

BioRica : A platform to describe and simulate multi-models systems in biology

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Bordeaux MBSAW 2012, September 2012

Plan

Introduction : Needs in Biology

The BioRica framework

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Applications : wine fermentation, bone formation

- Wine fermentation

- Bone formation

Conclusions and future works

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Wine fermentation

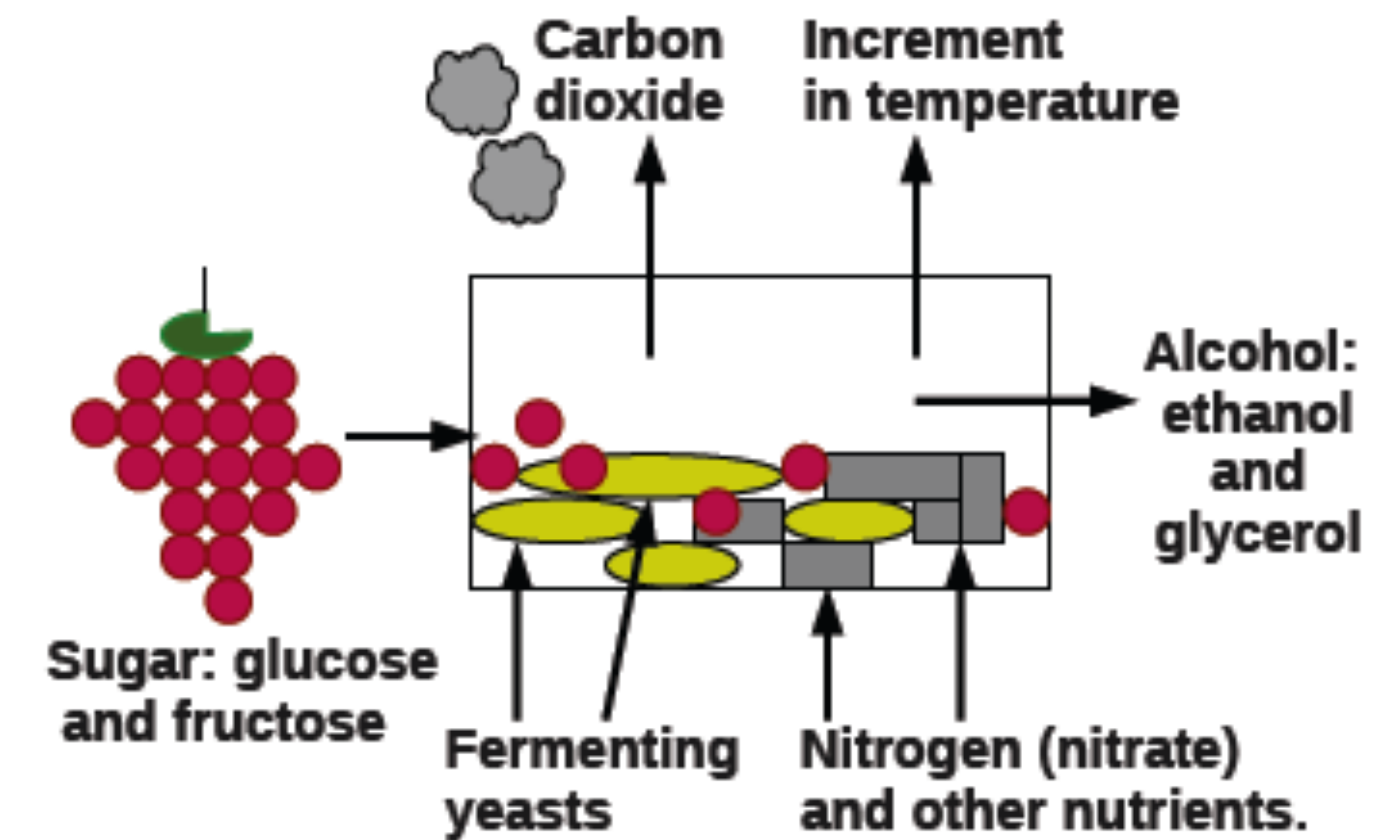
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Understanding Biological Systems Example : Wine fermentation

[Assar et al., 2010]

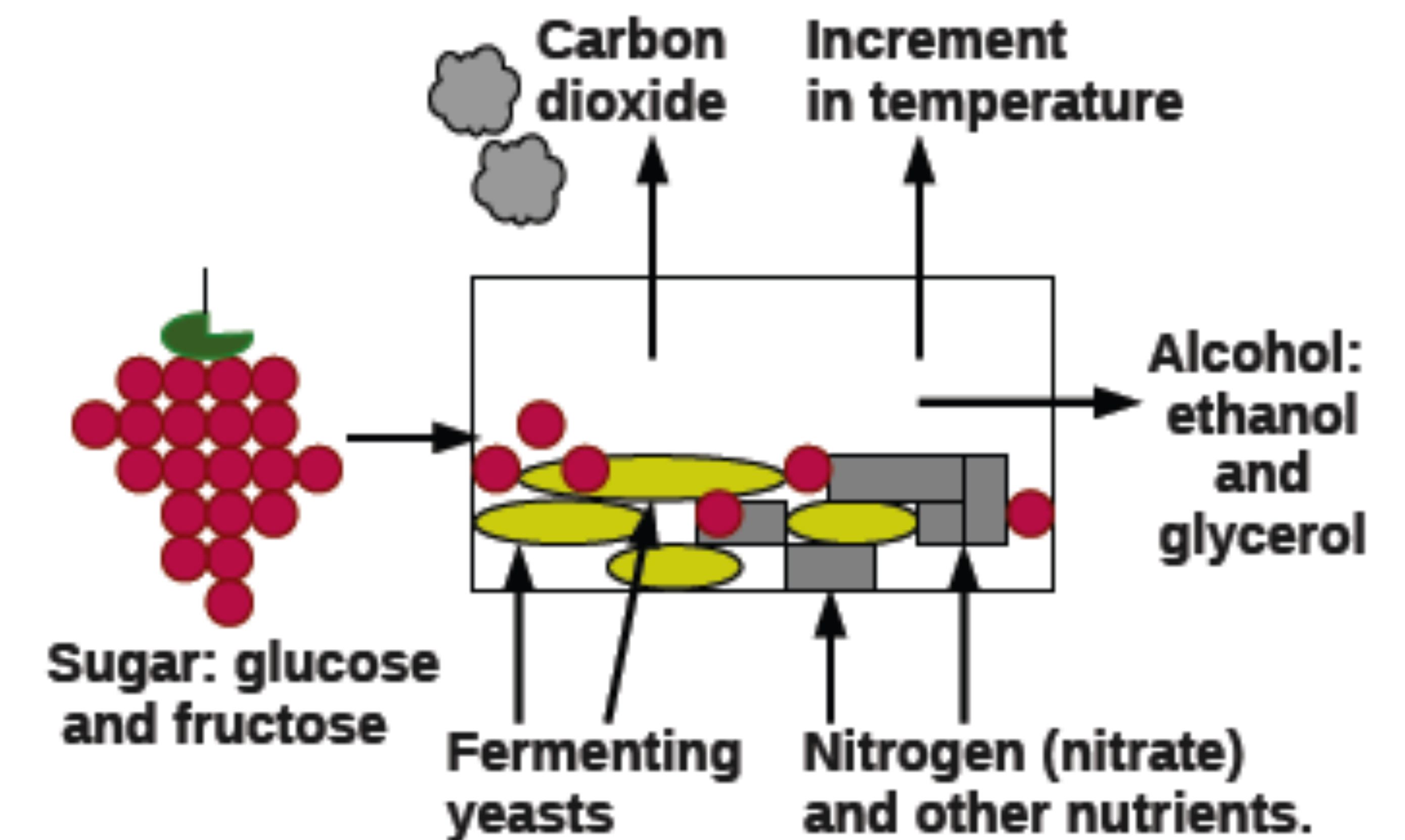
Interconnected components :



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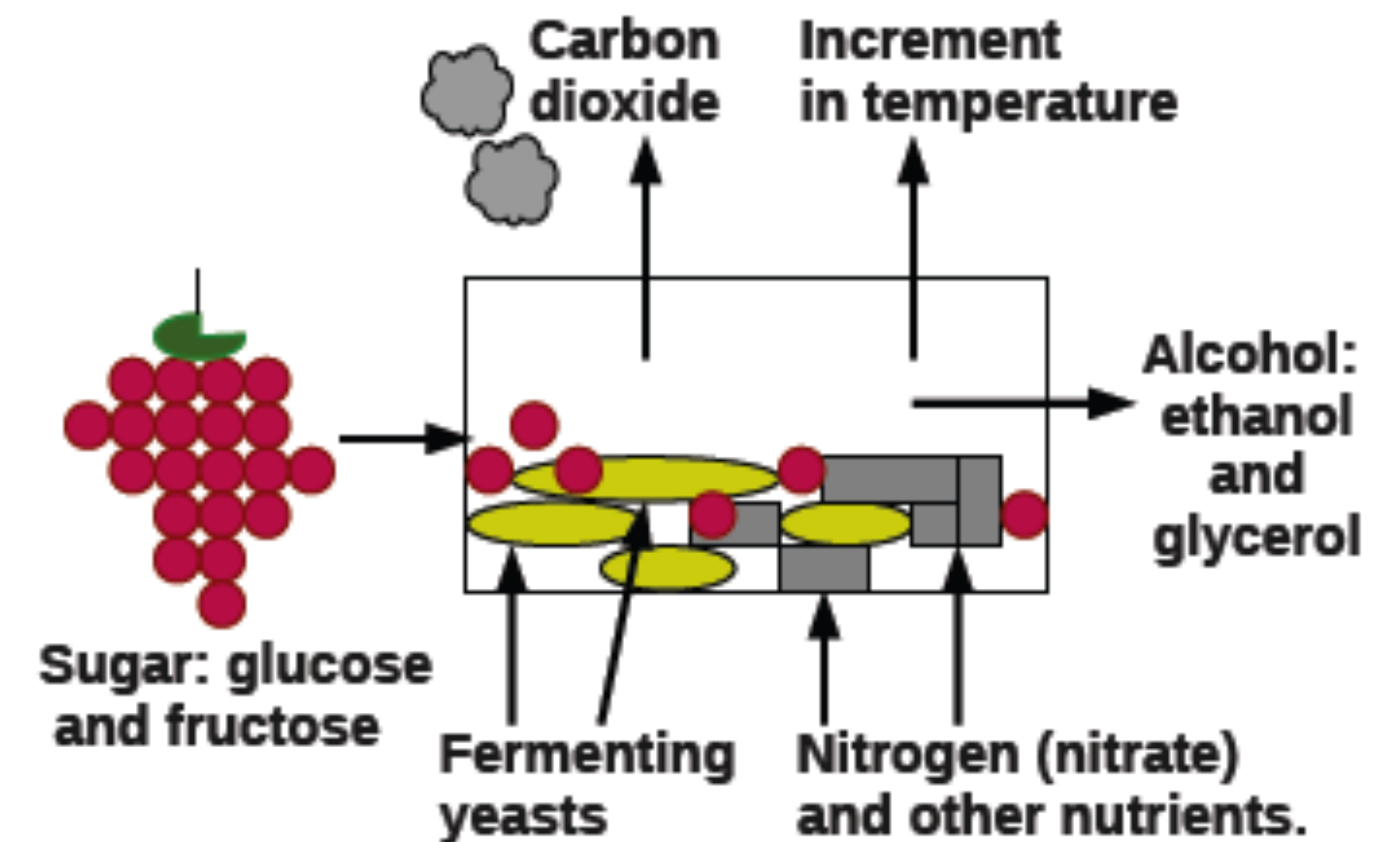


Emerging from their interactions : Wine or good wine !

