Journées Starting Block - CRIStAL — 2020-09-15

BioComputing

Maxime FOLSCHETTE

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http://maxime.folschette.name/
Analysis of the Dynamics

Efficient reachability analysis
Dynamical patterns enumeration
Hepatocellular carcinoma progression

Machine Learning

Constraints on hybrid parameters
Learning models from time series data
Cerebral aneurysms & Myopathy

New projects

Diabetes Understanding & Prediction
Marine ecological systems (algae)
The Modeling Problem
Experiments *in silico*
Experiments \textit{in silico}

- Biological system
- Experiments \textit{in vivo / ex vivo}

**WET LAB**

**DRY LAB**
The Modeling Problem

Experiments *in silico*

**WET LAB**

- Biological system
- Experiments *in vivo / ex vivo*

**DRY LAB**

Model
Présentation équipe BioComputing  ◦  The Modeling Problem

Experiments *in silico*

- Biological system
- Experiments *in vivo / ex vivo*
- Validation *in silico*
- Model

WET LAB

DRY LAB
Présentation équipe BioComputing • The Modeling Problem

**Experiments *in silico***

- Biological system
- Experiments *in vivo / ex vivo*
- Model
- Validation *in silico*

WET LAB

DRY LAB
Experiments *in silico*

- **WET LAB**
  - Biological system
  - Experiments *in vivo / ex vivo*

- **DRY LAB**
  - Model
Experiments in silico
Experiments *in silico*
Experiments *in silico*
Experiments *in silico*

- Biological system
- Experiments *in vivo / ex vivo*
- Predictions *in silico*
- Model

WET LAB

DRY LAB
Experiments *in silico*

- **Biological system**
- **Experiments *in vivo / ex vivo***
- **Predictions *in silico***
- **Model**
Preliminary Abstraction

DNA -> Transcription -> RNA -> Translation -> Protein
Preliminary Abstraction

Gene $a$

$+$

RNA $a$

$+$

Protein $a$

$+$

$-$
Preliminary Abstraction
Discretization and Asynchronism

[Richard et al., 2008]
Discretization and Asynchronism

[Richard et al., 2008]

• Discrete levels and thresholds
Discretization and Asynchronism

[Richard et al., 2008]

- Discrete levels and thresholds
- Nature of interactions
Preliminary Abstraction

\[ \{ 1 = \text{active} \\ 0 = \text{inactive} \} \]
Preliminary Abstraction

\[
\begin{align*}
2 &= \text{saturation} \\
1 &= \text{traces} \\
0 &= \text{complete degradation}
\end{align*}
\]
Discrete Networks / Thomas Modeling

**Discrete Networks / Thomas Modeling**

Discrete Networks / Thomas Modeling

The state-graph depicts explicitly the whole dynamics.

<table>
<thead>
<tr>
<th>abz</th>
<th>000</th>
<th>010</th>
<th>001</th>
<th>011</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>110</td>
<td>101</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>210</td>
<td>201</td>
<td>211</td>
<td></td>
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</table>

- Stable state = state with no successors
- Complex attractor = minimal loop or composition of loops from which the dynamics cannot escape
- Reachability = from 201, can I reach 000?
### The Modeling Problem

#### State-graph

The state-graph depicts explicitly the whole dynamics

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- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from 201, can I reach 000?
The state-graph depicts explicitly the whole dynamics

abz
000 010 001 011
100 → 110 101 111
200 210 201 211

- **Stable state**: state with no successors
- **Complex attractor**: minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability**: can I reach 000 from 201?
The state-graph depicts explicitly the whole dynamics.

- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from 201, can I reach 000?
The state-graph depicts explicitly the whole dynamics

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- **Reachability** = from 201, can I reach 000?
Analysis of Big Models
## Combinatorial explosion

<table>
<thead>
<tr>
<th>Model</th>
<th>Possible states</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Model" /></td>
<td>4</td>
</tr>
<tr>
<td><img src="image" alt="Model" /></td>
<td>8</td>
</tr>
<tr>
<td><img src="image" alt="Model" /></td>
<td>16</td>
</tr>
<tr>
<td><img src="image" alt="Model" /></td>
<td>1024</td>
</tr>
<tr>
<td><img src="image" alt="Model" /></td>
<td>1048576</td>
</tr>
<tr>
<td><img src="image" alt="Model" /></td>
<td>1267650600000000000000000000000</td>
</tr>
</tbody>
</table>

**Analysis of Big Models**

- **Combinatorial explosion**

  - **Model**
    - `a` to `b`
    - `c` to `a` to `b`
    - `d` to `a` to `b`
    - `c` to `a` to `b`
    - `...`
    - `(10)`
    - `(20)`
    - `(100)`

