Model Checking Emergent Behavior in Networks of Cardiac Myocytes: A Spatial Approach

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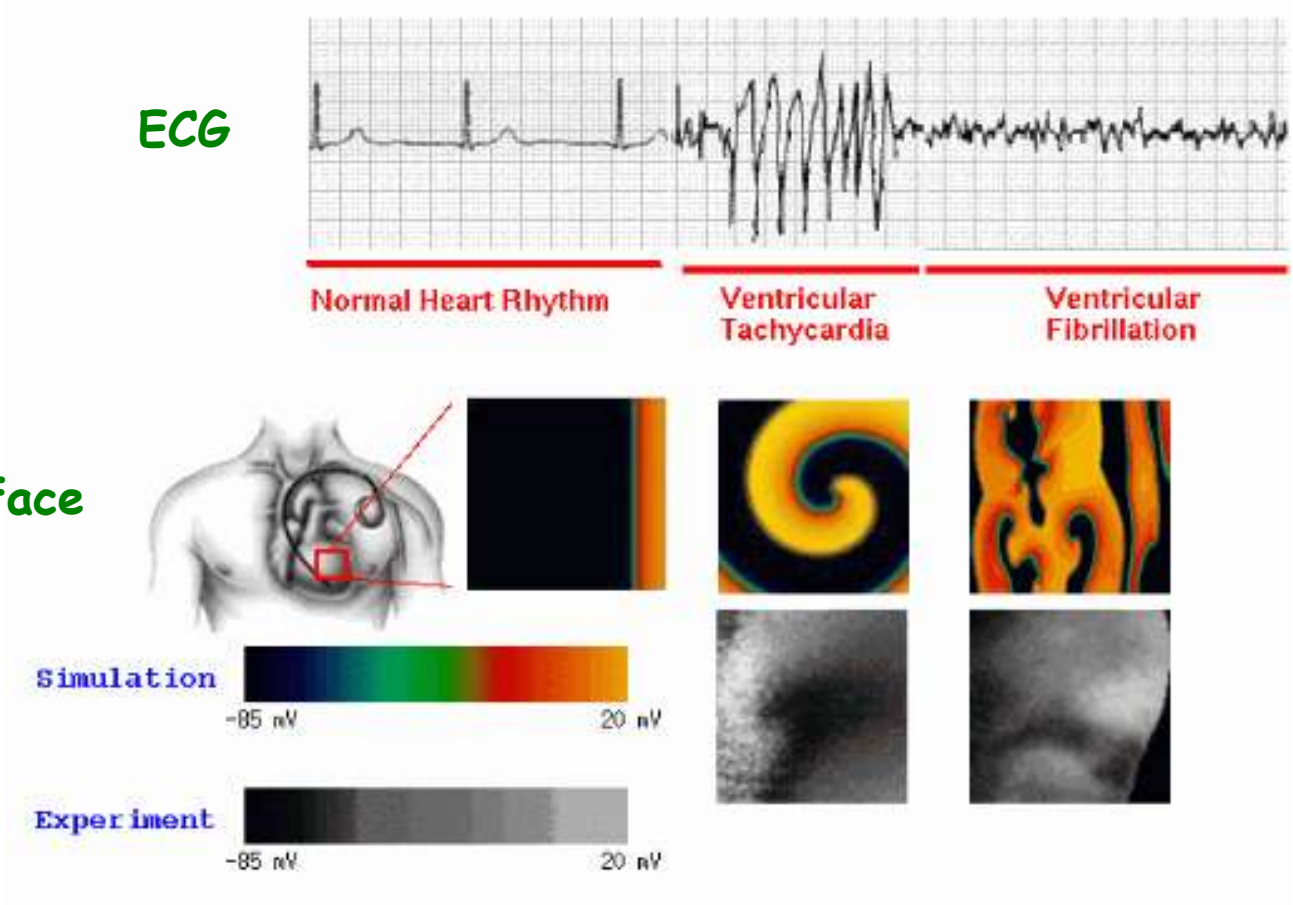
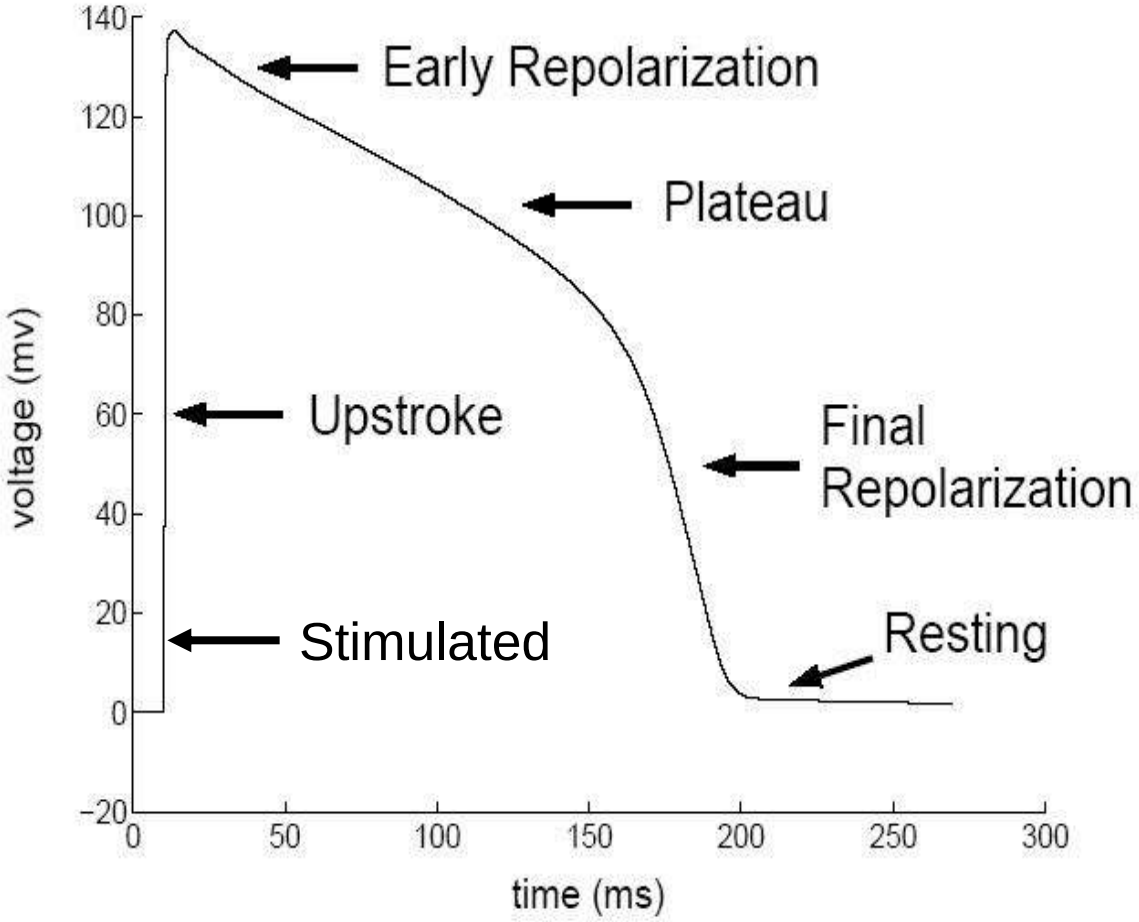
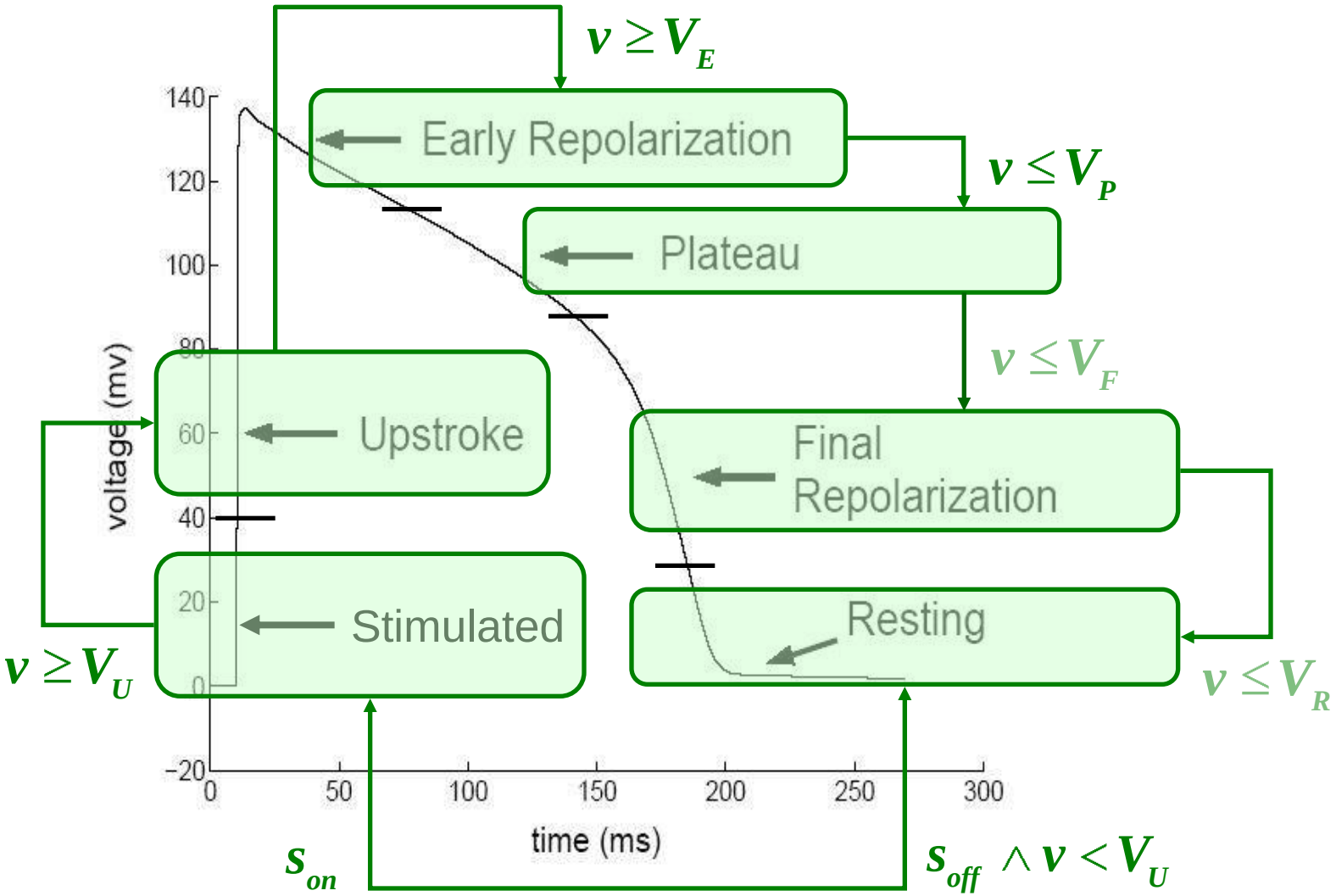
Emergent Behavior in Cardiac Tissue