Understanding Biological Systems Example : Wine fermentation

[Assar et al., 2010]

Interconnected components :



Emerging from their interactions : Wine or good wine !

Hierarchical levels :

- Inter yeasts : Consumption of sugar, growth.
- Intra yeasts : glycolysis.

Changes in conditions change behaviors :

- Quantity of population and resources :
 - many yeasts consuming scarce resources provokes competition.
- Heat accelerates fermentation.

Describing biological systems by mathematical models

- Systems Biology paradigm [Kitano, 2002].
- Modular and hierarchical approach
 - defining their components : sub-models,
 - defining the relations between them : composition of models.
- Many possible types of models

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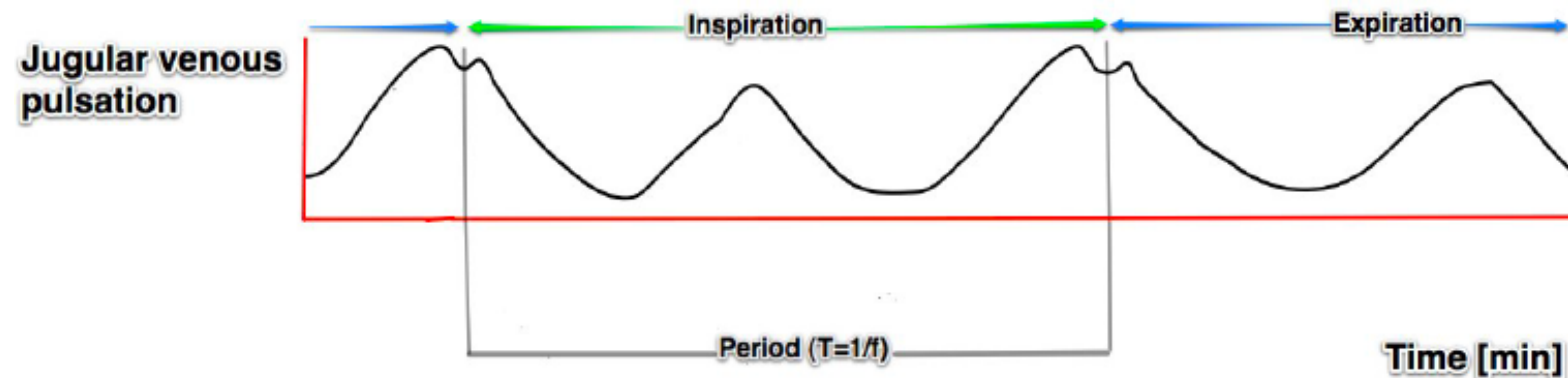
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- Hybrid systems mix all these behaviors.

Example : controlling pulse

- Pulse (continuous variable f) measures the heart rate.
- Artificial pacemaker regulates the beating of the heart.



TYPE OF MODE TRANSITIONS

- **DETERMINISTIC:** IF $f < 60$ TURN ON THE PACEMAKER,
IF $f > 70$ TURN OFF
- **NON-DETERMINISTIC:** IF $f < 70$ TURN ON OR TURN OFF
- **STOCHASTIC:** IF $f < 70$ TURN ON WITH PROBABILITY 0.9

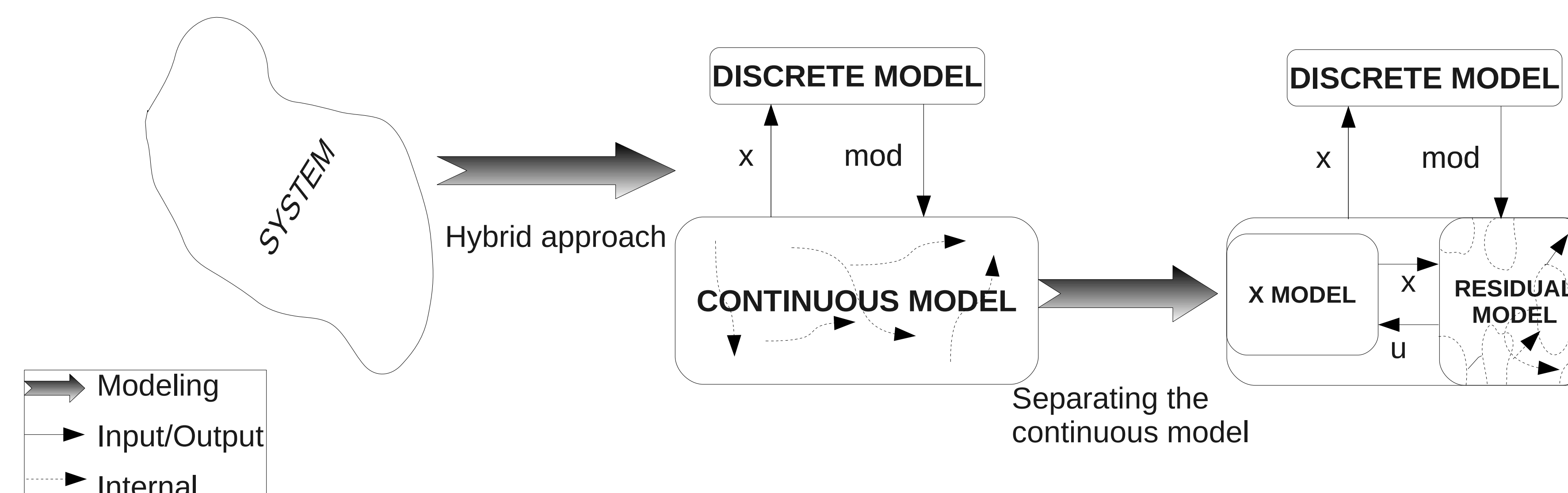
Biological systems as Hybrid systems

Biological systems

- Hierarchically connected modules define the behaviors (**composition**).
- Changes in conditions change the behaviors (**discrete changes**).
- Erroneous and incomplete information may occur (**randomness and non-determinism**).

Using hybrid systems and composition [Assar, 2011]

Identifying discrete and continuous parts, decomposing and combining.



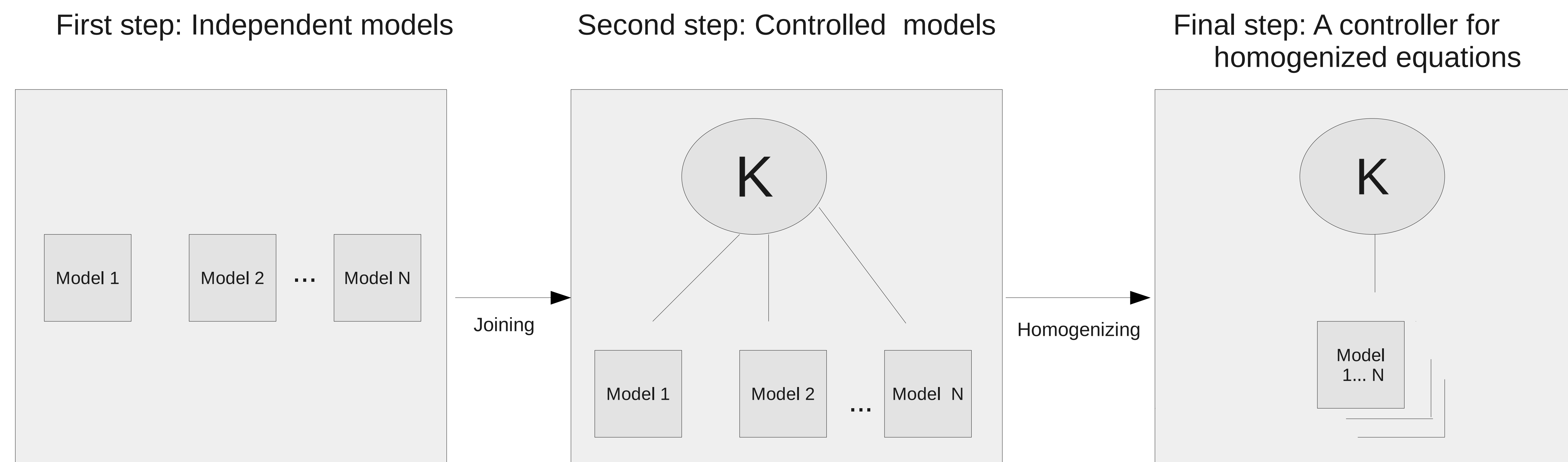
Reusing and reconciling models by composition

- Application and improvement of models,
- Combination of connected biological processes,
- Validated models fitting specific needs and data,
- Reducing monetary cost.

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Reconciliation of models [Assar et al., 2010] :



- Best model selection according to observable factors.
- Models with better answers in general conditions.
- Reconciled models can be reused (step 2) or rewritten (step 3).

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Requirements

- Applying AltaRica [Arnold et al., 1999] ideas to biological systems.

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- Requirements derived from concrete examples :
 1. Solve continuous models : diff. eqns, with different comp. degrees and timescales.
 2. Describe and solve discrete models given by STS.
 3. Use this wide range of models in the same framework.
 4. Implement composition.
 5. Incorporate hierarchy between models.
 6. Implement reusing and reconciliation of models.

