Verification of Dynamic Properties by Model Checking

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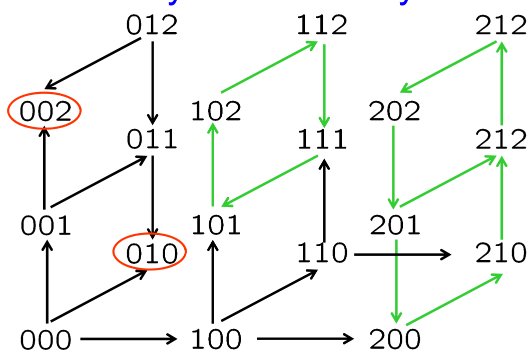
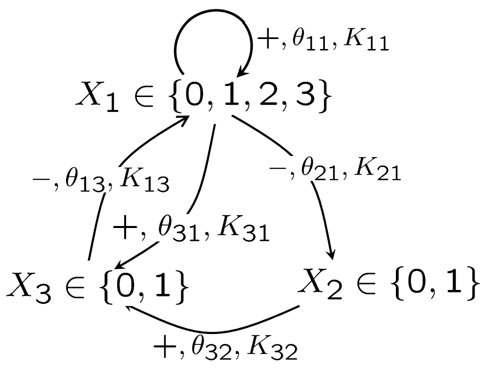
SS 2015

Steady states and cycles

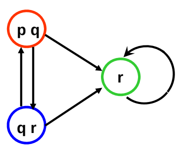


Interaction graph: topology

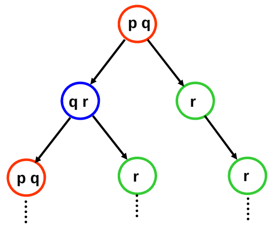


Model checking

Transition system or Kripke model

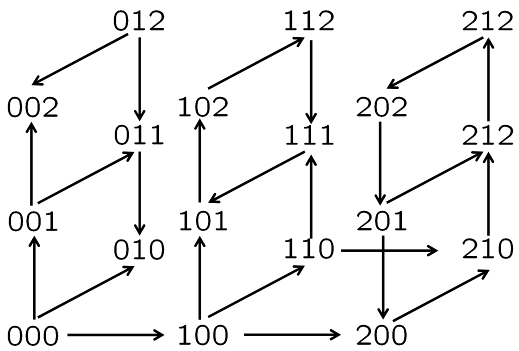


Infinite computation tree



check dynamics properties using *some* temporal logic

State transition graph: dynamics

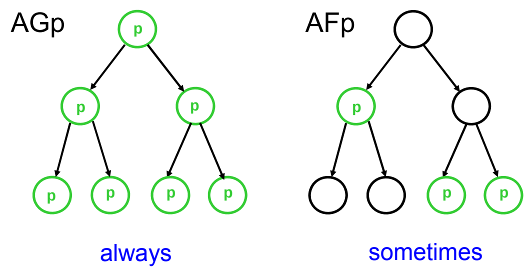


1. Temporal logic

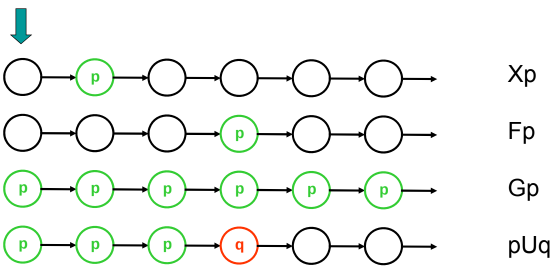
Computation Tree Logics

- Atomic formulae/properties: p, q, r, …
  e.g. p ≡ "gene P is on"
- Boolean operators: $\neg$, $\wedge$, $\vee$, $\Rightarrow$
- Linear time operators
  - X p : p holds next time
  - F p : p holds sometimes in the future
  - G p : p holds globally in the future
  - p U q : p holds until q holds
- Path quantifiers
  A : for every path, E : there exists a path

