-exact (FIREFRONT algorithm)

$\alpha = \frac{1}{16}$ max iterations $= 10$

States with no successors are attractors and accumulate probability

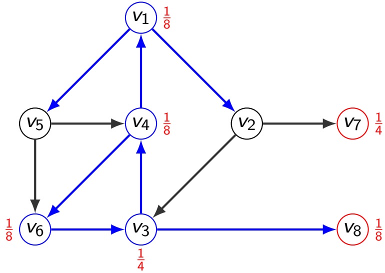
Iteration $= 3$
$F = \{v_3, v_4, v_6\}$
$N = \emptyset$
$A = \{v_7\}$



$\alpha = \frac{1}{16}$ max iterations = 10

States with no successors are attractors and accumulate probability

Iteration = 4
$F = \{v_1, v_3, v_4, v_6\}$
$N = \emptyset$
$A = \{v_7, v_8\}$

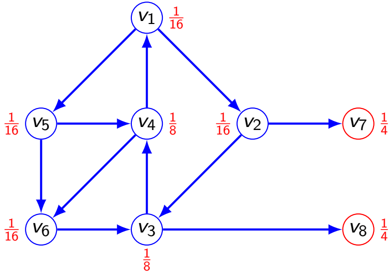


Approach: Quasi-exact (FireFront algorithm)

$\alpha = \frac{1}{16}$ max iterations $= 10$

States with no successors are attractors and accumulate probability

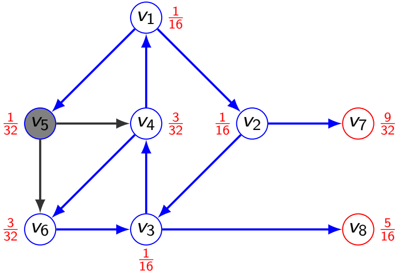
Iteration $= 5$
$F = \{v_1, v_2, v_3, v_4, v_5, v_6\}$
$N = \emptyset$
$A = \{v_7, v_8\}$



$\alpha = \frac{1}{16}$ max iterations $= 10$

States accumulate probability given by multiple predecessor states
States with probability below α are moved to a special set – neglected states – and are no longer explored

Iteration $= 6$
$F = \{v_1, v_2, v_3, v_4, v_6\}$
$N = \{v_5\}$
$A = \{v_7, v_8\}$

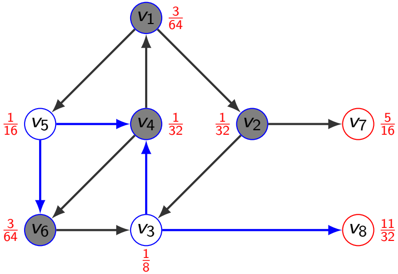


Approach: Quasi-exact (FireFront algorithm)

$\alpha = \frac{1}{16}$ max iterations $= 10$

States in the neglected set still accumulate probability and can be moved back to the firefront

Iteration $= 7$
$F = \{v_3, v_5\}$
$N = \{v_1, v_2, v_4, v_6\}$
$A = \{v_7, v_8\}$



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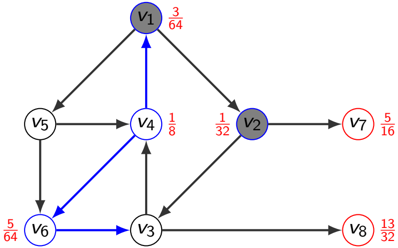
Iteration = 8
$F = \{v_4, v_6\}$
$N = \{v_1, v_2\}$
$A = \{v_7, v_8\}$



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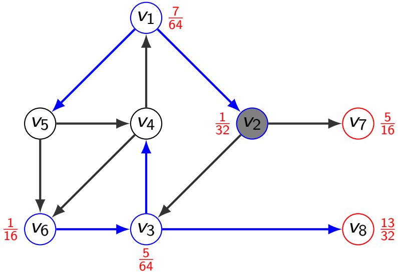
Iteration $= 9$
$F = \{v_1, v_3, v_6\}$
$N = \{v_2\}$
$A = \{v_7, v_8\}$