Extensions Requirements :

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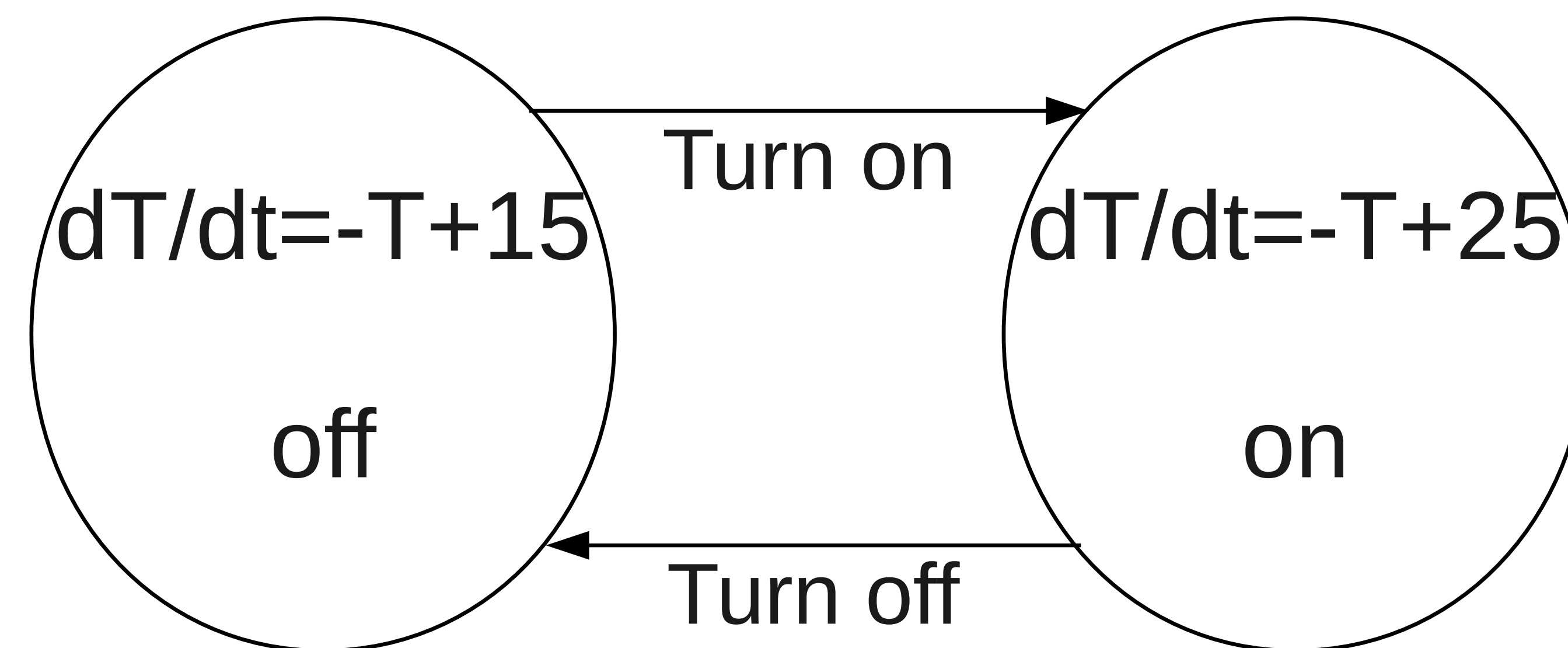
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Contributions :

- Inclusion of differential equations
systems and Hybrid Systems with
general transitions (1 and 2).
- Adopting the Python libraries (1
and 2).
- Specification of hybrid systems :
composing, assuring integrity, and
hierarchy (4, 5 and 6).
- Implementation of Hybrid systems
and reconciliation (1, 2 and 6).

Implementing Hybrid systems : example

(A)



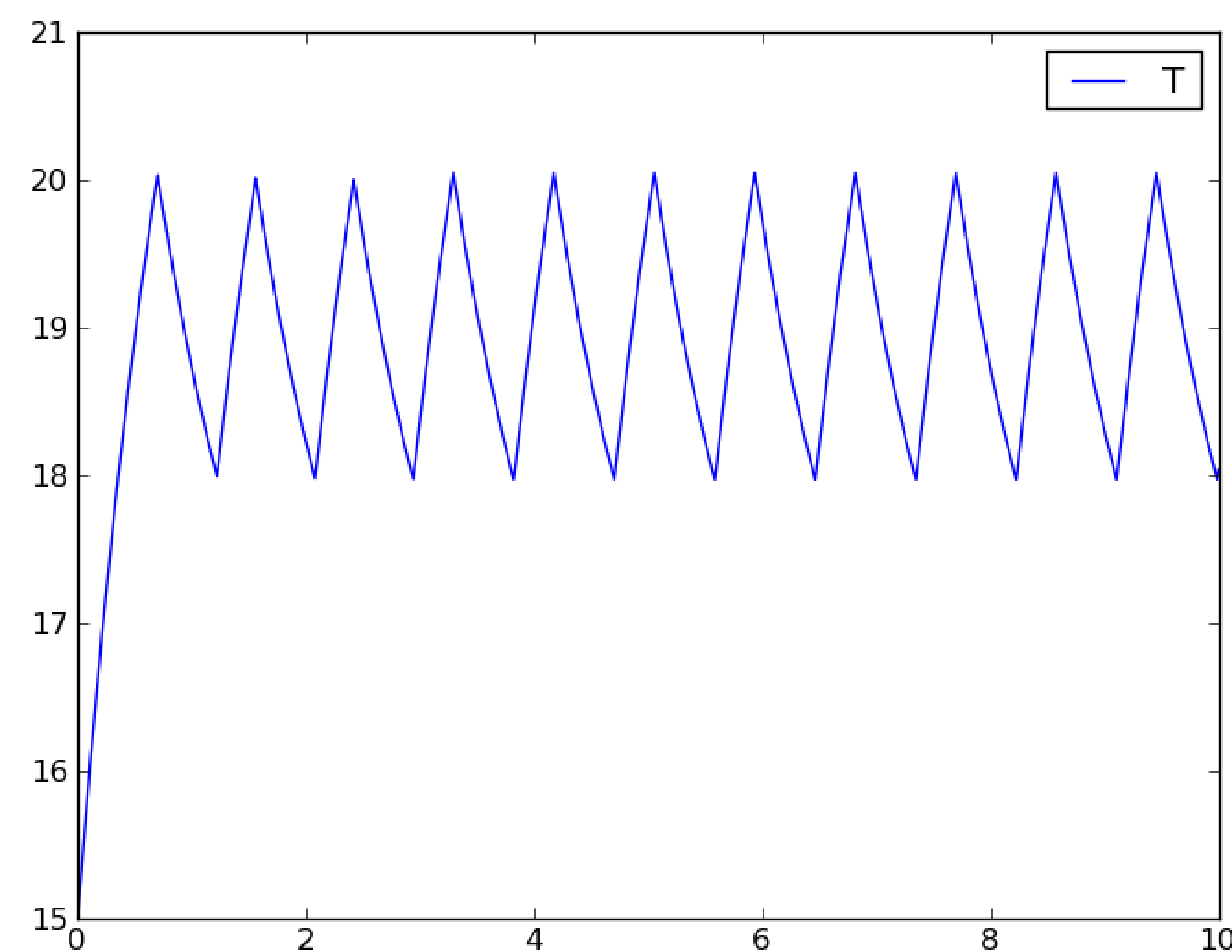
(B)

```
node RADIATOR
  state T:FLOAT;K:{15,25};
  event turn_on,turn_off;
  eq:diff
    dT=-T+K;
  trans

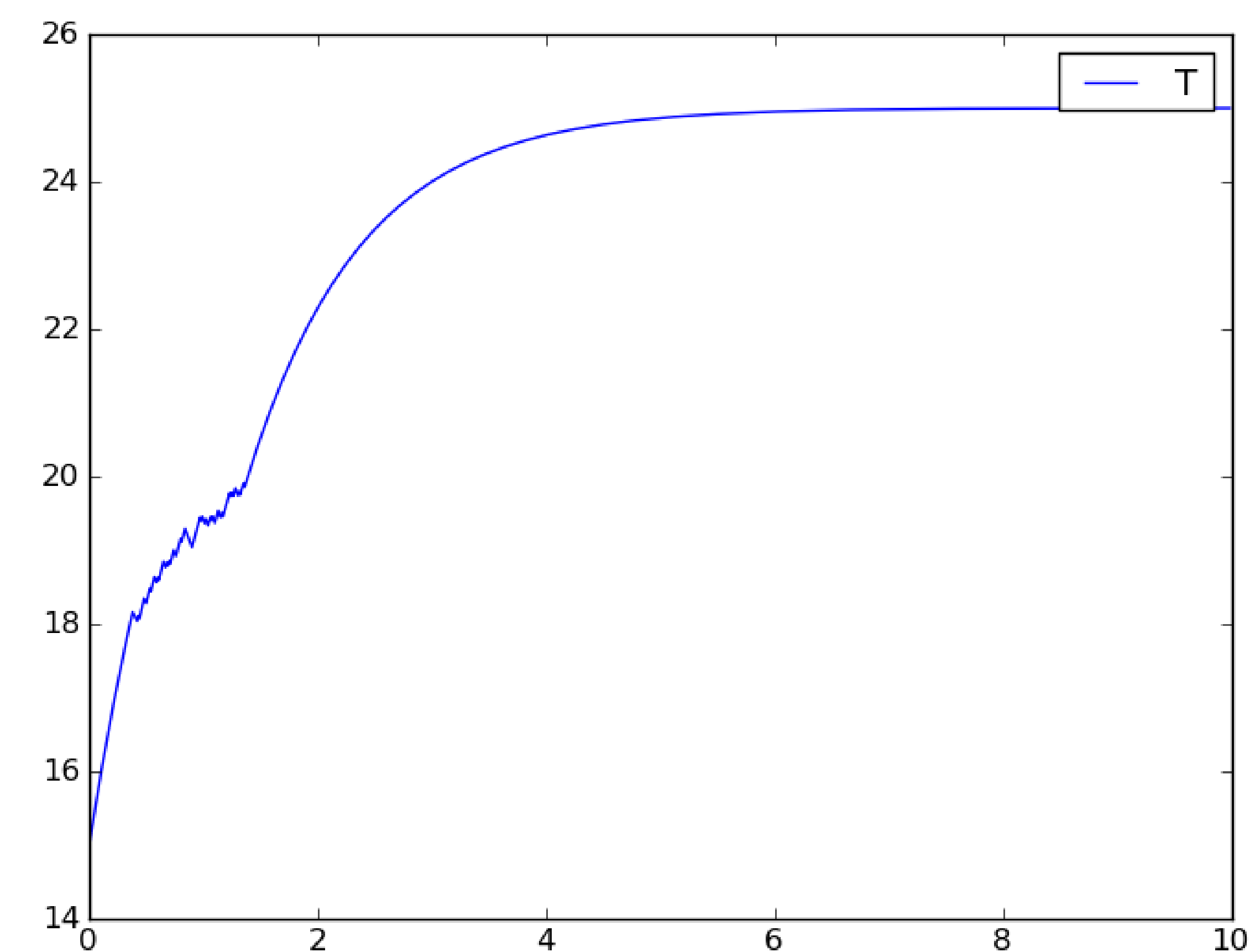
  #B.1: deterministic
    T<=18 |- turn_on -> K:=25;
    T>=20 |- turn_off -> K:=15;
  #B.2: non-deterministic
    T>=18 & T<=20 |- turn_on->K:=25;
    T>=18 & T<=20 |- turn_off->K:=15;

  init
    T:=15,K:=25;
  #B.3: stochastic
  extern
    choice<turn_on>:2;
edon
```