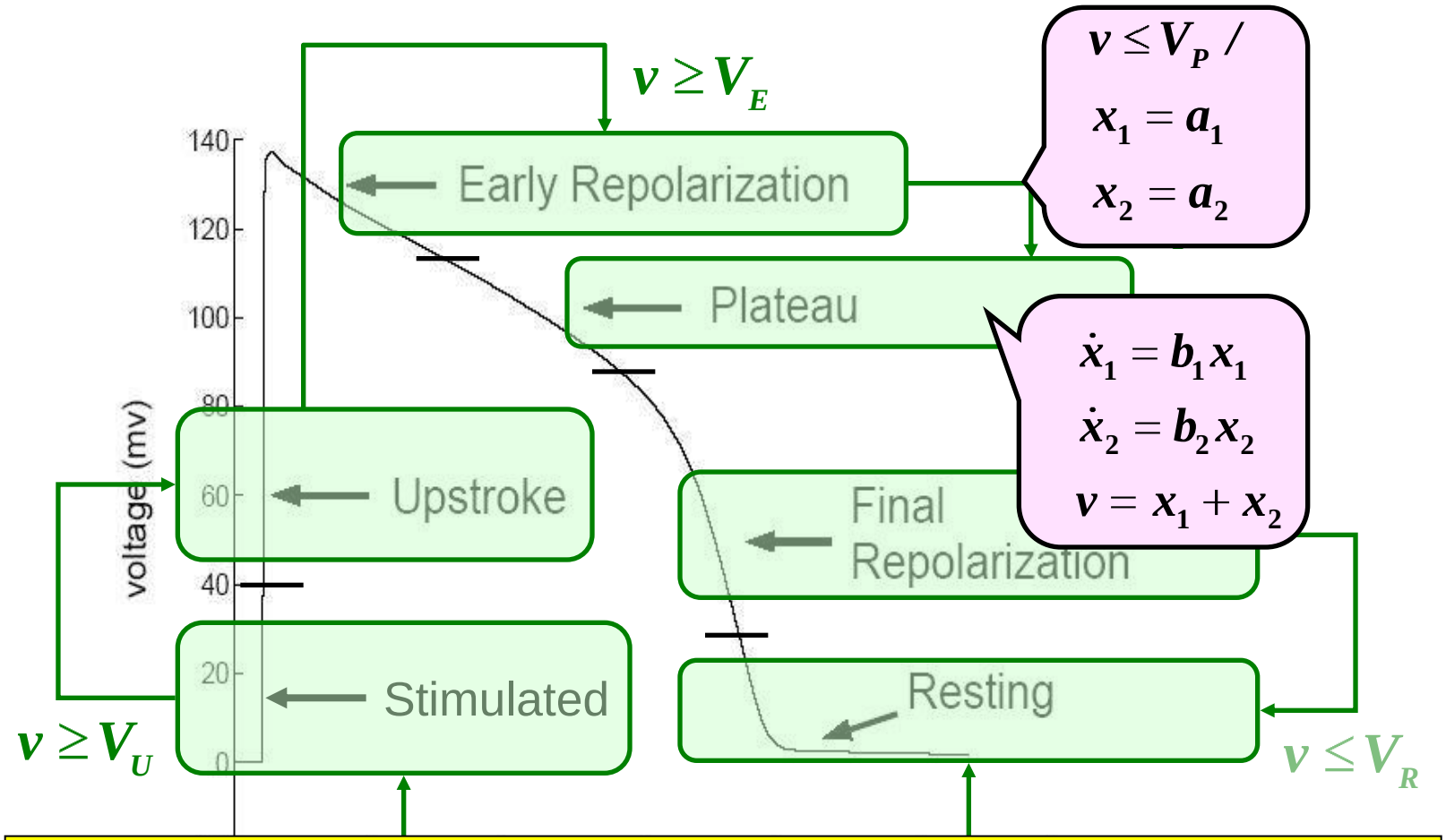
Hybrid Automaton Model: Cardiac Cell



Hybrid Automaton Model: Cardiac Cell

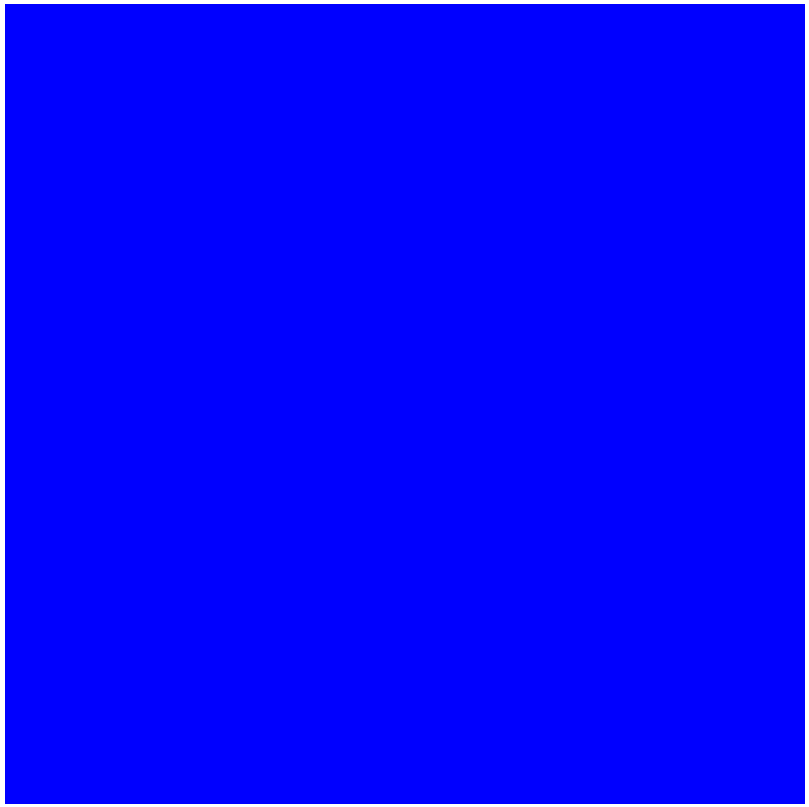


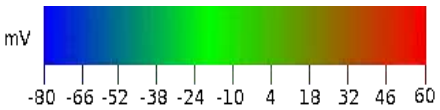
Hybrid Automaton Model: Cardiac Cell

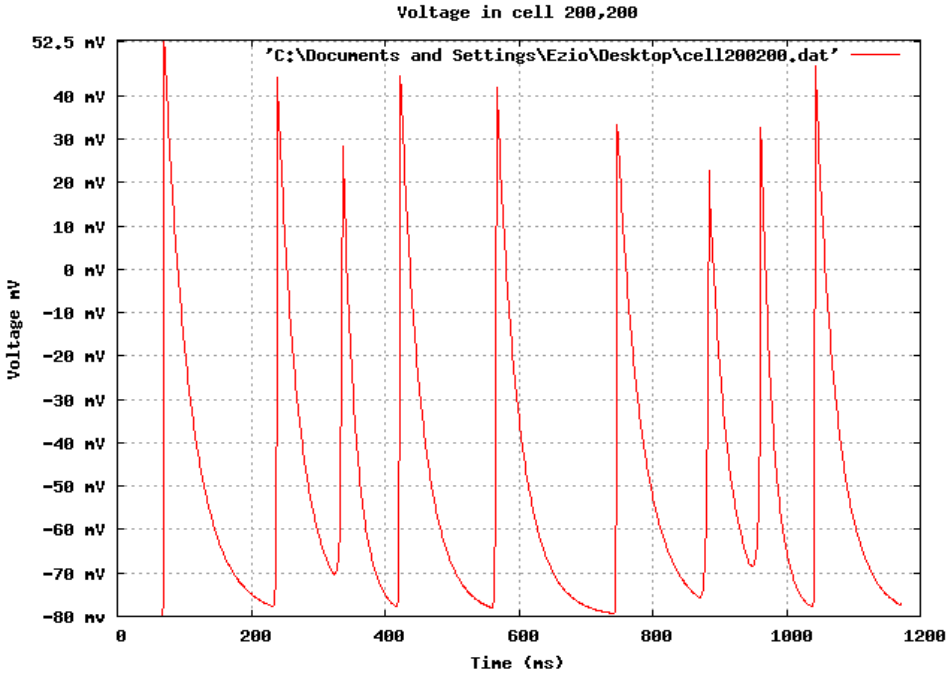


P. Ye, E. Entcheva, S.A. Smolka and R. Grosu. **A Cycle-Linear Hybrid-Automata Model for Excitable Cells.** *IET Systems Biology, vol. 2(1), pp. 24-32, January, 2008.*

