Dynamical Models in Life Sciences – an Overview

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What to Model?

ENTITIES:
Atoms, molecules, genes, proteins, cells, tissues, organs, populations, ...

SPACIAL ARRANGEMENT:
Sequences, folds, (3D) structures, compartments, ...

INTERACTIONS:
(Bio)chemical reactions, protein-protein, drug-target, gene regulation, ...

PHYSICAL CONSTRAINTS:
(Partial/Formal) charges, thermodynamics, mechanical constraints, ...

ENVIRONMENT:
Temperature, light, pH, aerobic/anaerobic atmosphere, ...

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"Ultimately, any model is just a very limited version of a complex system."
(KISS)

Model Analysis

Verification (validation), screening, identification of key components, hypothesis generation, . . .

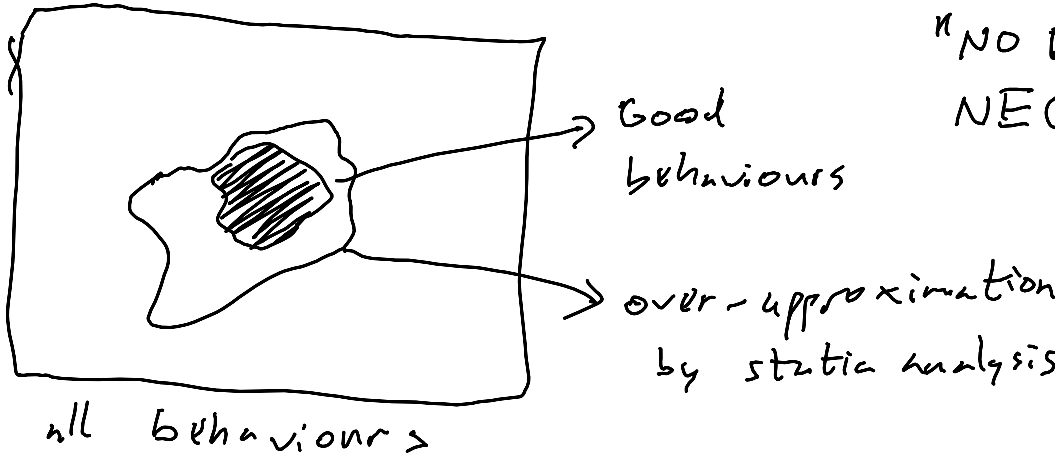
Simulation

Akin to running "in-silico experiments".
Sampling possible behaviours.

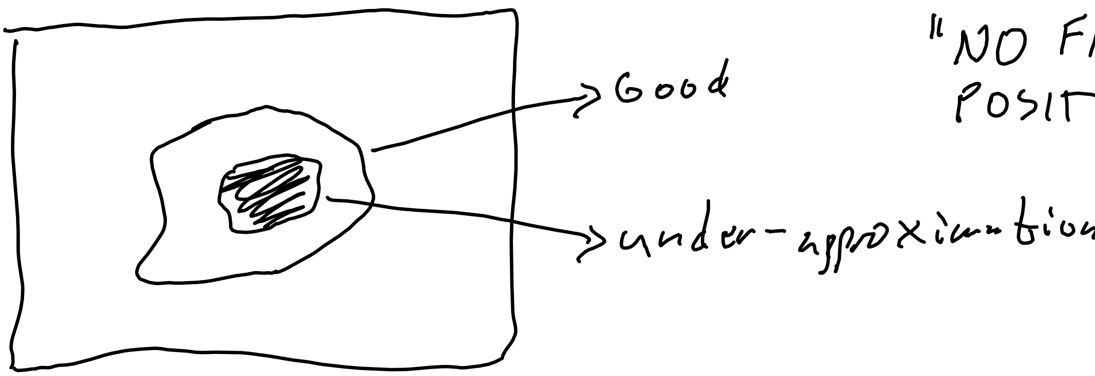
Formal Verification

Static analysis – (Partial) results based on structure only.
Dynamic analysis – Exhaustive exploration of the model dynamics.

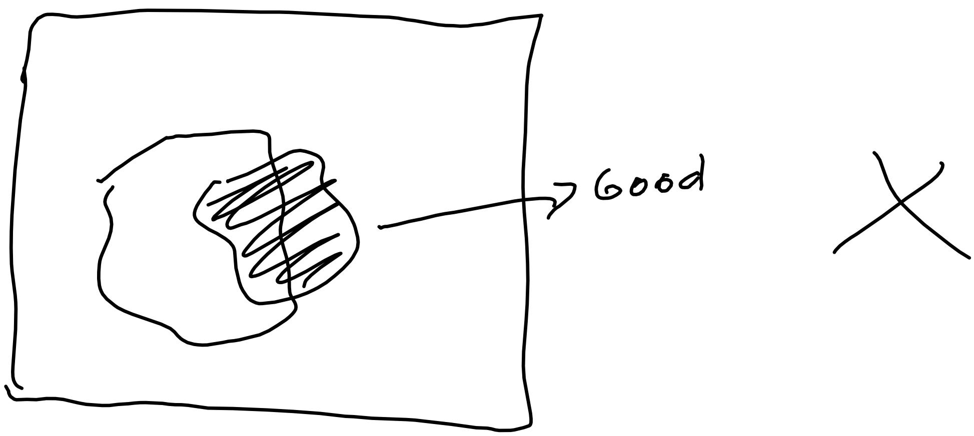
STATIC ANALYSIS is typically an over-/under-approximation



"NO FALSE NEGATIVES"



"NO FALSE POSITIVES"



Formal Specification

MODEL:

Syntax – “A collection of signs and symbols”.
Semantics – Interpretation of the signs and symbols.