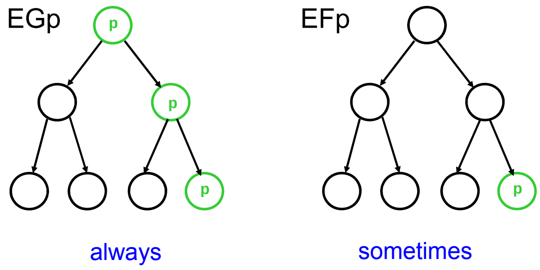
For all paths …



Linear time operators



There exists a path …



CTL

- There exist different computation tree logics: CTL*, LTL, CTL, …
- In CTL, each of the linear time operators G, F, X, and U must be immediately preceded by a path quantifier.
- Example : AG (EF p)
- Mostly used CTL operators :
  AG, AF, EG, EF

Examples

- EF(p $\wedge$ EF q): Can q hold after p holds ?
- AF(AG p): Must the system reach a state where p holds forever ?
- EG((p $\Rightarrow$ EF($\neg$ p)) $\wedge$ ($\neg$ p $\Rightarrow$ EF(p))):
  Can the system exhibit cyclic behavior w.r.t. property p?

Logic: Syntax and semantics

- Syntax
  When a sequence of symbols is a formula ?
- Semantics
  What is the meaning of the formula ?
  When is it true or false ?

CTL Semantics

Given a Kripke model M = (S, $\rightarrow$, L), a state $s \in S$, and a CTL formula ϕ, the satisfaction relation

$M,s \models \phi$ (shortly $s \models \phi$)

is inductively defined as follows:

- $s \models p$ iff $p \in L(s)$
- $s \models \neg \phi$ iff not $s \models \phi$
- $s \models \phi \wedge \psi$ iff $s \models \phi$ and $s \models \psi$
- $s \models \phi \vee \psi$ iff $s \models \phi$ or $s \models \psi$

Kripke model

Formulas are interpreted over Kripke models

M = (S, $\rightarrow$, L)

- S is a finite set of states,
- $\rightarrow \subseteq S \times S$: total transition relation
  (i.e., for each $s \in S$, there exists $s' \in S$ with $s \rightarrow s'$),
- Labeling $L : S \rightarrow 2^{AP}$ defines for each state s the set L(s) of atomic formulas true in s.

CTL Semantics II

- $s \models AF\ \phi$ iff for all paths $s = s_1 \rightarrow s_2 \rightarrow \ldots$ we have $s_i \models \phi$, for some $i \geq 1$.
- $s \models EF\ \phi$ iff for some path $s = s_1 \rightarrow s_2 \rightarrow \ldots$ we have $s_i \models \phi$, for some $i \geq 1$.
- $s \models AG\ \phi$ iff for all paths $s = s_1 \rightarrow s_2 \rightarrow \ldots$ we have $s_i \models \phi$, for all $i \geq 1$.
- $s \models EG\ \phi$ iff for some path $s = s_1 \rightarrow s_2 \rightarrow \ldots$ we have $s_i \models \phi$, for all $i \geq 1$.

CTL Syntax

- Atomic formulas are CTL formulas.
- If ϕ and ψ are CTL formulas, then
  $\neg \phi$, $\phi \wedge \psi$, $\phi \vee \psi$,
  AF ϕ, EF ϕ,
  AG ϕ, EG ϕ,
  AX ϕ, EX ϕ,
  A[ϕ U ψ], E[ϕ U ψ]

are CTL formulas.