HA Network (Spatial) Simulation

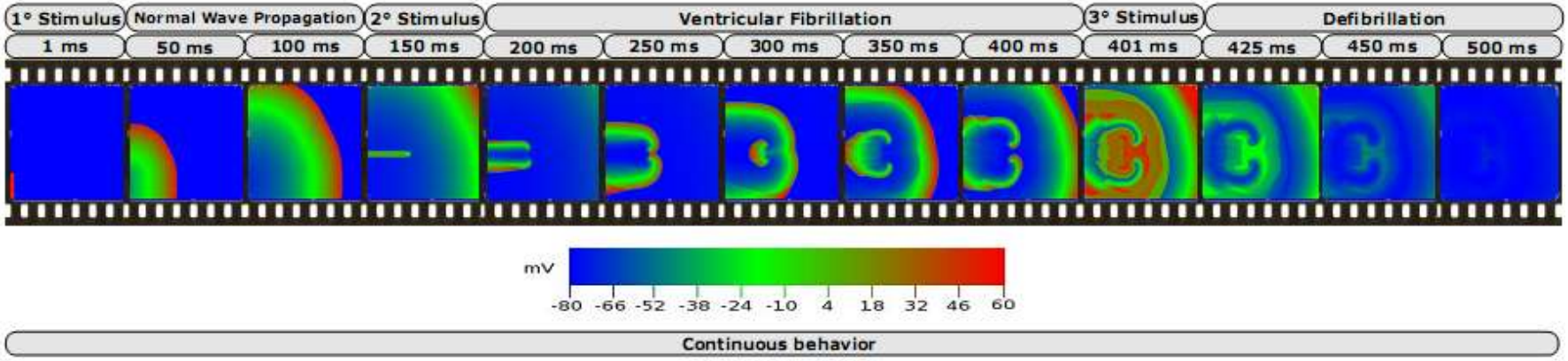


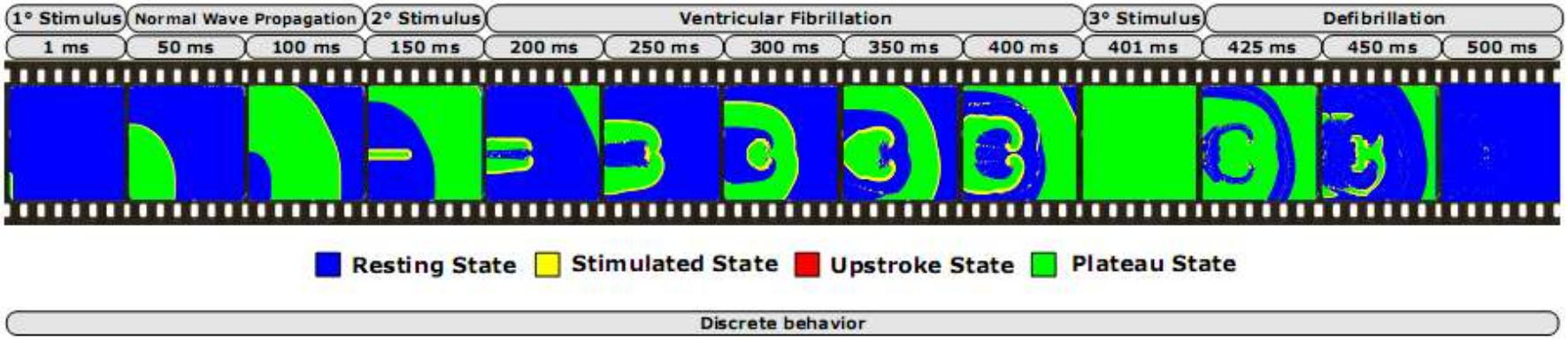




- Fibrillation/Defibrillation protocol
- 400 x 400 HA cell array

(Finite) Mode Abstraction

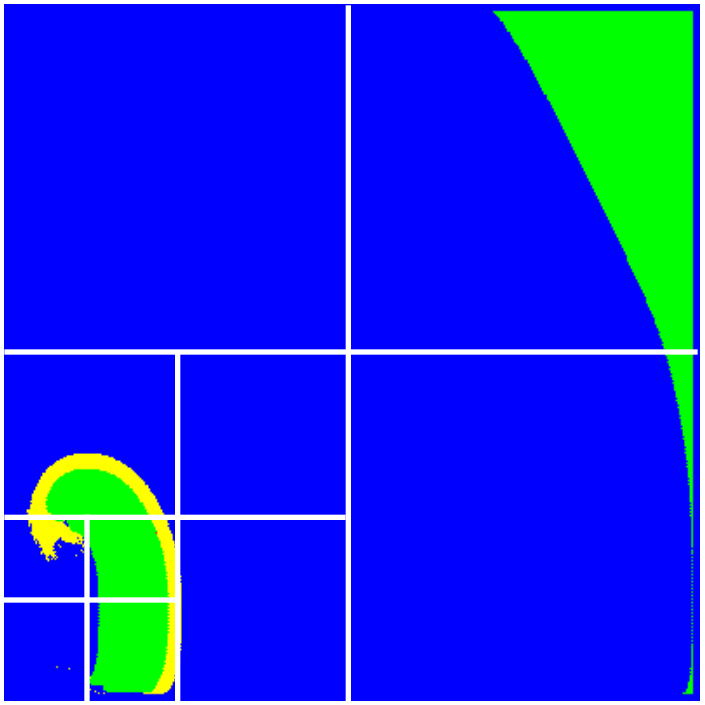




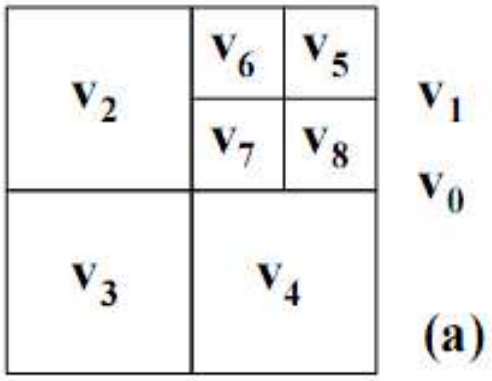
- **Preserves** spatial properties ($4^{160,000}$ images)