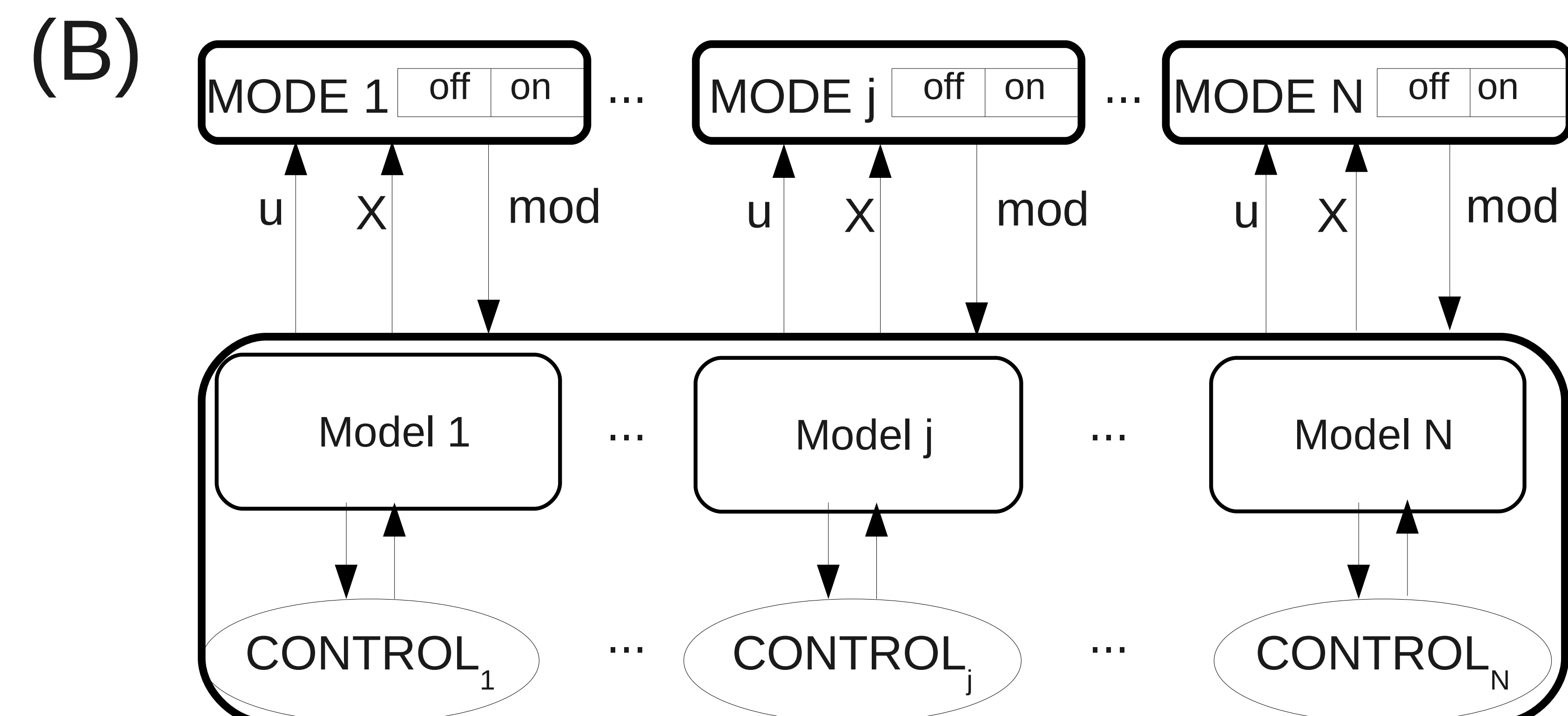
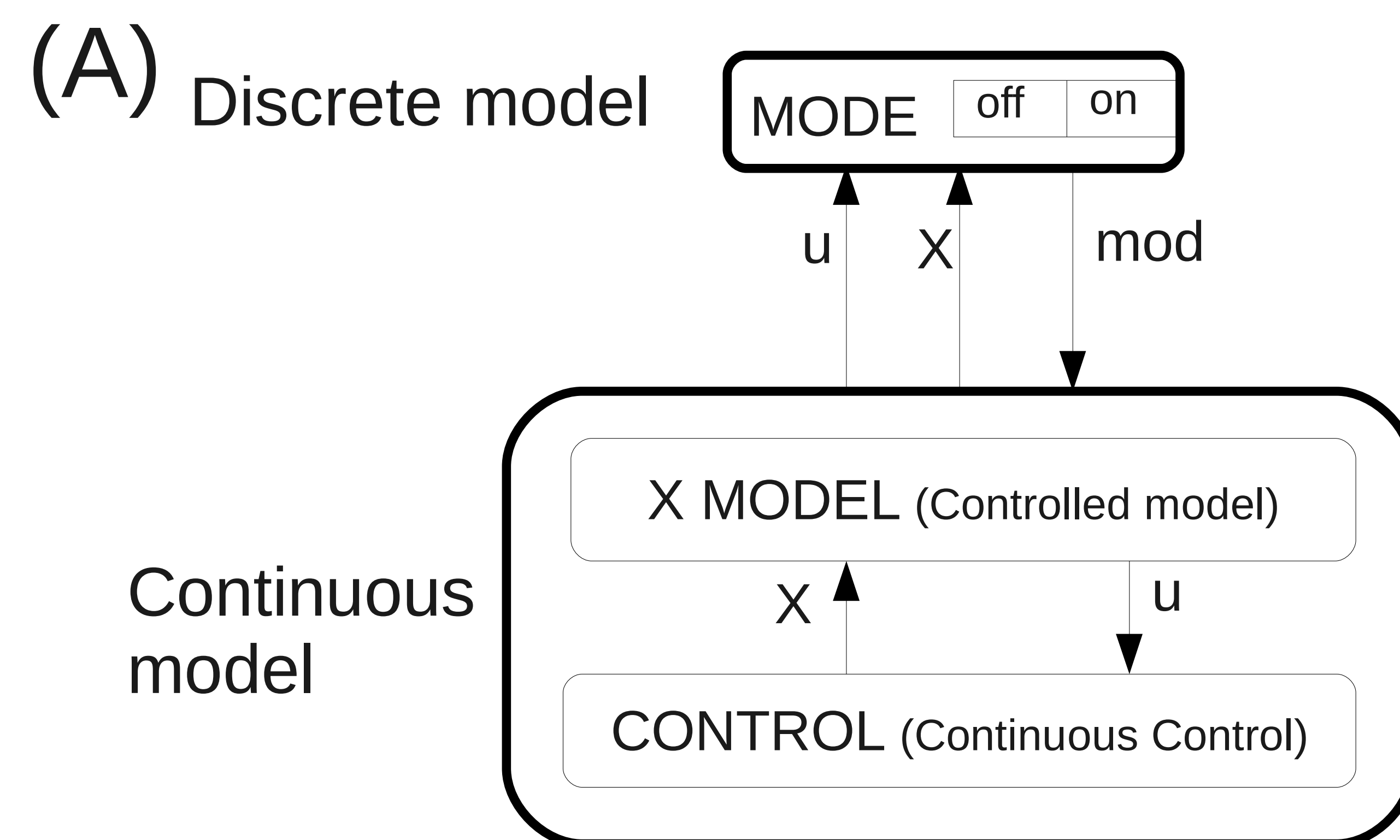
(C)



(D)