CTL Semantics III

- $s \models AX\ \phi$ iff for all $s' \in S$ with $s \rightarrow s'$ we have $s' \models \phi$.
- $s \models EX\ \phi$ iff for some $s' \in S$ with $s \rightarrow s'$ we have $s' \models \phi$.
- $s \models A[\phi\ U\ \psi]$ iff for all paths $s = s_1 \rightarrow s_2 \rightarrow \ldots$ there exists $i \geq 1$ such that $s_i \models \psi$ and $s_j \models \phi$, for all $1 \leq j < i$.
- $s \models E[\phi\ U\ \psi]$ iff for some path $s = s_1 \rightarrow s_2 \rightarrow \ldots$ there exists $i \geq 1$ such that $s_i \models \psi$ and $s_j \models \phi$, for all $1 \leq j < i$.

2. Model checking algorithm

Model checking algorithm

- Input: Kripke model M = (S, →, L) and CTL formula ϕ
- Output: Set of states in M that satisfy ϕ
- Labeling algorithm: Label states of M with the subformulas of ϕ that are satisfied there, starting with the smallest subformulas and working outwards towards ϕ.

Model checking

- M Kripke model (or transition system)
- ϕ temporal logic formula
- Find all states s of M such that

$$s \models \phi$$

- Efficient model checking algorithms and software tools exist for the logic CTL.

Model checking algorithm (II)

- Let g be a subformula of ϕ and suppose all immediate subformulas of g have already been labeled.
- Determine states to be labeled by g a follows:

If g is

✓ false : no state is labeled

✓ p : label s with p if $p \in L(s)$

✓ $f_1 \wedge f_2$: label s with $f_1 \wedge f_2$ if s is already labeled with both f_1 and f_2.

✓ $\neg$ f : label s with $\neg$ f if s is not already labeled with f.

Equivalences

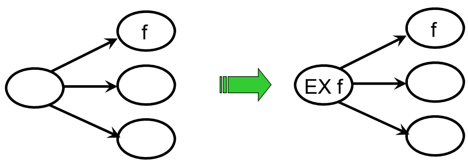
- AX f = $\neg$ EX ($\neg$ f)
- AG f = $\neg$ EF ($\neg$ f)
- EG f = $\neg$ AF ($\neg$ f)
- EF f = E[true U f]
- A[f U g] = $\neg$ E[$\neg$ g U ($\neg$ f $\wedge$ $\neg$ g)] $\wedge$ AF g

⇒ any CTL formula can be expressed using only the operators EX, EU, and AF.

Model checking algorithm (III)

✓EX f :

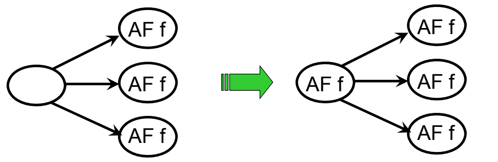
label s with EX f if one of its successors is labeled with f.



Model checking algorithm (IV)

✓AF f :

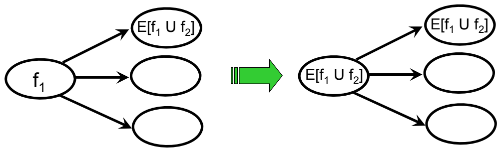
- If any state is labeled with f, label it with AF f.
- Repeat : label any state with AF f if all successor states are labeled with AF f, until there is no change.



Model checking algorithm (V)

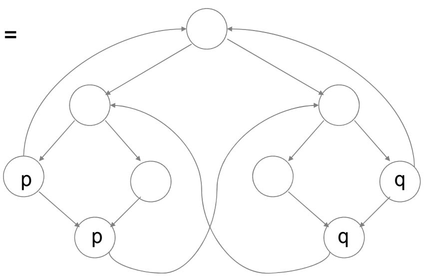
✓ $E[f_1 \text{ U } f_2]$:

- If any state is labeled with f_2, label it with $E[f_1 \text{ U } f_2]$.
- Repeat : label any state with $E[f_1 \text{ U } f_2]$ if it is labeled with f_1 and at least one of its successors is labeled with $E[f_1 \text{ U } f_2]$, until there is no change.