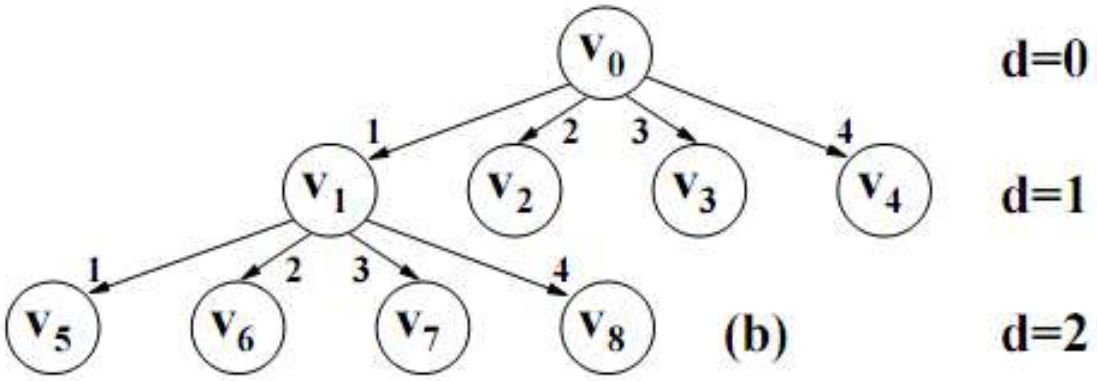
Problem to Solve

- Does a (mode-abstracted) snapshot of an HA network contain a spiral?
- Can we check for spirals efficiently?
- Spatial Abstraction!



Superposition Quadtrees (SQTs)



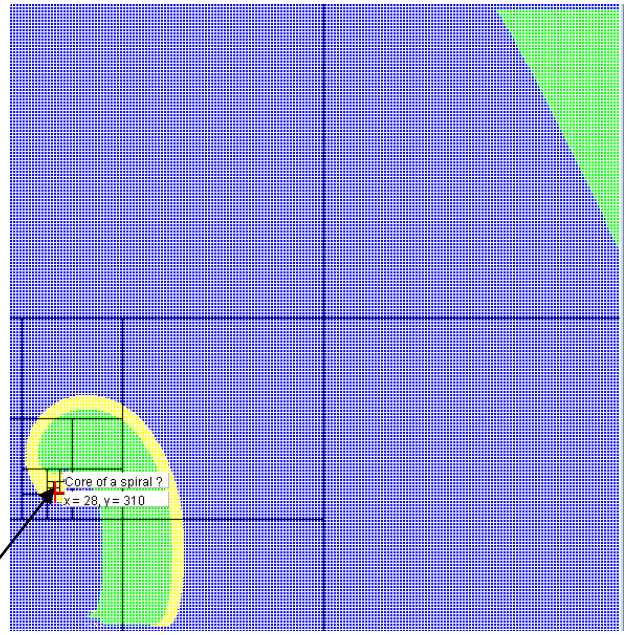


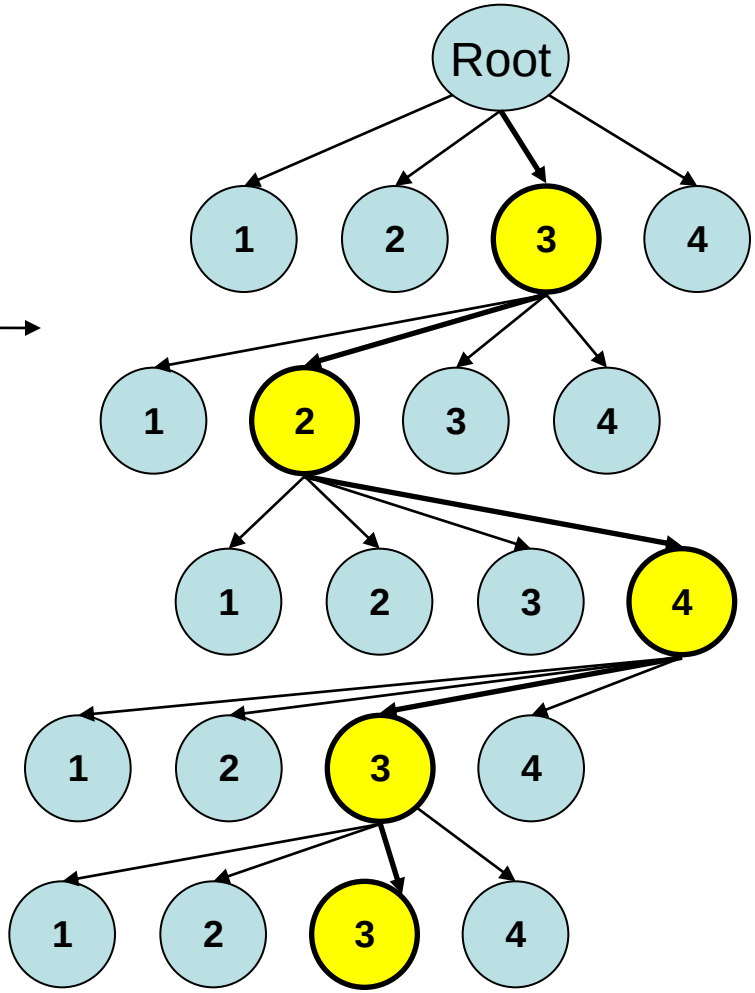
$\exists!m \in \{s,u,p,r\}.\ p_l(m) = 1$

$$p_i(m) = \frac{1}{4}\sum_{j=1}^{4} p_{ij}(m_j)$$

Abstract position and compute PMF $p(m) \equiv P[D=m]$

Path to the Core of a Spiral





Click the core to determine quadtree and path leading to the core

Temporal-Logic Model Checking

- $M \models \varphi$?
- M is a Kripke structure (system model)
- φ is a temporal-logic formula (property)
- LTL (Linear Temporal Logic)
- State explosion !!

Spatial-Logic Model Checking

- Spiral detection can be cast as problem of Spatial-Logic Model Checking
- SQTs as Kripke structures
- Linear Spatial Superposition Logic (LSSL): (bounded) LTL interpreted over SQTs
- Space-Time duality!

Linear Spatial-Superposition Logic

Syntax

atomic formulas

$$\varphi ::= \top \mid \bot \mid P[D = m] \sim d \mid \neg\phi \mid \varphi \vee \psi \mid X\varphi \mid B\varphi \mid \varphi U \varphi \mid \varphi R \varphi$$
$$\sim ::= < \mid \leq \mid = \mid \geq \mid >$$

Semantics

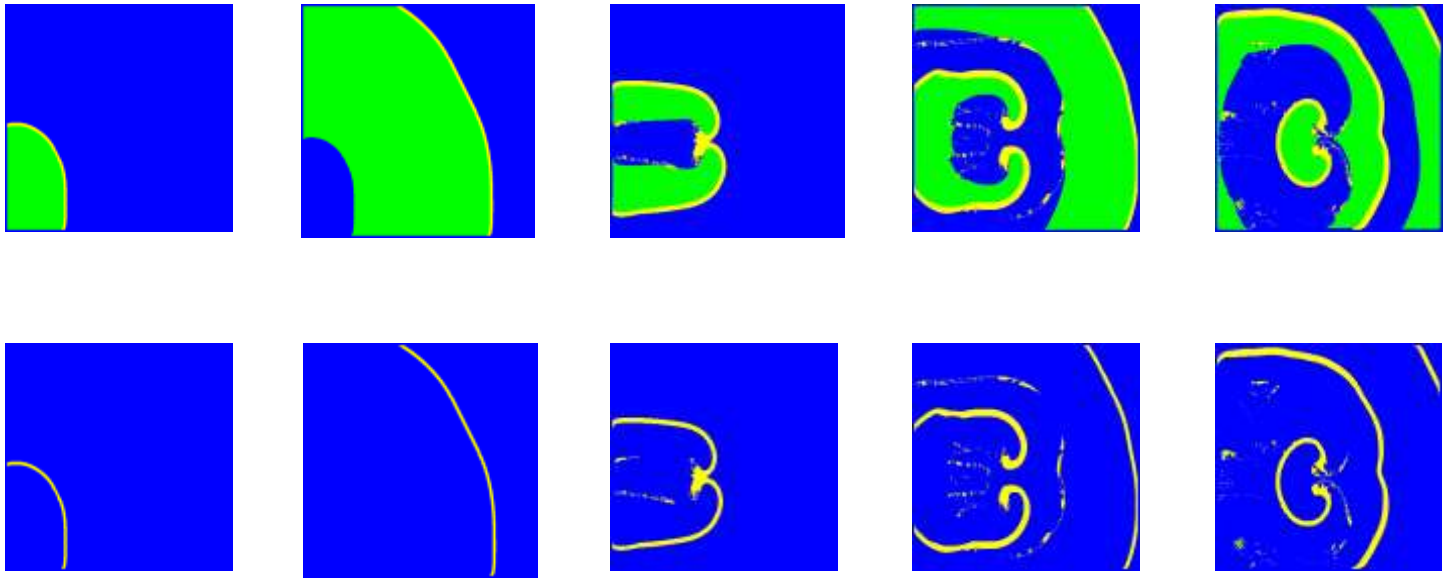
$$\pi \models^i_k \top \quad and \quad \pi \not\models^i_k \bot$$
$$\pi \models^i_k p \Leftrightarrow p \in L(\pi[i])$$
$$\pi \models^i_k \neg\varphi \Leftrightarrow \pi \not\models^i_k \varphi$$
$$\pi \models^i_k \varphi \vee \psi \Leftrightarrow \pi \models^i_k \varphi \ or \ \pi \models^i_k \psi$$
$$\pi \models^i_k X\varphi \Leftrightarrow i < k \ and \ \pi \models^{i+1}_k \varphi$$
$$\pi \models^i_k B\varphi \Leftrightarrow 0 < i \leq k \ and \ \pi \models^{i-1}_k \varphi$$
$$\pi \models^i_k \varphi U \psi \Leftrightarrow \exists j.\ i \leq j \leq k.\ \pi \models^j_k \psi \ and \ \forall n.\ i \leq n < j.\ \pi \models^n_k \varphi$$
$$\pi \models^i_k \psi R \varphi \Leftrightarrow \forall j.\ i \leq j \leq k.\ \pi \models^j_k \varphi \ or \ \exists n.\ i \leq n < j.\ \pi \models^n_k \psi$$