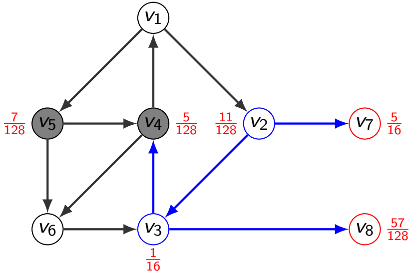


Approach: Quasi-exact (FireFront algorithm)

$\alpha = \frac{1}{16}$ max iterations $= 10$

Execution halts when the firefront is empty or the maximum number of iterations is reached

Iteration $= 10$
$F = \{v_2, v_3\}$
$N = \{v_4, v_5\}$
$A = \{v_7, v_8\}$



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Iteration $= 10$
$F = \{v_2, v_3\}$
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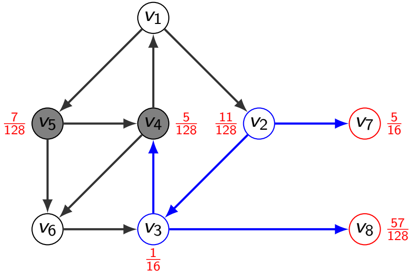
Residual $= \frac{31}{128}$



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- The maximum number of iterations and the α parameters control the **running time** and the **precision**

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- The maximum number of iterations and the α parameters control the **running time** and the **precision**

- Cannot directly identify complex attractors
- Large transient cycles may take too long to distribute probability
- "Wide" STGs may hurry every state to the neglected set
  - Lowering α may help, but the #states in the firefront grows very fast

Approach: Stochastic (Monte Carlo algorithm)

- Exploration starts at a given initial state v_1
- Next state is picked at random from set of successors (random walk)
- Exploration stops when a stable state is reached
- Repeat for n simulations
- Number of trajectories towards an attractor measures its probability

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Problems

- May get stuck in large transients
- Is not able to identify complex attractors (unless they are already known)

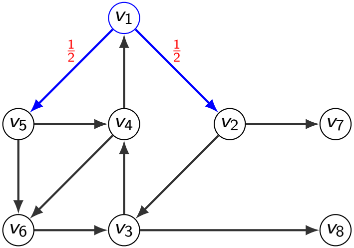
Approach: Stochastic (AVATAR algorithm)

Intuition

- Modified Monte Carlo simulation
- When a cycle is detected, the STG is re-wired to remove the cycle – new **incarnation** of the STG
  - Transitions between cycle members are replaced by transitions to the cycle exits
  - Equivalent to performing a random walk over Markov chains (proven)

Approach: Stochastic (Avatar algorithm)

$$Q^0 = \begin{pmatrix} 0 & \frac{1}{2} & 0 & 0 & \frac{1}{2} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{2} & 0 & 0 & 0 & \frac{1}{2} & 0 \\ 0 & 0 & 0 & \frac{1}{2} & 0 & 0 & 0 & \frac{1}{2} \\ \frac{1}{2} & 0 & 0 & 0 & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$



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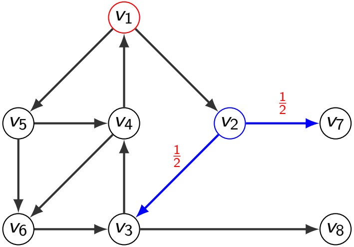

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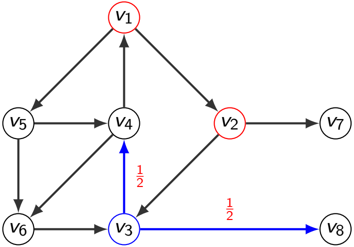

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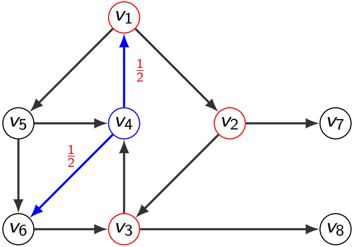