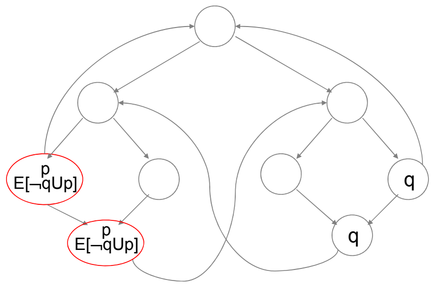
Example: Input

M =



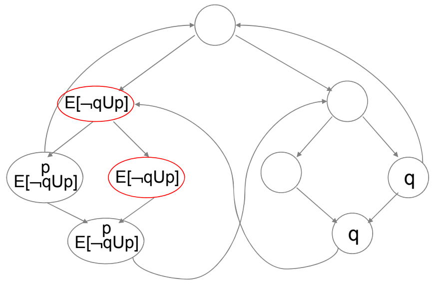
ϕ = AF(E[¬q U p] v EXq)

Example: EU



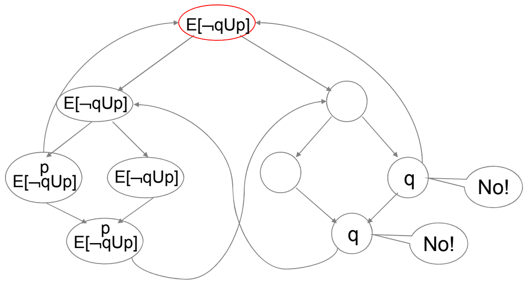
Label with E[¬qUp] all states which satisfy p

Example: EU (contd)



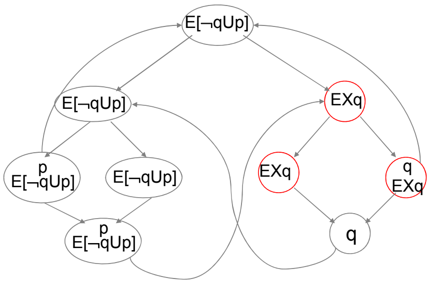
Label any state s with E[¬qUp] if it is labeled with ¬q and at least one of its successor is already labeled with E[¬qUp]

Example: EU (contd)



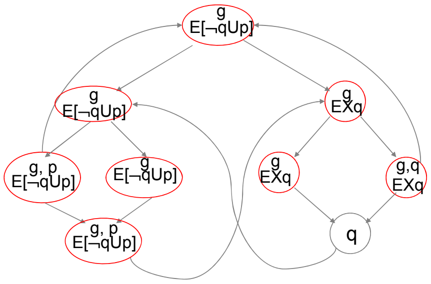
Label any state s with E[¬qUp] if it is labeled with ¬q and at least one of its successor is already labeled with E[¬qUp]

Example: EX



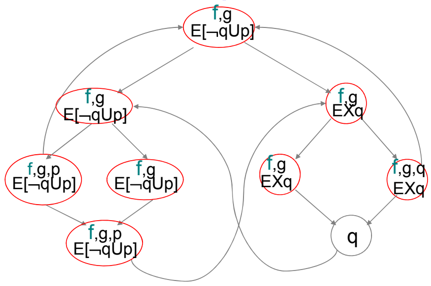
Label with EXq any state s with one of its successors already labeled with q

Example: ∨



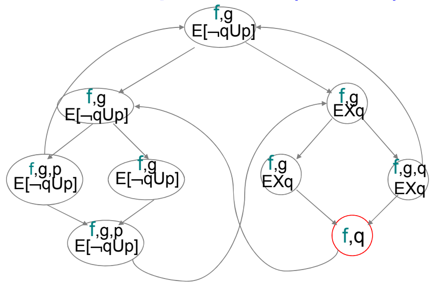
Label with g= E[¬qUp] v EXq any state s already labeled with E[¬qUp] or EXq