concretization

superposition

What is the LSSL Formula for a Spiral?

- Measure density of mode stimulated



- Yellow modes represent the wave front

LSSL Formula for a Spiral

LSSL formula φ for path to core of spiral:

$$X^7(P(D=s) \leq 0.875) \wedge X^2(P(D=s) > 0.049) \vee$$
$$X^7(P(D=s) > 0.875) \wedge X^3(P(D=s) \leq 0.078) \wedge (P(D=s) > 0.025)$$

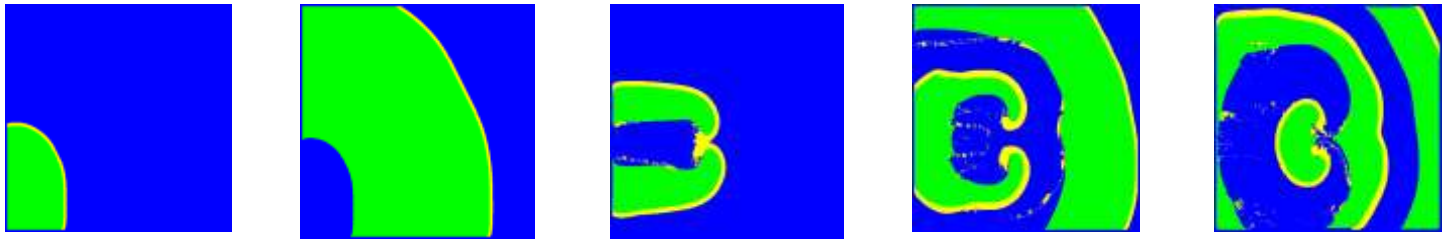
Yikes!

Use Machine Learning!

Spiral detection for SQT T: reduces to BMC of $T \models \varphi$

Learning φ

User selects spiral core (if present) in a series of (mode-abstracted) images:

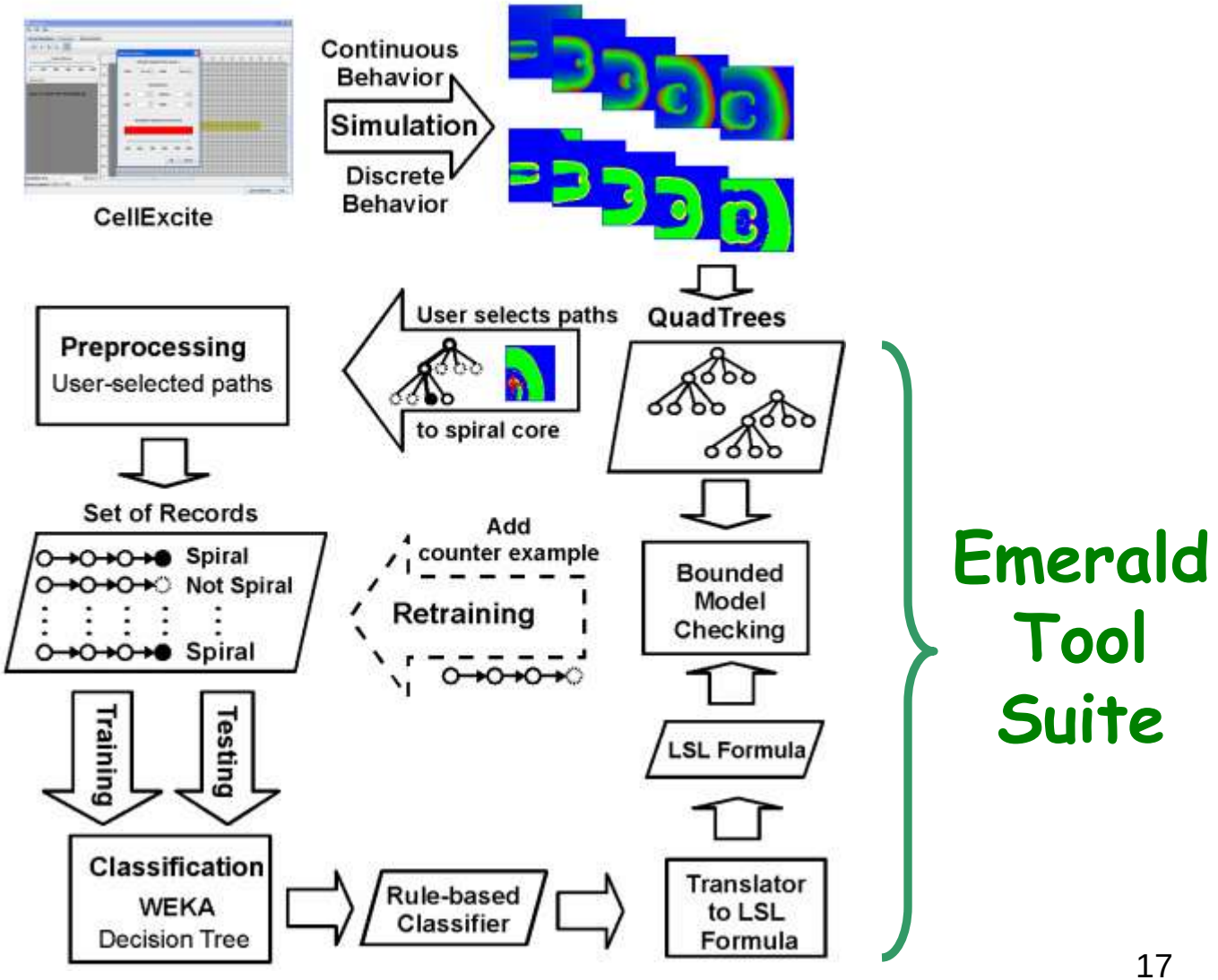


1 2 3 4 5

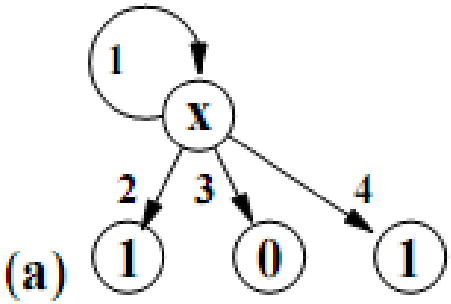
Results in training data for a WEKA path classifier

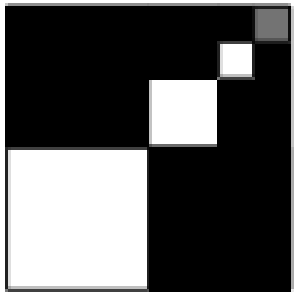
Record	a1	a2	a3	a4	…	Spiral
1	…	…	…	…	…	N
2	…	…	…	…	…	N
3	…	…	…	…	…	Y
4	…	…	…	…	…	Y
5	…	…	…	…	…	Y

Overview of Our Approach

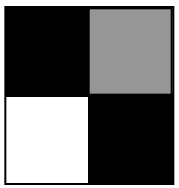


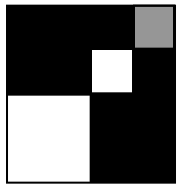
LSSL: The Unbounded Case!