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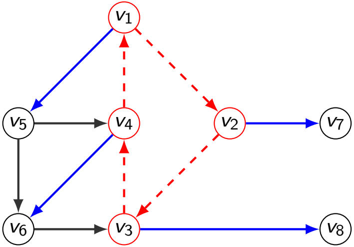
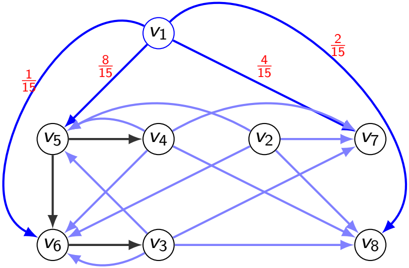
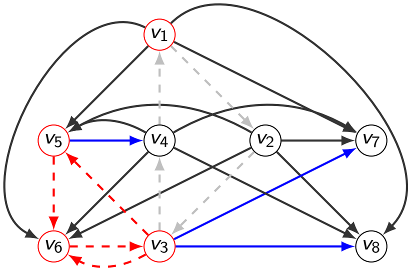


$$Q^1 = \begin{pmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{8}{15} & \frac{1}{15} & \frac{4}{15} & \frac{2}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{1}{15} & \frac{2}{15} & \frac{8}{15} & \frac{4}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{2}{15} & \frac{4}{15} & \frac{1}{15} & \frac{8}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{4}{15} & \frac{8}{15} & \frac{2}{15} & \frac{1}{15} \\ 0 & 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

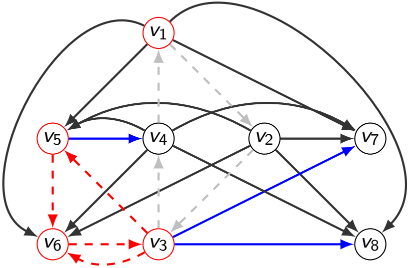


$$Q^1 = \begin{pmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{8}{15} & \frac{1}{15} & \frac{4}{15} & \frac{2}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{1}{15} & \frac{2}{15} & \frac{8}{15} & \frac{4}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{2}{15} & \frac{4}{15} & \frac{1}{15} & \frac{8}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{4}{15} & \frac{8}{15} & \frac{2}{15} & \frac{1}{15} \\ 0 & 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$



Approach: Stochastic (Avatar algorithm)

$$Q^1 = \begin{pmatrix} \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{8}{15} & \frac{1}{15} & \frac{4}{15} & \frac{2}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{1}{15} & \frac{2}{15} & \frac{8}{15} & \frac{4}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{2}{15} & \frac{4}{15} & \frac{1}{15} & \frac{8}{15} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \frac{4}{15} & \frac{8}{15} & \frac{2}{15} & \frac{1}{15} \\ 0 & 0 & 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$



And so forth...

Approach: Stochastic (AVATAR algorithm)

- The number of simulation runs controls the **running time** and **precision**

Approach: Stochastic (AVATAR algorithm)

- The number of simulation runs controls the **running time** and **precision**

- Huge transients and complex attractors may exhaust memory
  (when they correspond to an entire portion of a very large state space)
- Very large cycles may not be easily re-wired
  (cycle re-wiring requires a matrix inversion step)

FireFront and Avatar

- An **oracle** may be provided to identify a known **complex attractor**

Optimizations & additional features

Avatar

- Prior to **cycle re-wiring** a phase of τ-expansion is performed
  - Cycles are expanded by τ steps in an attempt to find a larger connected component to re-wire

Optimizations & additional features

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  - The value of τ is doubled for every new **incarnation** in the same simulation run

Optimizations & additional features

AVATAR

- Prior to **cycle re-wiring** a phase of τ-expansion is performed
  - Cycles are expanded by τ steps in an attempt to find a larger connected component to re-wire
  - The value of τ is doubled for every new **incarnation** in the same simulation run
  - If the number of re-wired transitions surpasses a predefined limit (default=2^{15}), the expansion phase is **unbounded**

Optimizations & additional features

Avatar

- **Complex attractors** identified in one run are used to create an **oracle** to identify member states in subsequent simulation runs