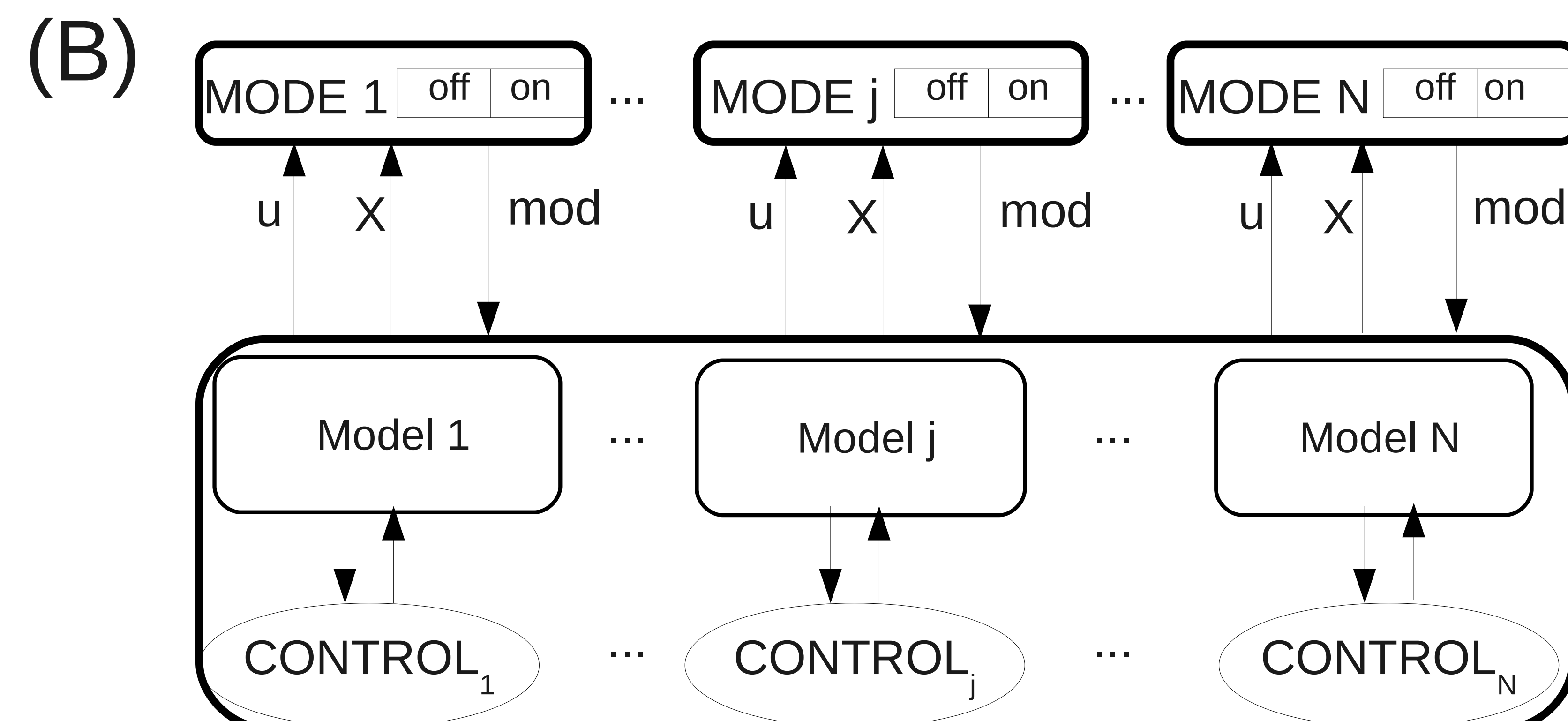
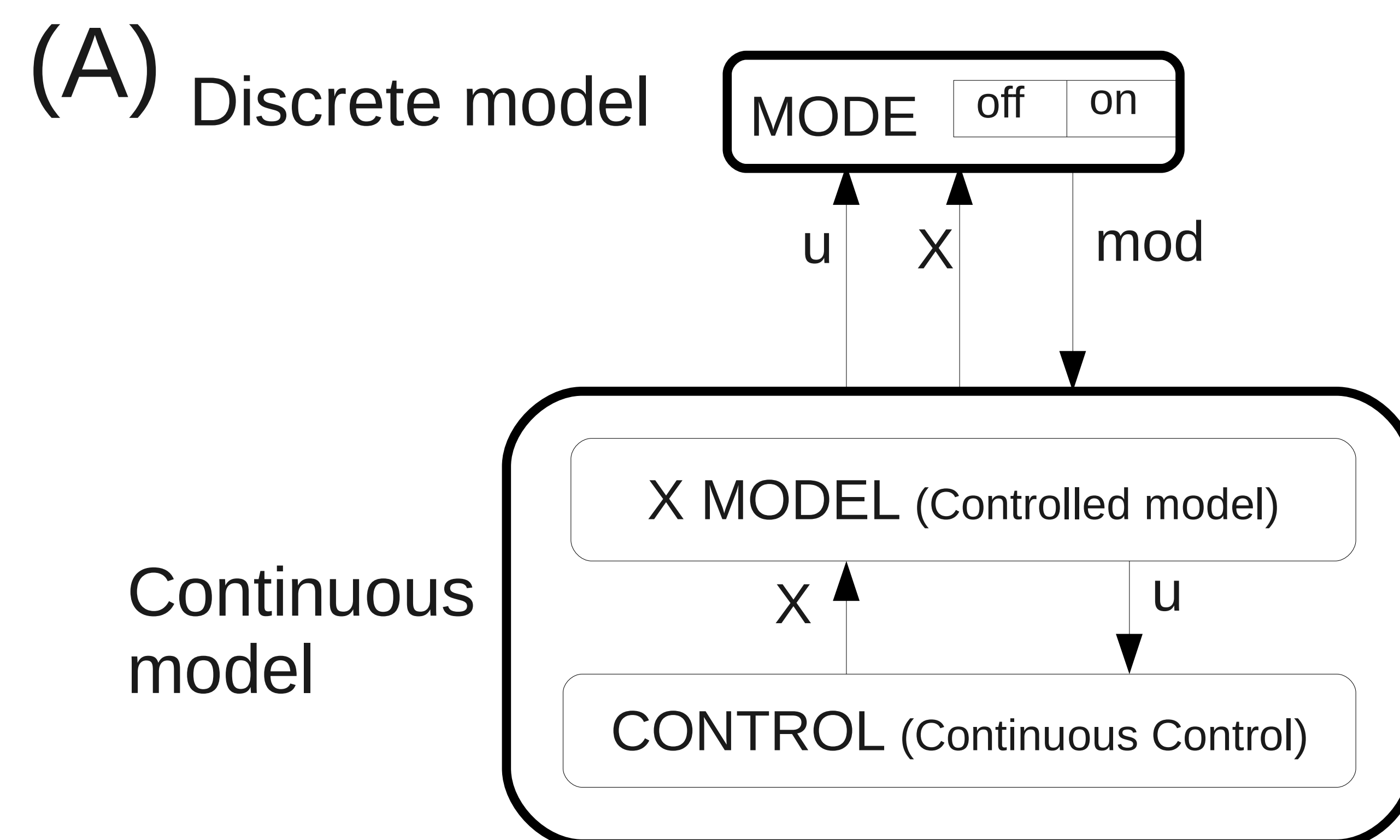


The interactions : two types of implementation descriptions



The interactions : two types of implementation descriptions With coefficient switches :

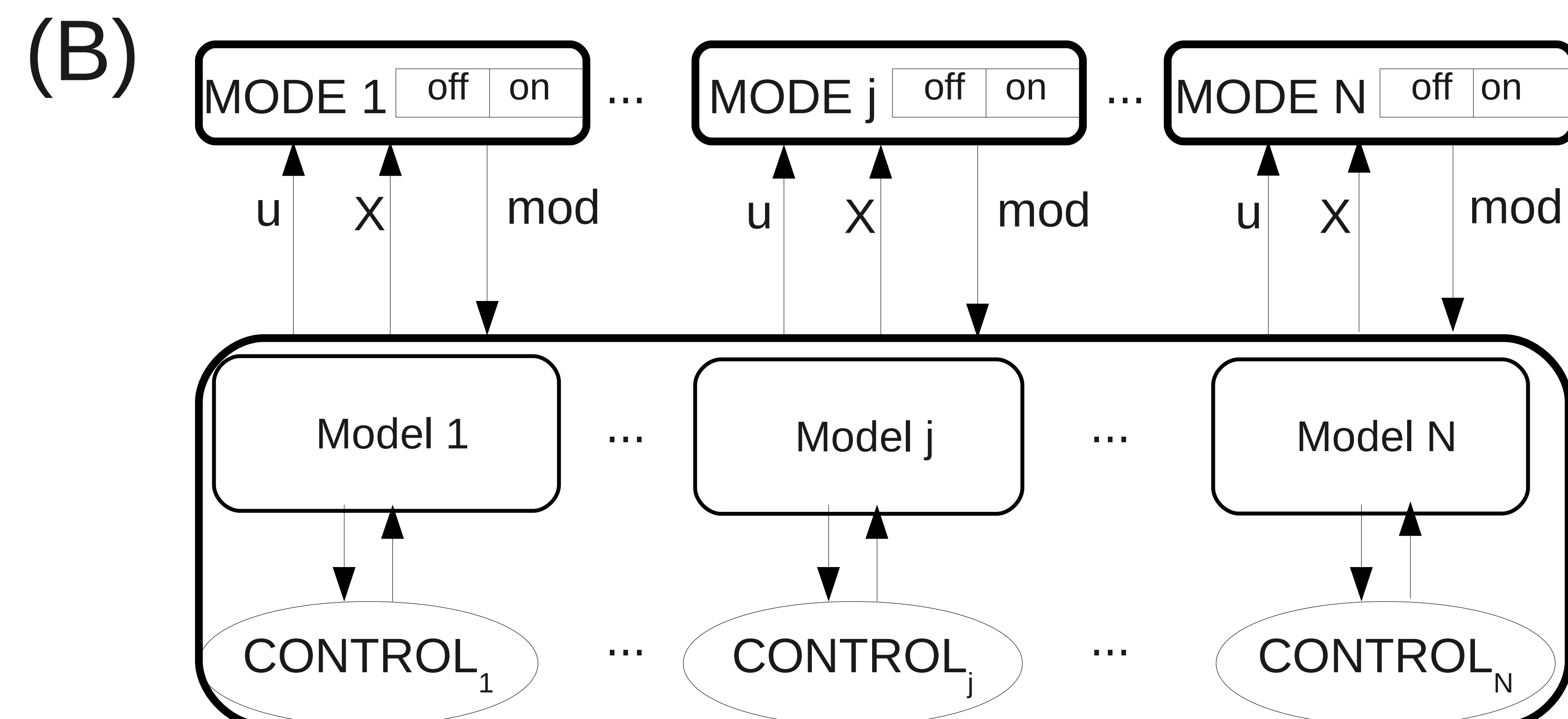
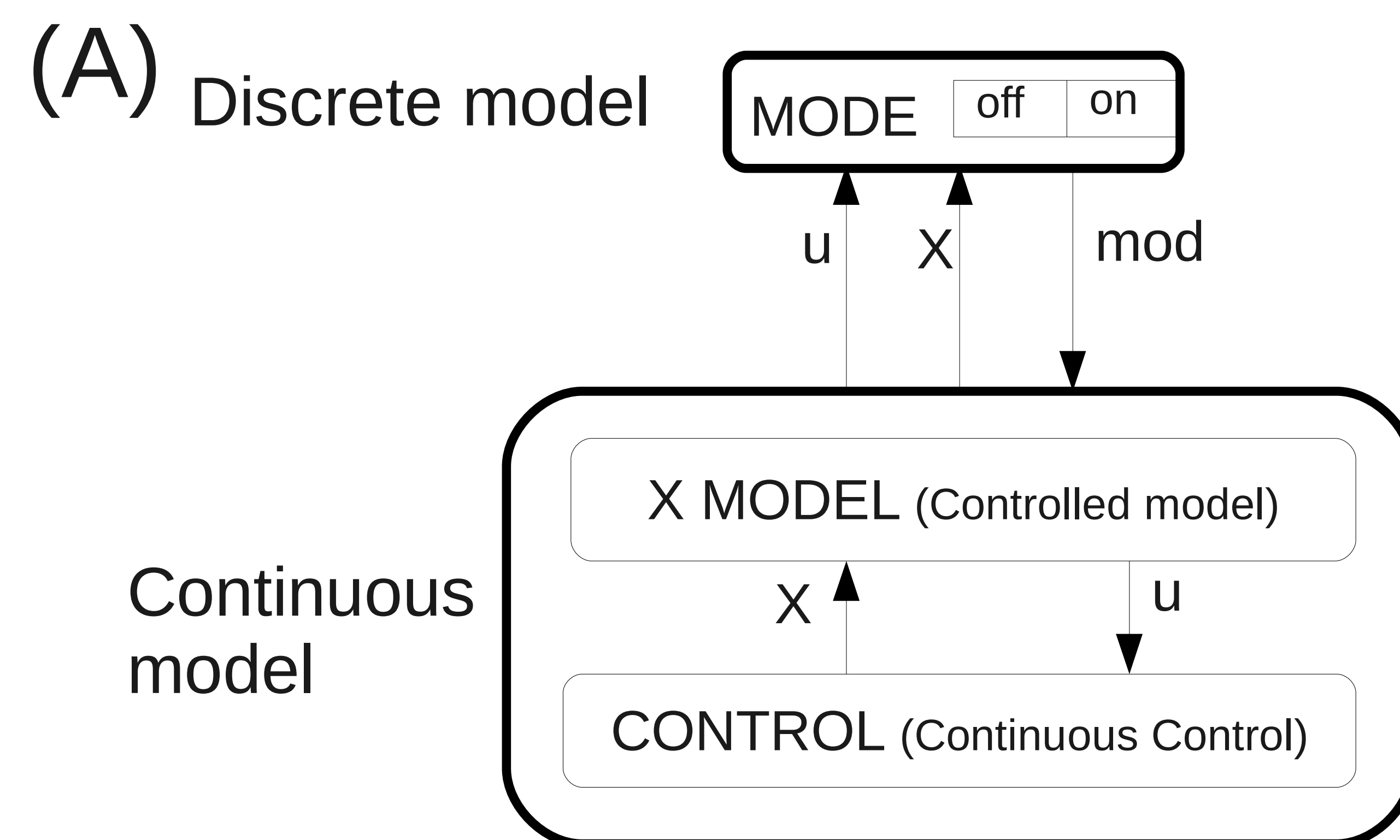
- Model structure conserved,
- Mode coefficients modeled by mode transitions,
- Favor interpretation.