- Ordinary Differential Equations (ODEs);
- Graph Transformation;
- Petri Nets;
- Markov Chains (stochastic models);
- Boolean Networks;
- ...

Dynamical Models

The model has **states** (configurations) which evolve in **time**.

Temporal Properties:

Logical time – One state succeeds another.
Chronological time – Each time point has an assigned state, the successor is a state at a later time point

Determinism:

Deterministic model – The successor state (state at a given time) is fixed.
Non-deterministic model – There are multiple possible successor states (states at a given time).
Stochastic model – The possible successor states (states at a given time) have a probability distribution.

Simulation

“Execution” of the model.

1. Chose an initial state and set it as current.
2. Pick one successor state of the current state and set it as current.
3. If the termination condition is met, stop, otherwise repeat step 2.

The result is a single “run”, in a way a “depth-first exploration”.

For deterministic models, the result for the same initial state is always the same run.
For nondeterministic or stochastic models, the simulation might produce different runs for the same initial state.

Advantages:

Typically relatively simple to implement.
Computationally inexpensive, applicable to larger models.

Disadvantages:

Non-exhaustive.

Formal Analysis

Comprehensive (exhaustive) exploration of the model behaviour.

Make statements about the possible behaviour based purely on the structure of the model. STATIC
Explicitly explore all possible behaviours. DYNAMIC

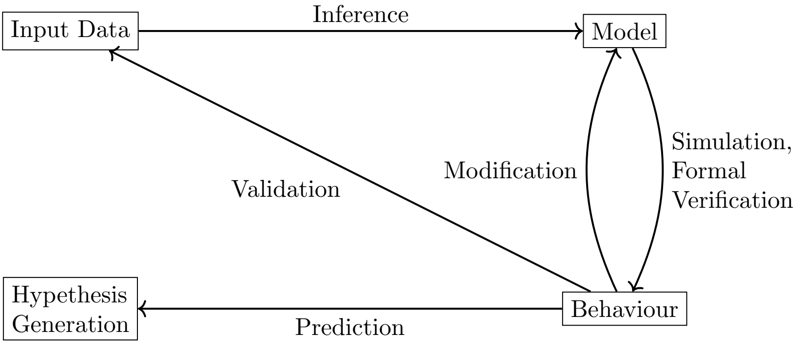
Advantages:

Very flexible, allows both positive and negative results about existence of a behaviour.
Results are generalisable, e.g. abstraction of parameters, ...
Allows reasoning about the model itself.

Disadvantages:

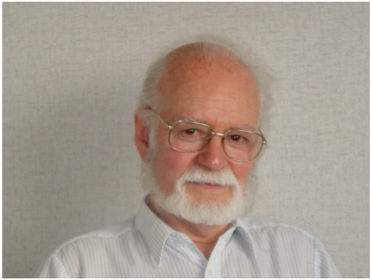
Computationally expensive.
Requires complex theories, making implementation more involved.

Formal Methods in Systems Life Sciences



Qualitative Models

Stuart Kauffman

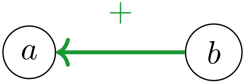


René Thomas

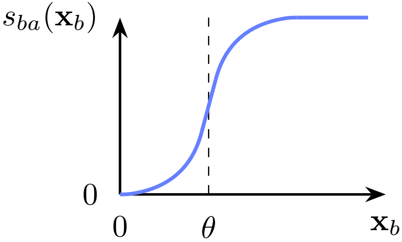
Gene expression can be “ON” or “OFF” (the gene is active/inactive).

Logical time (succession of states).

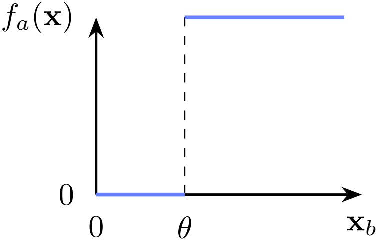
Discretisation



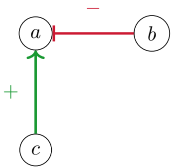
Quantitative



Qualitative



Interplay of Interactions



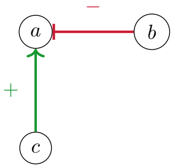
Quantitative

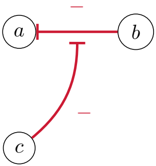
Addition, multiplication, . . .

Qualitative

Propositional logic (conjunction, disjunction).

Interplay of Interactions





High-order interaction

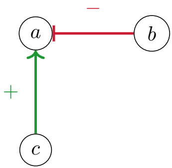
Quantitative

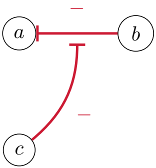
Addition, multiplication, ...

Qualitative

Propositional logic (conjunction, disjunction).

Interplay of Interactions





High-order interaction

QUANTITATIVE

Addition, multiplication, ...

QUALITATIVE

Propositional logic (conjunction, disjunction).

HIGH-ORDER INTERACTION:

Defining property: “If *b* is inactive, then *c* has no effect on *a*”.

Quantitative vs Qualitative

Qualitative models are strong abstractions.

Quantitative

- Interplay functions;
- Interaction weight;
- Interaction thresholds;
- Threshold functions;

Qualitative

- Interplay functions;
- Maximum values (activation levels);
- Interaction thresholds (multivalued only);