$$x = \frac{x+2}{4} \Rightarrow x = \frac{2}{3}$$





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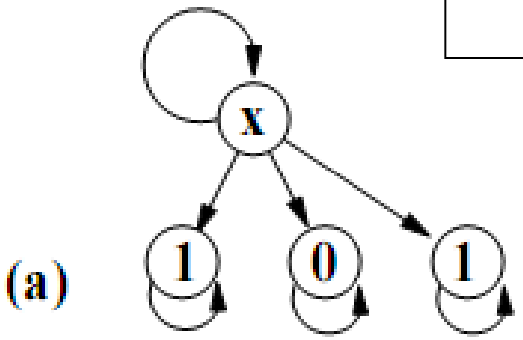


$$\neg G\left(\ P[D=b] = \frac{2}{3}\ \right)$$

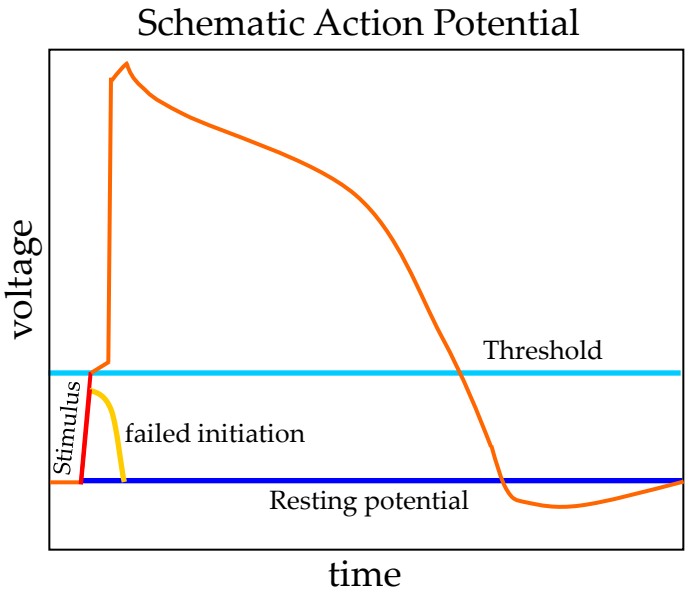
Conclusions

- Model checking emergent behavior, spatially
- Future Work: spatio-temporal model checking (videos!)

Action Potential (AP)

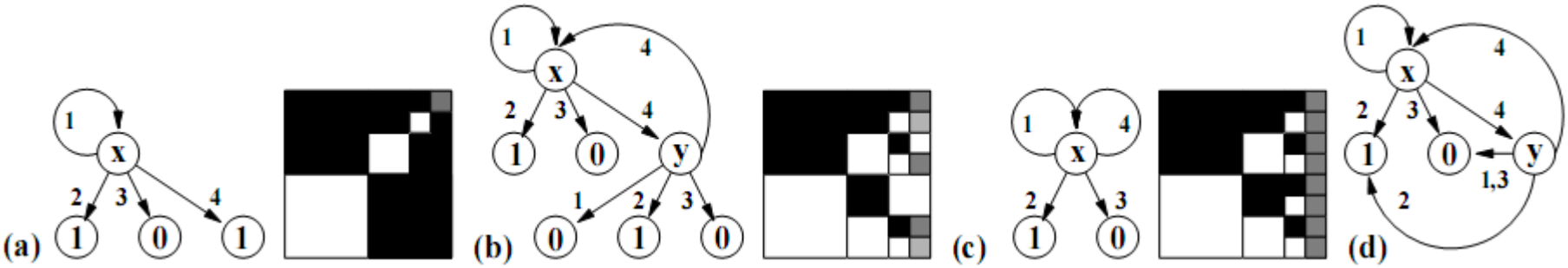
Membrane's AP depends on:

- **Stimulus (voltage or current):**
  - **External**
  - **Neighboring cells**
- **Cell's state**

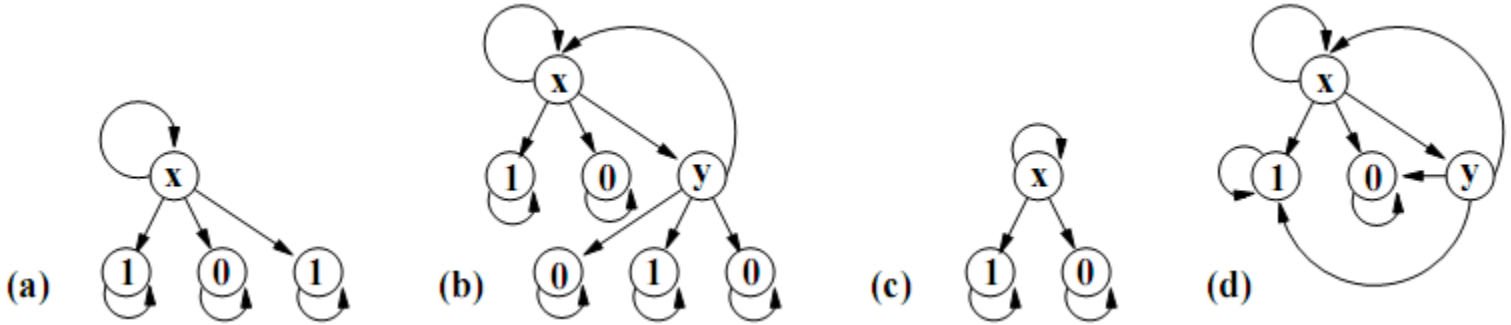


Thank you for the attention !!!

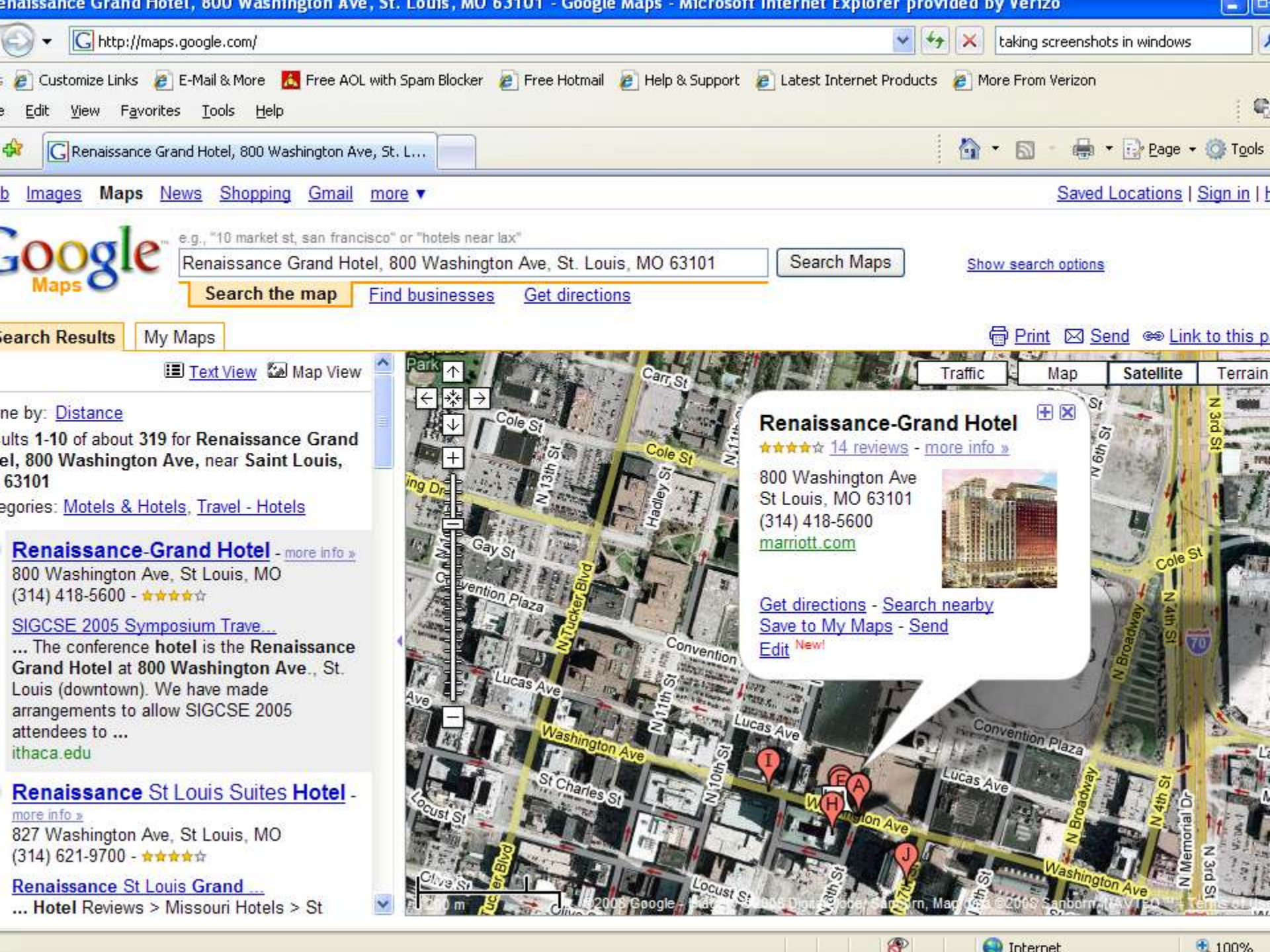
SQGs and Kripke Structures (KSs)