Optimizations & additional features

Avatar

- **Complex attractors** identified in one run are used to create an **oracle** to identify member states in subsequent simulation runs
- **Large transients** re-wired in one run are also carried to subsequent runs

Avatar

The initial conditions of the simulation runs may be:

- identical (fixed or random)
- a sample (of the entire state space, or a portion of the state space identified by an oracle)

Outline

Synthetic models

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Random model 1	0	10	1	1	1 024
Random model 2	0	10	1	1	1 024
Random model 3	0	15	1	1	32 768
Random model 4	0	15	2	0	32 768

Model characteristics

Random models generated using BoolNet (Müssel *et al.*, *Bioinformatics* 2010)

Selected 4 models:

- 2 models with 10 components + 2 models with 15 components
  - each component with 2 randomly selected regulators
  - logical parameters randomly selected
- Selected models capable of generating a common basin of attraction

Synthetic models: Random model 1

Name	# Components		# Attractors		State space size
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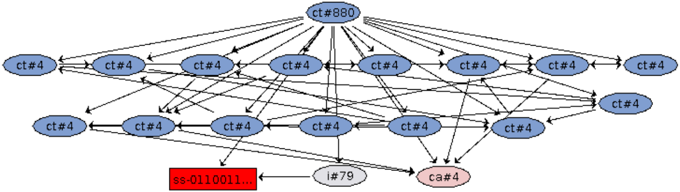

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Name	# Components		# Attractors		State space size
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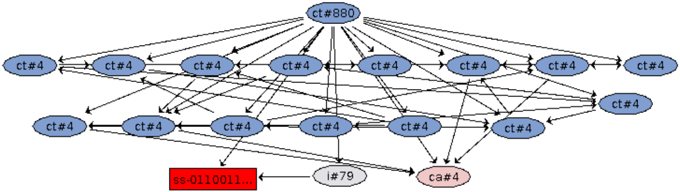


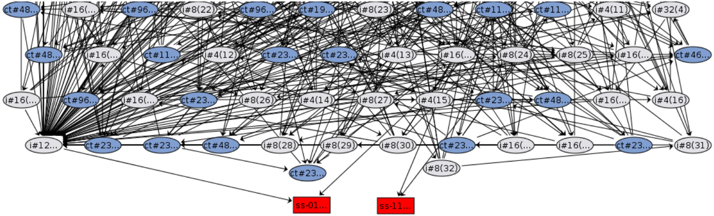
Initial conditions	FireFront ($\alpha = 10^{-5}$)				Avatar (10^4 runs)		
	Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
uncommitted	57s	SS1 (0.67)	0.33	10^3	12.4min	SS1 (0.67) CA2 (0.33)	9.18 5.3

Residual: Neglected + Firefront sets

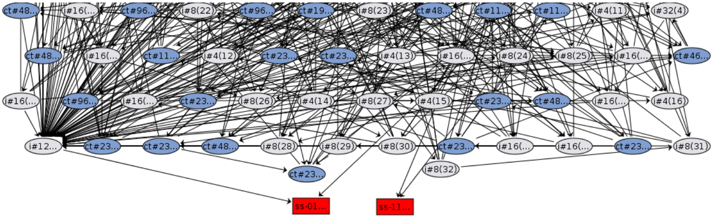
Synthetic models: Random model 4

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Random model 4	0	15	2	0	32 768

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Random model 4	0	15	2	0	32 768



Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Random model 4	0	15	2	0	32 768



Initial conditions	FireFront ($\alpha = 10^{-5}$)				Avatar (10^4 runs)		
	Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
uncommitted	3.2h	SS1 (0.40) SS2 (0.51)	0.09	38	7.6min	SS1 (0.46) SS2 (0.54)	20.64 15.11

Biological models: Mammalian cell cycle

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Mammalian Cell Cycle	1	9	1	1	1 024

Model characteristics

Has small state space

- Half the state space towards a stable state
- Half the state space towards a complex attractor

(Fauré *et al.*, *Bioinformatics* 2006)