Example: AF



Label with f= AF(E[¬qUp]vEXq) any state already labeled with g= E[¬qUp]vEXq

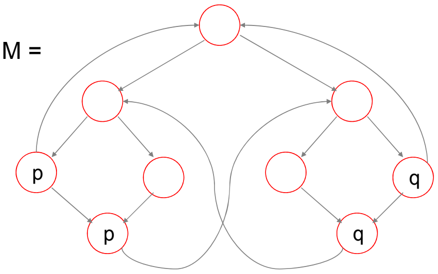
Example: AF (contd)



Label any state s with f if all successors of s are already labeled with f

Example: Output

M =



All states satisfy AF(E[¬q U p] v EXq)

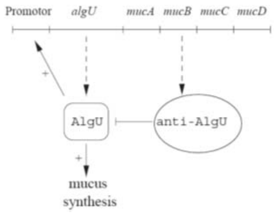
3. Biological application

SMBioNet

Bernot/Comet/Richard/Guespin 2004

- Model checking applied to gene regulatory networks
- Input
  - Regulatory network
  - Functional circuits, steady states
  - Biological properties formulated in CTL
- Output : List of compatible models (each defined by its logical parameters) ⇒ reverse engineering
- Software package: http://smbionet.lami.univ-evry.fr

Regulatory network



Is this biological knowledge compatible with a model exhibiting multiple steady states, where one state regularly produces mucus and the other does not ?

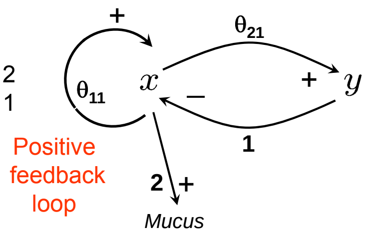
Application : *Pseudomonas aeruginosa*

- Bacteria commonly present in the environment.
- They secrete mucus only in lungs affected by cystic fibrosis (major cause of mortality).
- Bacteria isolated from cystic fibrosis' lungs continue to grow in laboratory for many generations (mucoid phenotype).
- A majority of these bacteria present a mutation (elimination of the anti-AlgU) .

Formalization

Two cases :

1. $\theta_{11} = 1 < \theta_{21} = 2$
2. $\theta_{11} = 2 > \theta_{21} = 1$



What are the possible dynamic behaviors of this network ?

Biological question

- Is the mutation the cause of the passage to the mucoid state, or could the mucoidy be induced by an epigenetic phenomenon?
- In this case, the mutation could be favored by another mechanism.

Model selection

- Many possible models
- Various combinations for logical parameters
- Use model checking to find out whether there exist models satisfying certain biological properties.
- SMBioNet software

Biological properties

- Multiple steady states: positive circuit should be functional, i.e., its characteristic state has to be steady.
- Temporal logic properties
  - Mucus is produced regularly

$$(x = 2) \Rightarrow AX\ AF(x = 2)$$

  - Mucus is never produced when starting in basal state

$$(x = 0) \Rightarrow AG(\neg(x = 2))$$

References

- E. Clarke, O. Grumberg, D.A. Peled: Model checking, MIT Press, 2000
- M. R. A. Huth, M. D. Ryan: Logic in Computer Science, Cambridge Univ. Press, 2000
- G. Bernot, J.-P. Comet, A. Richard and J. Guespin: Application of formal methods to biological regulatory networks: extending Thomas' asynchronous logical approach with temporal logic. J. Theor. Biol. 229, 339 – 347, 2004

Example

- 648 parameter settings at the beginning
- Snoussi constraints: 56 parameter sets resp. 38 different Kripke models
- Functionality of positive circuit: 19 models
- CTL formulas: 4 models

Epigenetic hypothesis is compatible with the model

Conclusion

- Discrete modeling
- Transition systems
- Temporal logic
- Model checking
  - Analyse all possible trajectories (≠ simulation)
  - Query the model / test properties
  - Reverse engineering
- Formal vs. numerical methods