Superposition Quadgraphs (Fractals): **modal SSL**



Kripke Structure: **linear / branching SSL**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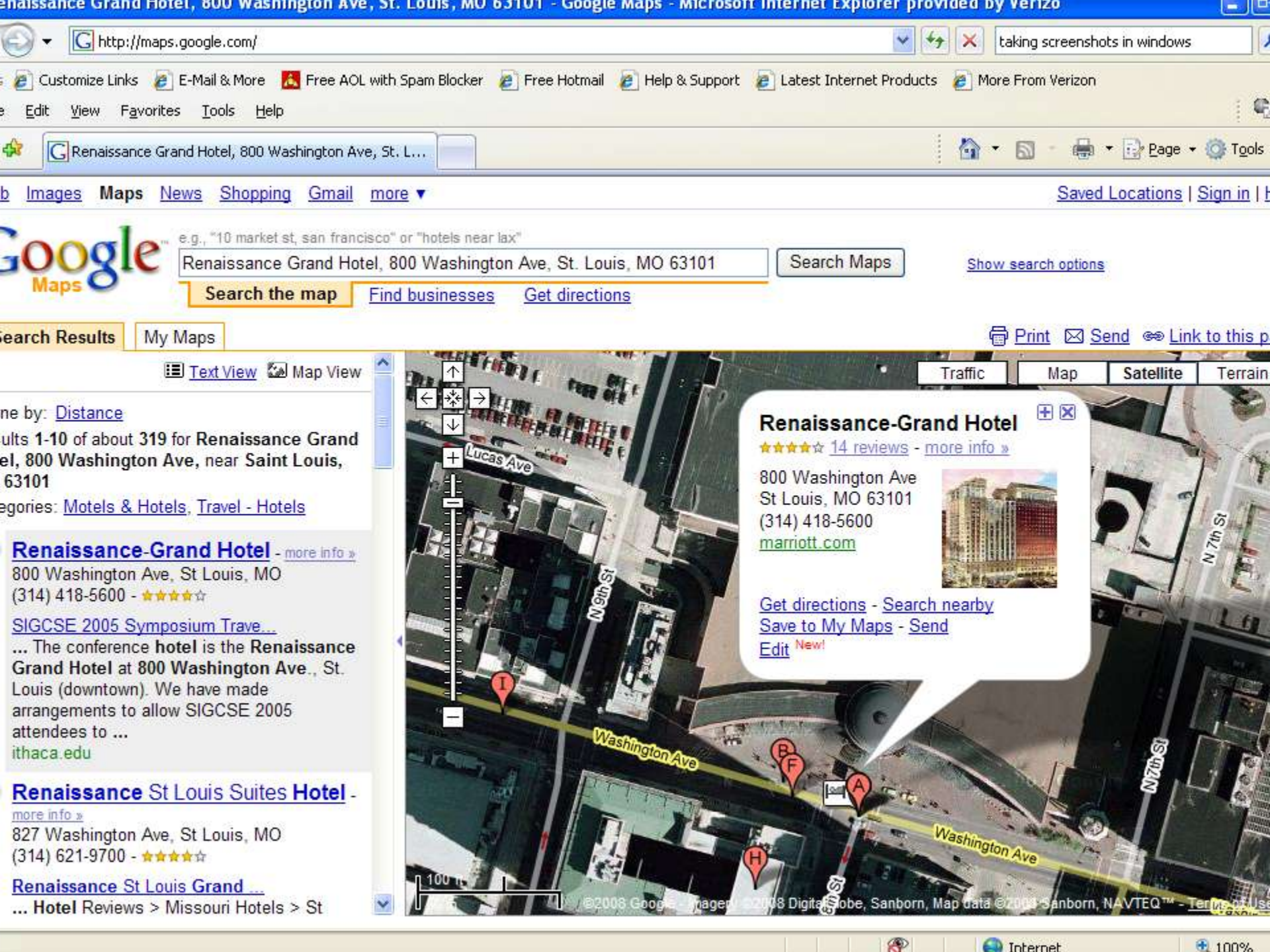
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Creating/Checking an LSSL formula

Decision tree algorithm: simplifies the CDF

if $a_7 \leq 0.875$ then {if $a_2 > 0.049$ then c else ¬c}

else if $a_3 \leq 0.078$ then { if $a_0 > 0.025$ then c else ¬ c} else ¬c

LSSL formula ϕ : gives meaning to attributes a_i

$X^7(P(D=s) \leq 0.875) \wedge X^2(P(D=s) > 0.049) \vee$

$X^7(P(D=s) > 0.875) \wedge X^3(P(D=s) \leq 0.078) \wedge (P(D=s) > 0.025)$

Spiral detection for SQT T: reduces to BMC of $T \models \phi$

Class Description Formula

Each record: corresponds to a discriminant rule

$$r_i \equiv (\wedge_{j \in I_i} a_{ij} = v_{ij} \Rightarrow c = v)$$

Table: corresponds to conjunction of rules

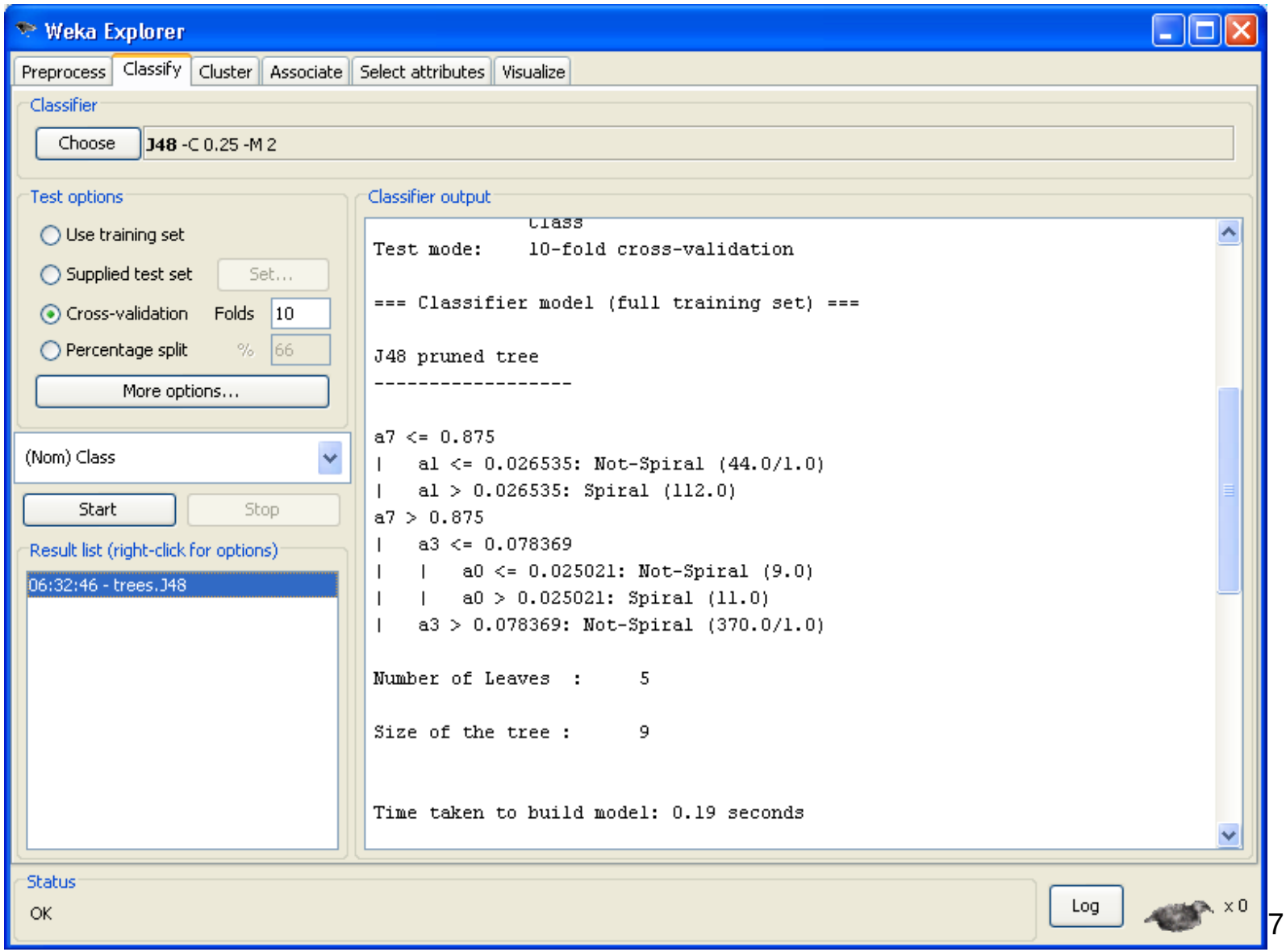
$$\wedge_{i=1}^{n} r_i = \wedge_{i=1}^{n} (\wedge_{j \in I_i} a_{ij} = v_{ij} \Rightarrow c = v)$$