Biological models: Mammalian cell cycle

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	Inputs	Proper	Stable	Complex	
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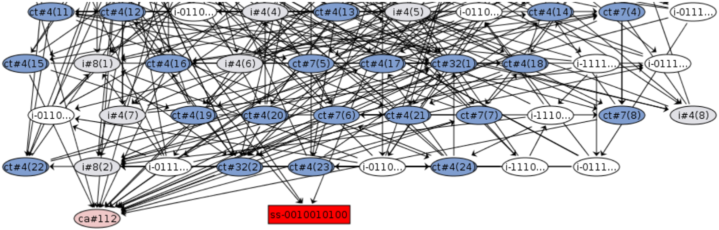

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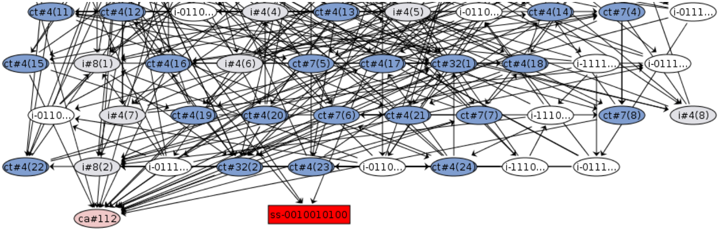

Initial conditions	FireFront ($\alpha = 10^{-5}$)				Avatar (10^4 runs)		
	Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
CycD $= 1$	2.08min	- - (0.00)	1.00	10^3	2.2min	CA1 (1.00)	5.95
sampling	N/A - due to sampling				2.35min	CA1 (0.50) SS2 (0.50)	4.32 2.76

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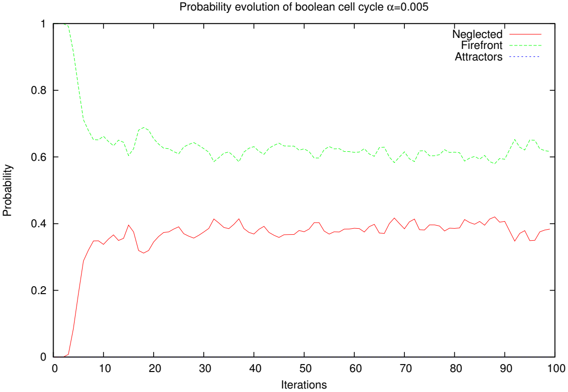
Mammalian Cell Cycle	1	9	1	1	1 024



Initial conditions	FIREFRONT ($\alpha = 10^{-5}$)				AVATAR (10^4 runs)		
	Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
CycD = 1	2.08min	- - (0.00)	1.00	10^3	2.2min	CA1 (1.00)	5.95
sampling	N/A - due to sampling				2.35min	CA1 (0.50) SS2 (0.50)	4.32 2.76

Biological models: Segment Polarity

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Segment Polarity (1-cell)	2	12	3	0	186 624
Segment Polarity (2-cells)	0	24	3	0	$\approx 9.7 \times 10^7$
Segment Polarity (4-cells)	0	48	15	0	$\approx 9.4 \times 10^{17}$

Model characteristics

- No complex attractors
- Multi-stability
- Big state space
- Many small transient cycles

(Sánchez *et al.*, *Int. J. Dev. Biol.* 2008)

Biological models: Segment Polarity

Name	# Components		# Attractors		State space size
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Name	Initial conditions	FireFront ($\alpha = 10^{-5}$)				Avatar (10^4 runs)		
		Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
Segment Polarity (1-cell)	Wg-expressing cell	5s	SS1 (0.84) SS2 (0.16)	$<10^{-3}$	43	617s	SS1 (0.84) SS2 (0.16)	
Segment Polarity (2-cells)	Pair rule	17.74h	SS1 (0.65) SS2 (0.10)	0.25	83	30m	SS1 (0.8904) SS2 (0.1093) SS3 (0.0003)	
Segment Polarity (4-cells)	Pair rule	111.7h	SS1 (0.13) SS2 (0.02) SS3 (0.01)	0.84	52	1.49h	SS7 (0.8702) SS1 (0.0619) SS5 (0.0528) SS4 (0.0135) SS3 (0.0014) SS6 (10^{-4}) SS2 (10^{-4})	