The interactions : two types of implementation descriptions
 With coefficient switches : With strong switches :

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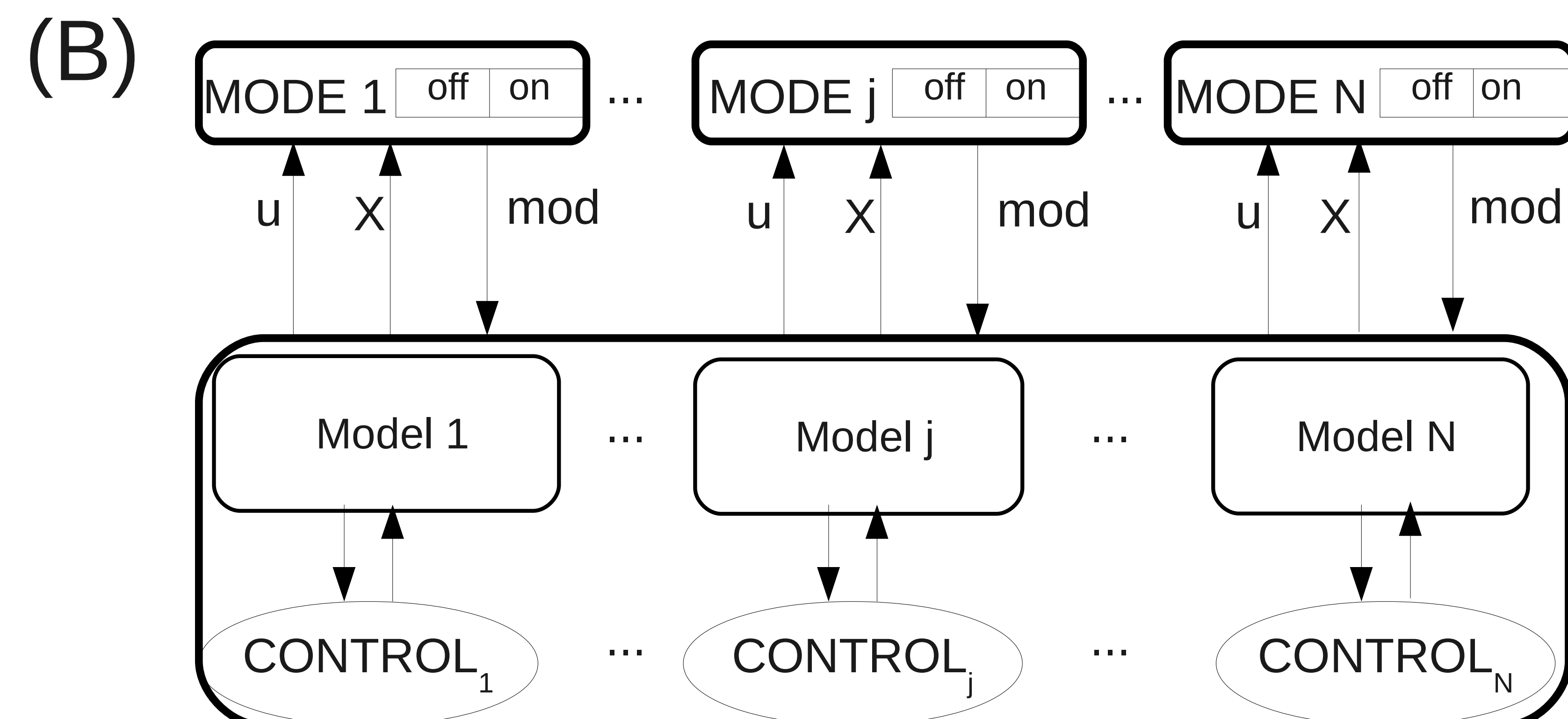
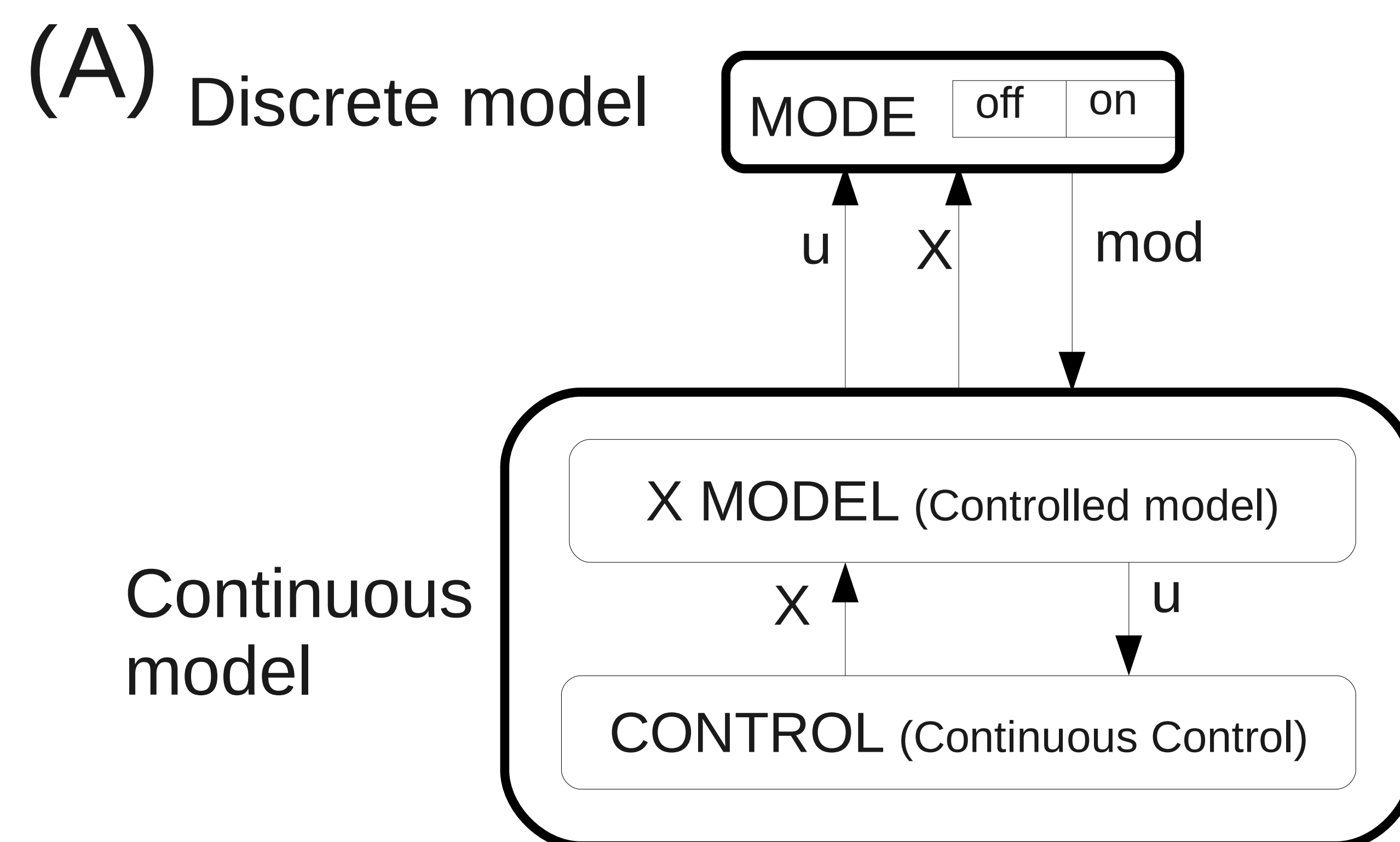
- Different model structures,
- Choosing which model to use : on-off modes,
- Reusing and reconciliation.



The interactions : two types of implementation descriptions
 With coefficient switches : With strong switches :

- Model structure conserved,
- Mode coefficients modeled by mode transitions,
- Favor interpretation.

- Different model structures,
- Choosing which model to use : on-off modes,
- Reusing and reconciliation.