  - **Possible states**
    - 4
    - 8
    - 16
    - 1024
    - 1048576
    - `1267650600000000000000000000000`
Combinatorial explosion

<table>
<thead>
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<tbody>
<tr>
<td>a (\rightarrow) b</td>
<td>4</td>
</tr>
<tr>
<td>c (\rightarrow) a (\rightarrow) b</td>
<td>8</td>
</tr>
<tr>
<td>d (\rightarrow) a (\rightarrow) b</td>
<td>16</td>
</tr>
<tr>
<td>(\vdots)</td>
<td>(\vdots)</td>
</tr>
<tr>
<td>(10)</td>
<td>1024</td>
</tr>
<tr>
<td>(20)</td>
<td>1048576</td>
</tr>
<tr>
<td>(100)</td>
<td>12,676,506,000,000,000,000,000,000,000,000</td>
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Analysis of Big Models

Présentation équipe BioComputing
Combinatorial explosion

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<tr>
<td><img src="image" alt="Diagram" /></td>
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Présentation équipe BioComputing  ○  Analysis of Big Models
# Combinatorial explosion

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Combinatorial explosion occurs when the number of possible states in a model grows exponentially with the number of components. The table above illustrates this with examples where the number of states increases significantly with the addition of components (a, b, c, and d). The last row shows the number of possible states for a scenario with 100 components, which is the result of a combinatorial explosion.
Combinatorial explosion

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### Combinatorial explosion

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<td>16</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Diagram" /></td>
<td>(10^2)</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Diagram" /></td>
<td>(10^3)</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Diagram" /></td>
<td>(10^4)</td>
</tr>
<tr>
<td><img src="https://via.placeholder.com/150" alt="Diagram" /></td>
<td>(10^5)</td>
</tr>
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</table>

Maxime FOLSCHEtte 11/23 Starting Block — 2020-09-15
Approximation of the Dynamics

[Folschette et al., *Theoretical Computer Science*, 2015a]
Approximation of the Dynamics

[Folschette et al., *Theoretical Computer Science*, 2015a]
Approximation of the Dynamics

[Paulevé et al., Mathematical Structures in Computer Science, 2012]
[Folschette et al., Theoretical Computer Science, 2015a]
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Approximation of the Dynamics

[Folschette et al., *Theoretical Computer Science*, 2015b]

Sufficient condition:
- No cycle
- No conflict
- All leaves are $\emptyset$

$P$ is true $\Rightarrow$ $R$ is true
Approximation of the Dynamics

[Folschette et al., *Theoretical Computer Science*, 2015b]

Sufficient condition:
- No cycle
- No conflict
- All leaves are $\emptyset$

$P$ is false $\Rightarrow$ Cannot conclude
Présentation équipe BioComputing ○ Analysis of Big Models

Leucine Reaction Network

[Allart et al., *Computational Methods in Systems Biology*, 2019]
Machine Learning
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
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Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)

Black box

Semantics → State graph

Identical

Semantics → State graph

\[
\begin{align*}
  z(1) & \leftarrow a(2). \\
  z(1) & \leftarrow b(1). \\
  z(1) & \leftarrow a(1) \land b(0). \\
  b(1) & \leftarrow a(2). \\
  b(0) & \leftarrow a(0). \\
  \ldots
\end{align*}
\]
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)

Biological system
Semantics
State graph

Semantics
State graph
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)

Biological system → Semantics → State graph
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
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Learning Models from Execution Traces

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Biological system → Semantics → State graph

No discretization (ACEDIA) ↔ Equivalent (discretization)

Semantics
Learning Models from Execution Traces

[Ribeiro et al., Inductive Logic Programming, 2018] (ACEDIA)
[Ribeiro et al., Inductive Logic Programming, 2017] (GULA)

Biological system

Semantics

Equivalent (discretization)

State graph

No discretization (ACEDIA)

Unknown semantics (GULA)
Osmotic stress in yeast

Osmotic stress = temporary addition of salt to solution thanks to microfluidic device

Segmentation

Individual cell tracking

Fluorescent microscope images

Individual cell fluorescence levels for
- modeling
- parameter estimation (stochastic)
Modeling of Diabetes
Présentation équipe BioComputing ○ Modeling of Diabetes

Gastro-Intestinal Anatomy

[https://foodandhealth.com/digestive-diseases-awareness/]
[Baud et al., Cell Metabolism, 2016]

Gastro-intestinal anatomy

Roux-En-Y Gastric Bypass

Maxime FOLSCHETTE

Starting Block — 2020-09-15
Effects of Bariatric Surgery  
Courtesy of Pattou and coll.

Glucose homeostasis restored by bariatric surgery
Glucose Flux

[Dalla Man et al., IEEE Transactions on Biomed. Eng., 2007]