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Name	# Components		# Attractors		State space size
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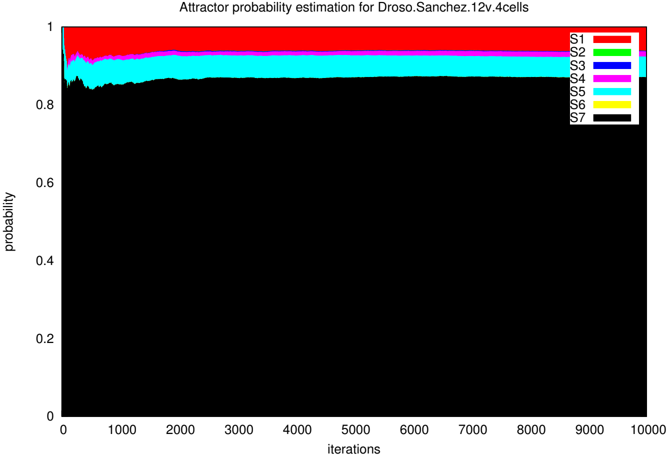

Biological models: Th differentiation

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Th differentiation reduced	13	21	434	0	$\approx 3.9 \times 10^{10}$

Model characteristics

- Multi-stability (input-dependent)
- Huge state space
- Many stable states

(Naldi *et al.*, *PLoS Comp Biol* 2010)

Legend:
SS1 - Th17
SS2 - Th2RORγt+
SS3 - Th0
SS4 - Anergic Th1RORγt+

Biological models: Th differentiation

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
Th differentiation reduced	13	21	434	0	$\approx 3.9 \times 10^{10}$

Initial conditions	FireFront ($\alpha = 10^{-5}$)				Avatar (10^4 runs)		
	Time	Attractors	Residual	Iterations	Time	Attractors (p)	Avg depth
Th17+inputsampling	N/A - due to sampling				1.5min	SS1 (0.63)	1.00
						SS2 (0.13)	7.00
						SS3 (0.12)	13.00
						SS4 (0.12)	4.00

Legend:
SS1 - Th17
SS2 - Th2RORγt+
SS3 - Th0
SS4 - Anergic Th1RORγt+

Biological models: Th differentiation

Name	# Components		# Attractors		State space size
	Inputs	Proper	Stable	Complex	
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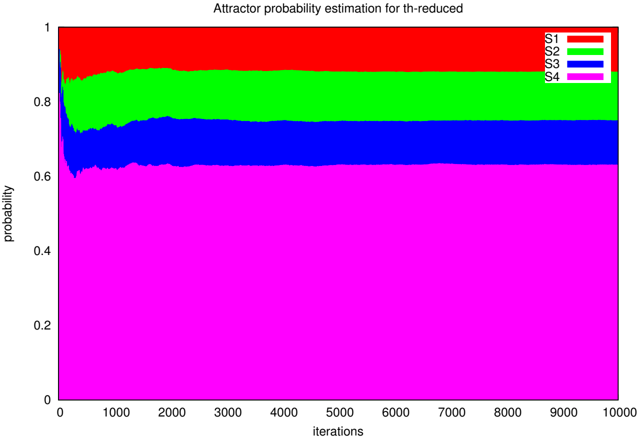