- Reconciliation of models as particular case
 - Strong switches : each module is a different model.
 - Different models could be unified : coefficient switches.

Modeling and guarantees Hybrid systems and composition allow us to describe hierarchical complex biological systems.

- Changes in conditions affecting equations : STS.
- Inclusion of randomness and non-determinism to model erroneous and incomplete information.
- Two descriptions according to the level of mode changes :
 - coefficient switches,
 - strong switches.
- Good theoretical properties :
 - Stability and decidability properties [Branicky, 1994, Henzinger, 1996],
 - The set of Hybrid systems is closed for composition and refinement ([Assar, 2011] using [De Alfaro et al., 2001]),
 - Consistency with respect to shared variables ([Assar, 2011]).

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The problem

- **Goal** : dynamics of ethanol production and resources consumption.
- **Facts** :
 - Many different models to explain the fermentation process : differential equations.
 - Many involved factors :
 - Agent : yeasts.
 - Resources : sugar and nitrogen.
 - Products : ethanol, carbon dioxide, heat.
- **Importance** : Predicting fermentation problems at time to solve them
 - Wine industry : 5 million of tonnes/year in France.
 - Losses from stuck and sluggish fermentations : 7 billion euros/year.

Wine fermentation : steps of our approach

- Sys. variables : concentration of biomass X , active biomass X_A , nitrogen N , ethanol $EtOH$, carbon dioxide CO_2 and sugar S .
- Steps of our approach [Assar et al., 2010] :
 - Symbolic step : homogenizing the models.
 - Statistical step : classification of the results
 - Using training data.
 - Constructive step : building the reconciled model.
 - Application step : predicting the consumption/production dynamics.

[Coleman et al., 2007]

$$\begin{aligned}
 X : \quad & \frac{dX}{dt} = \mu \cdot X_A \\
 X_A : \quad & \frac{dX_A}{dt} = (\mu - \tau) \cdot X_A \\
 N : \quad & \frac{dN}{dt} = -v_N \cdot X_A \\
 EtOH : \quad & \frac{d[EtOH]}{dt} = v_{EtOH} \cdot X_A \\
 S : \quad & \frac{dS}{dt} = -v_S \cdot X_A \\
 CO_2 : \quad &
 \end{aligned}$$

[Scaglia et al., 2009]

$$\begin{aligned}
 \frac{dX}{dt} &= (F_\mu \cdot \mu - F_\tau \cdot \tau) \cdot X - F_\mu \cdot \beta \cdot X^2 \\
 \frac{d[EtOH]}{dt} &= \frac{1}{Y_{CO_2/EtOH}} \cdot \frac{dCO_2}{dt} \\
 \frac{dS}{dt} &= -((v_S + v_{S_0}) \cdot X - \frac{0.00002}{Y_{X/S}} \cdot X^2) \\
 \frac{dCO_2}{dt} &= v_{CO_2} \cdot X + \frac{d(CO_2Form)}{dt}
 \end{aligned}$$

[Pizarro et al., 2007]

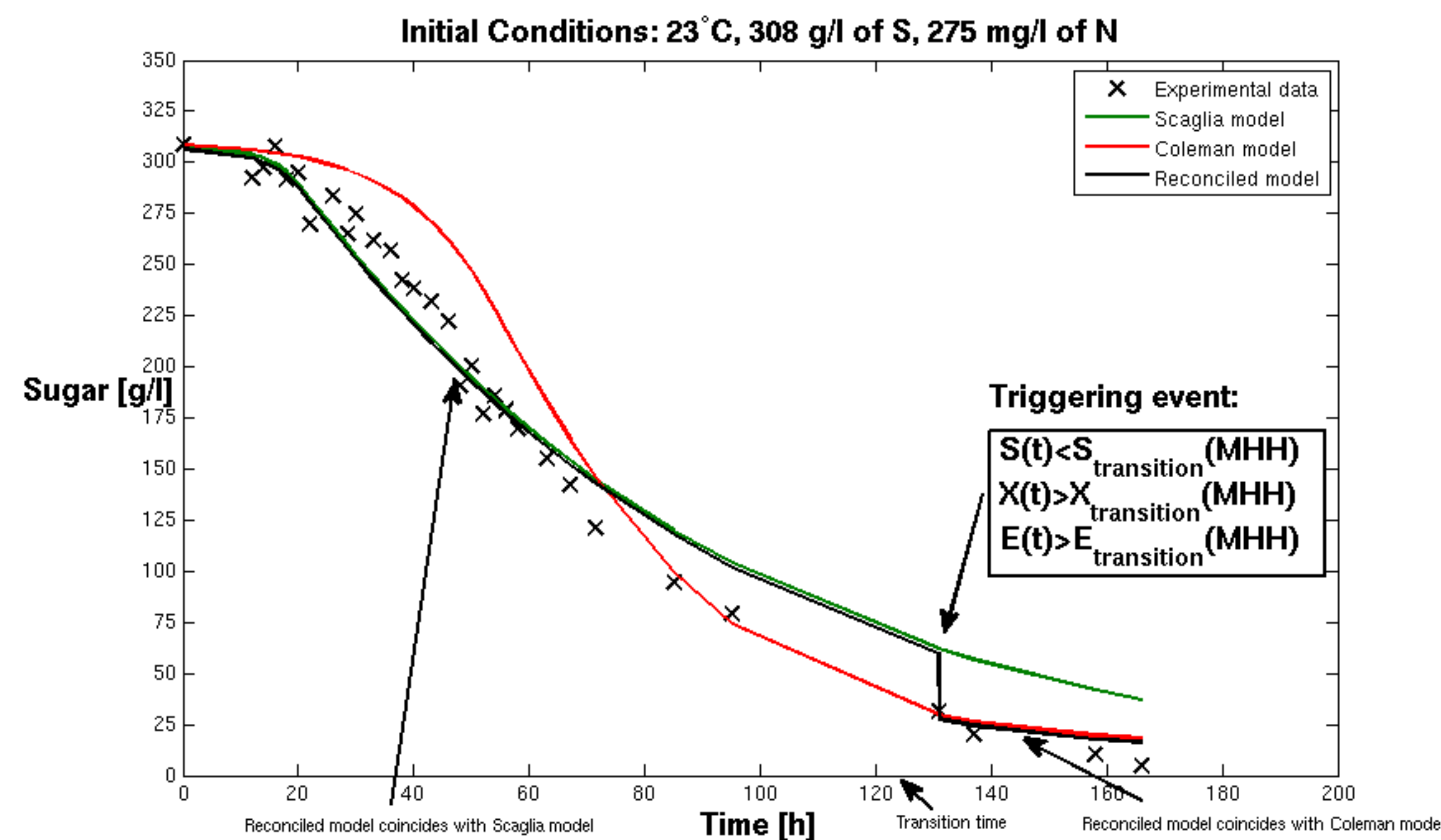
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Training data

Temperature	Sugar	Nitrogen	Biomass	Ethanol	Sugar
Low (0-19 °C)	Moderate (160-240 [g/l])	Moderate (50-240 [mg/l])			
		High (240-551 [mg/l])			1
	High (240-308 [g/l])	Moderate			
		High	2		3
Moderate (20-27 °C)	Moderate	Moderate	1	1	1
		High	1	1	6 1
	High	Moderate	1		
		High	1		2
High (28-35 °C)	Moderate	Moderate	1	1	1
		High	2	1	2
	High	Moderate			
		High			1

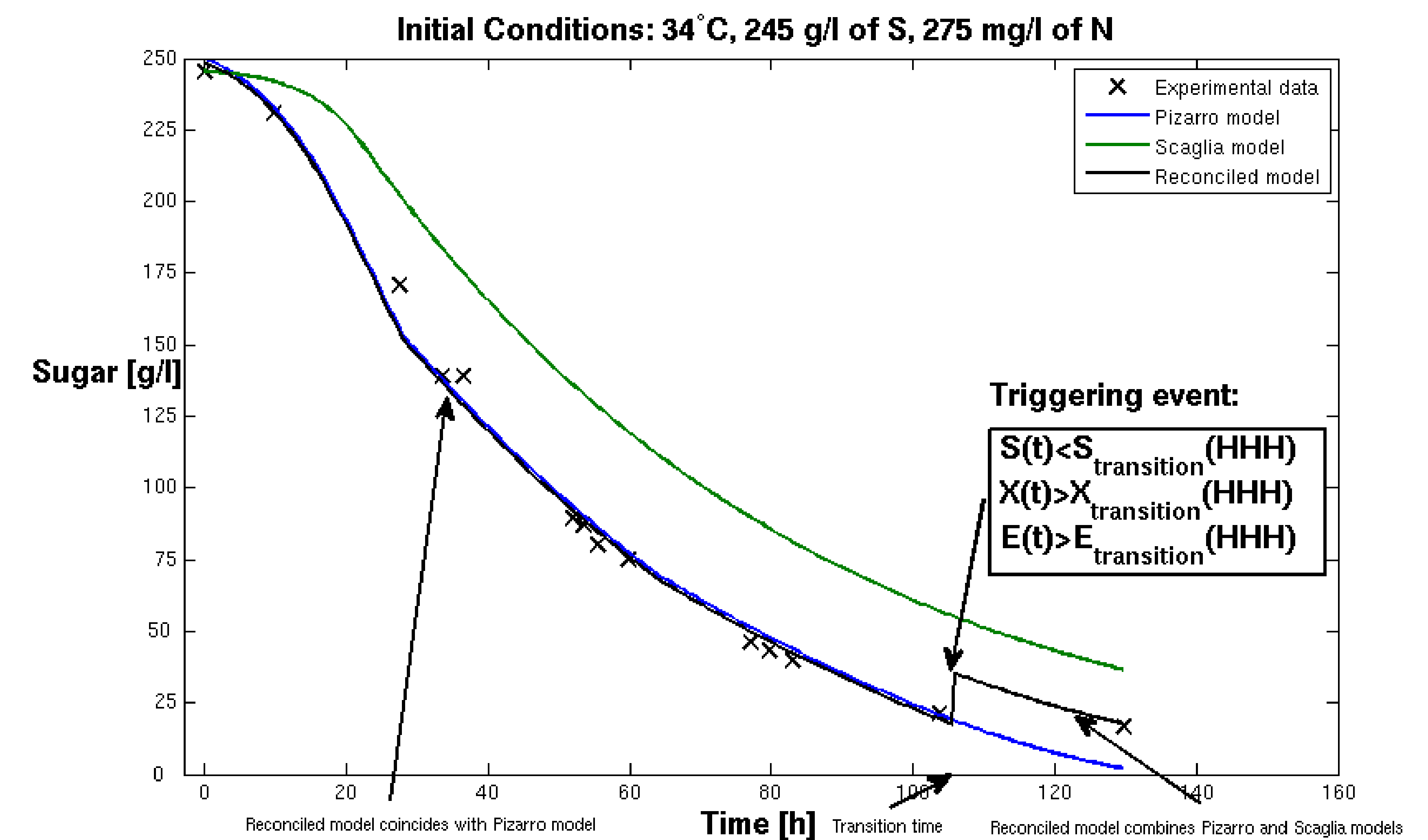
Pizarro data ([22])Malherbe data ([15])Mendes-Ferreira data ([16])

MHH : coefficient switches.