$$= (\vee_{i=1}^{n} \wedge_{j \in I_i} a_{ij} = v_{ij}) \Rightarrow (c = v)$$

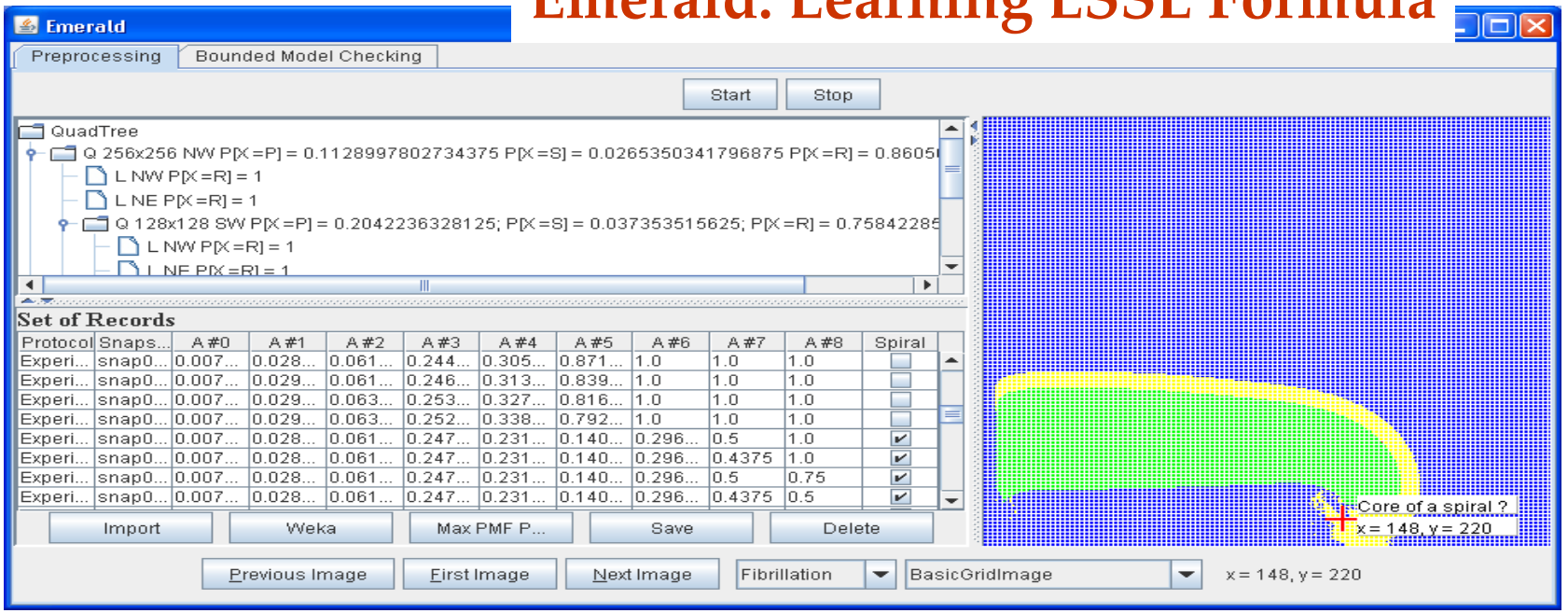
Class description formula (CDF): the antecedent

$$\vee_{i=1}^{n} \wedge_{j \in I_i} a_{ij} = v_{ij}$$

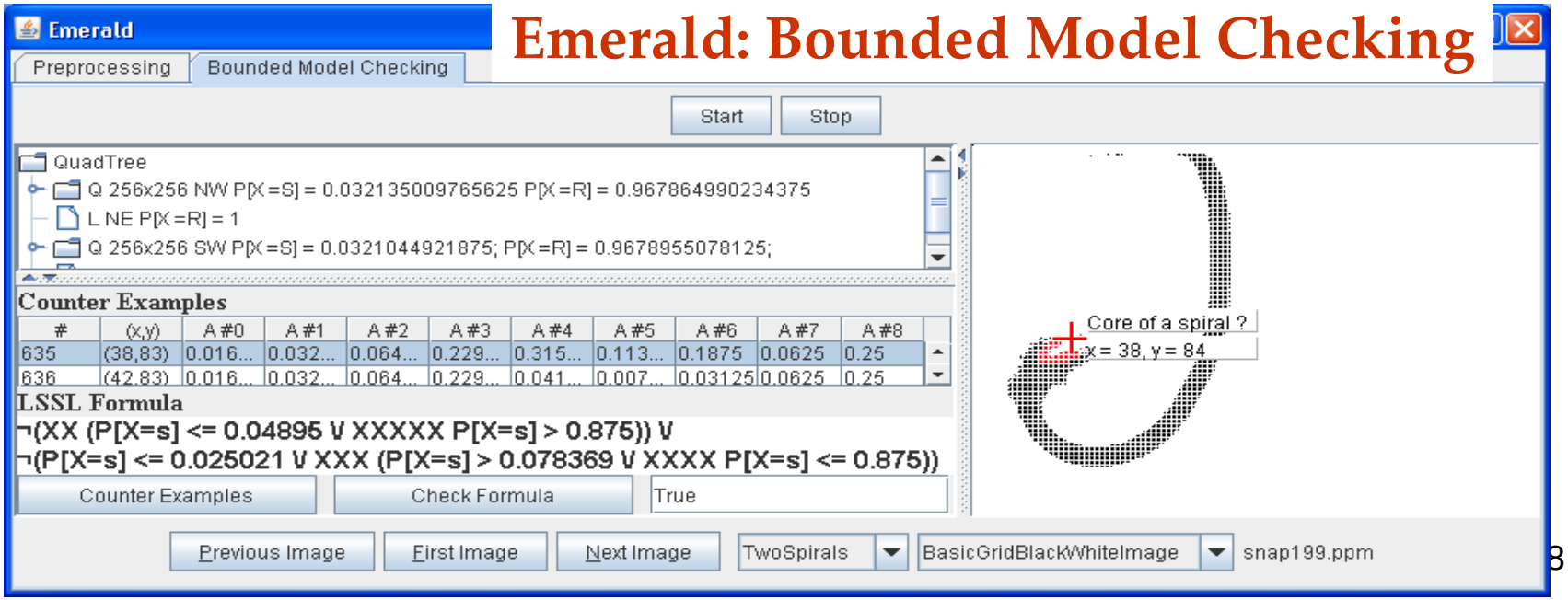
Using Weka


Weka Explorer
Preprocess
Classify
Cluster
Associate
Select attributes
Visualize
Classifier
Choose
J48 -C 0.25 -M 2
Test options
Use training set
Supplied test set
Set...
Cross-validation
Folds
10
Percentage split
%
66
More options...
(Nom) Class
Start
Stop
Result list (right-click for options)
06:32:46 - trees.J48
Classifier output
Test mode: 10-fold cross-validation
=== Classifier model (full training set) ===
J48 pruned tree
a7 <= 0.875
| a1 <= 0.026535: Not-Spiral (44.0/1.0)
| a1 > 0.026535: Spiral (112.0)
a7 > 0.875
| a3 <= 0.078369
| | a0 <= 0.025021: Not-Spiral (9.0)
| | a0 > 0.025021: Spiral (11.0)
| a3 > 0.078369: Not-Spiral (370.0/1.0)
Number of Leaves : 5
Size of the tree : 9
Time taken to build model: 0.19 seconds
Status
OK
Log
x 0

Emerald: Learning LSSL Formula



Emerald: Bounded Model Checking



Results

Path Classifier	Test Set 550	Test Set 600	Test Set 650
Trained (512 Paths)	87.00%	88.83%	88.23%
Retrained (512 Paths + 67 Counter-Examples)	97.10%	97.33%	93.07%

Prediction accuracy for spiral detection in Emerald