Legend:
SS1 - Th17
SS2 - Th2RORγt+
SS3 - Th0
SS4 - Anergic Th1RORγt+

Complete results

Name	Initial conditions	FireFront ($\alpha = 10^{-5}$) Time	Attractors (p)	Residual	Iterations	Avatar (10^4 runs) Time	Attractors (p)	Avg depth	BoolNet (10^4 runs) Time	Attractors (p)
Random 1	uncommitted	57s	PA1 (0.67)	0.33	10^3	12.4min	PA1 (0.67) CA2 (0.33)	9.18 5.3	19s	PA1 (0.67) CA2 (0.33)
Random 2	uncommitted	2s	PA1 (0.25)	0.75	10^3	1.8min	PA1 (0.25) CA2 (0.75)	6.43 9.18	19s	PA1 (0.25) CA2 (0.75)
Random 3	uncommitted	30s	PA1 (0.21)	0.79	10^3	5.3min	PA1 (0.21) CA2 (0.79)	8.83 8.45	20s	PA1 (0.20) CA2 (0.80)
Random 4	uncommitted	3.2h	PA1 (0.40) PA2 (0.51)	0.09	38	7.6min	PA1 (0.46) PA2 (0.54)	20.64 15.11	19s	PA1 (0.46) PA2 (0.54)
Synthetic 1	uncommitted	82h	PA1 (0.56)	0.44	10^3	35min	PA1 (0.58) CA1 (0.42)	18.45 9.01	185.5h	PA1 (0.60) CA2 (0.40)
Synthetic 2	uncommitted	51.6h	PA1 (0.06) PA2 (10^{-4})	0.94	10^3	58.5min	PA1 (0.07) PA2 (0.93)	27.15 13.85	120h	PA1 (0.08) PA2 (0.92)
Mammalian Cell Cycle	CycD = 1	2.08min	- - (0.00)	1.00	10^3	2.2min	CA1 (1.00)	5.95	3.25min	CA1 (1.00)
Mammalian Cell Cycle	sampling	N/A - due to sampling				2.35min	CA1 (0.50) PA2 (0.50)	4.32 2.76	1.83min	CA1 (0.50) PA2 (0.50)
Segment Polarity (1-cell)	Wg-expressing cell	5s	PA1 (0.84) PA2 (0.16)	$<10^{-3}$	43	8.2min	PA1 (0.84) PA2 (0.16)	8.84 11.17	N/A - Boolean only	
Segment Polarity (2-cells)	Pair rule	17.2h	PA1 (0.65) PA2 (0.10)	0.25	83	25.2min	PA1 (0.89) PA2 (0.11) PA3 (10^{-4})	38.83 18.64 49.00	N/A - Boolean only	
Segment Polarity (4-cells)	Pair rule	105.7h	PA1 (0.13) PA2 (0.02) PA3 (0.01)	0.84	52	1.2h	PA1 (0.87) PA2 (0.06) PA3 (0.06) PA4 (0.01) PA5 (10^{-3}) PA6 (10^{-4}) PA7 (10^{-4})	59.12 43.40 36.51 67.01 55.10 96.50 138.00	N/A - Boolean only	
Th differentiation reduced	Th17+inputsampling	N/A - due to sampling				1.5min	PA1 (0.63) PA2 (0.13) PA3 (0.12) PA4 (0.12)	1.00 7.00 13.00 4.00	N/A - Boolean only	

Outline

Conclusions

Challenge

- Characterize and quantify the attractors in the context of **discrete asynchronous** dynamics
- The difficulty lies in the size and structure of the state spaces

Conclusions

Challenge

- Characterize and quantify the attractors in the context of **discrete asynchronous** dynamics
- The difficulty lies in the size and structure of the state spaces

- There is no ideal solution
  The structure of the state space is **unknown** *a priori*
- We propose two approaches to tackle the problem

Conclusions

- Best approach to use depends on the structure of the STG
- The number and size of transient cycles have an impact on both FireFront and Avatar

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FireFront

- Fast and quasi-exact for STGs which are not too "wide"

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- The number and size of transient cycles have an impact on both FireFront and Avatar

FireFront

- Fast and quasi-exact for STGs which are not too "wide"

Avatar

- Well-suited to deal with cycles (complex attractors and transients)
- Rare attractors may need many simulation runs to be found

Prospects

- Instead of considering **equiprobable** successor states, **weights** can be introduced (per component)
- Integrate the approaches in GINsim

Thank you!

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	Previous	Current
NDM	PTDC/EIACCO/099229/2008	EXCL/EEI-ESS/0257/2012
PTM	SFRH/BPD/75124/2010	PEst-OE/EEI/LA0021/2013
		IF/01333/2013

Availability

http://compbio.igc.gulbenkian.pt/nmd/node/59

Questions?!

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Instituto Gulbenkian de Ciência

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