- Models homogenized in an unique node *MODEL*,
- Transient phase : Scaglia,
stable : Coleman.

HHH : Strong switches.



- One node and mode variable per model,
- Transient phase :
[Pizarro et al., 2007],
stable : combining Pizarro and Scaglia models.

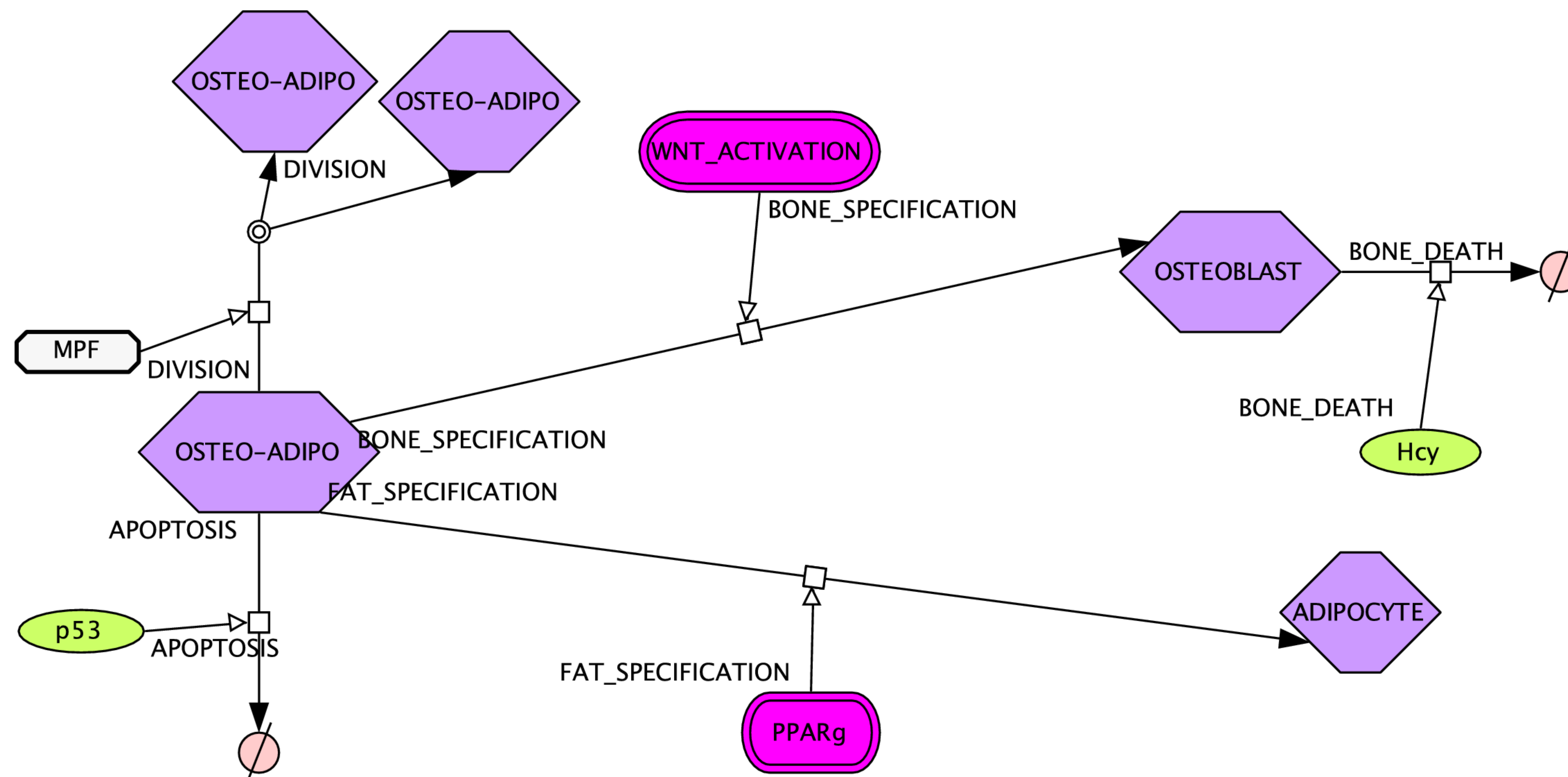
Conclusions

- Predicting fermentation problems :
 - when sugar becomes scarce appears resources competence (Scaglia model).
- Avoiding problems
 - changing factor conditions.
- Possibility to apply the same approach
 - to reconcile other wine models,
 - into other biological applications.

Bone formation

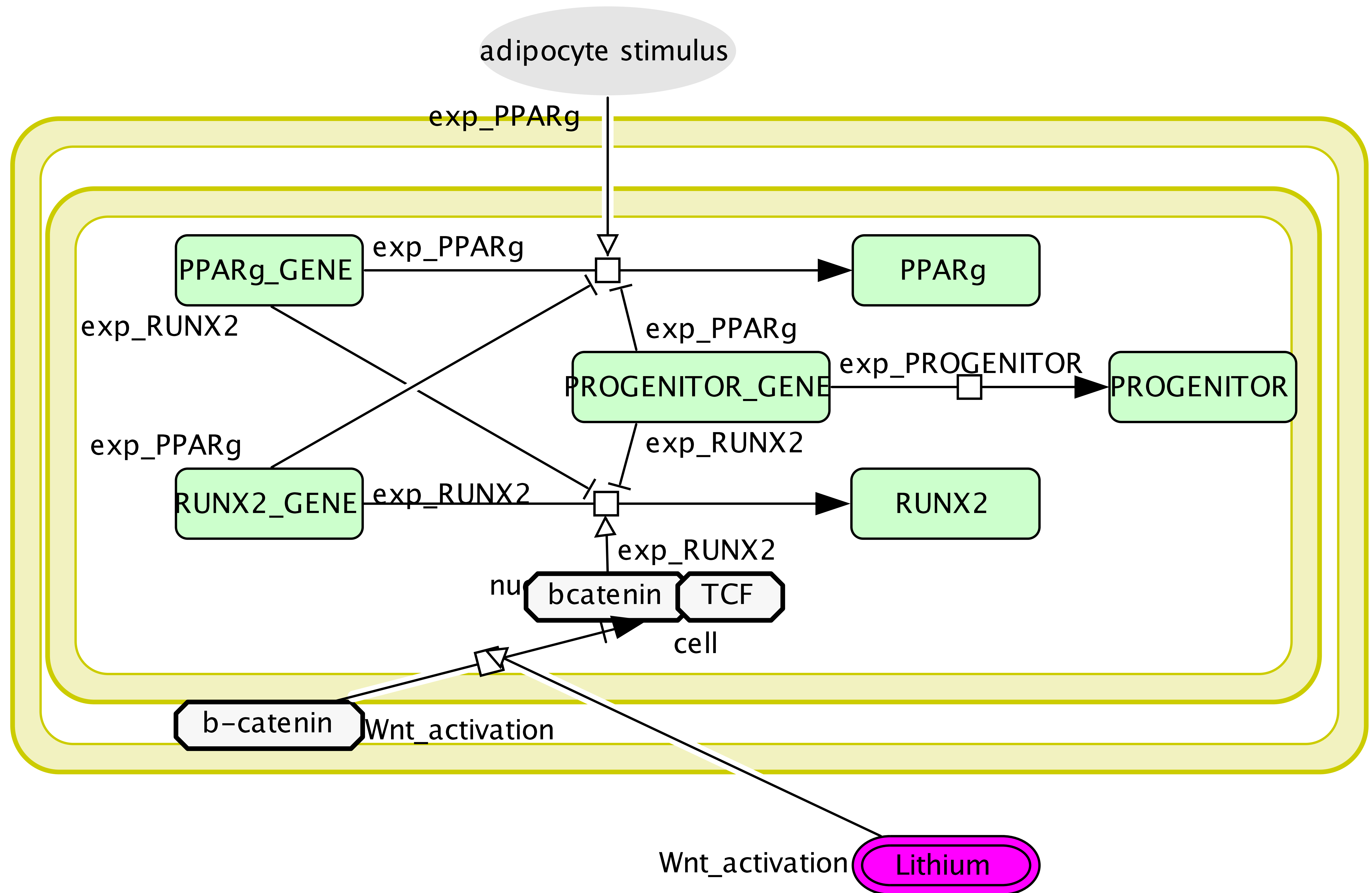
- **Question** : dynamics of bone formation from osteo-adipo progenitor cells.
- **Facts** :
 - Process with many hierarchy levels : tissues, cells, and genes.
 - many factors involved in this process : aging and fat accumulation.
 - changes in conditions affect its behavior.
- **Importance** : finding and validating new treatments for bone mass disorders, with
 - less limitations,
 - less side effects,
 - more adapted to patient-specific conditions.

Bone/fat formation from precursor cells [Assar et al., 2012]

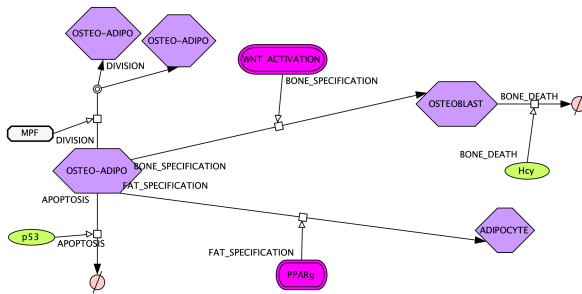


- x_P Progenitors : *OCT4* or *SOX2*.
- x_O Osteoblasts : *RUNX2*.
- x_A Adipocytes : *PPAR γ* .
- A GRN : each one self-activated, mutually inhibited.
- Mode coeffs : z_D , z_O , z_A .

Osteo-adipo diagram

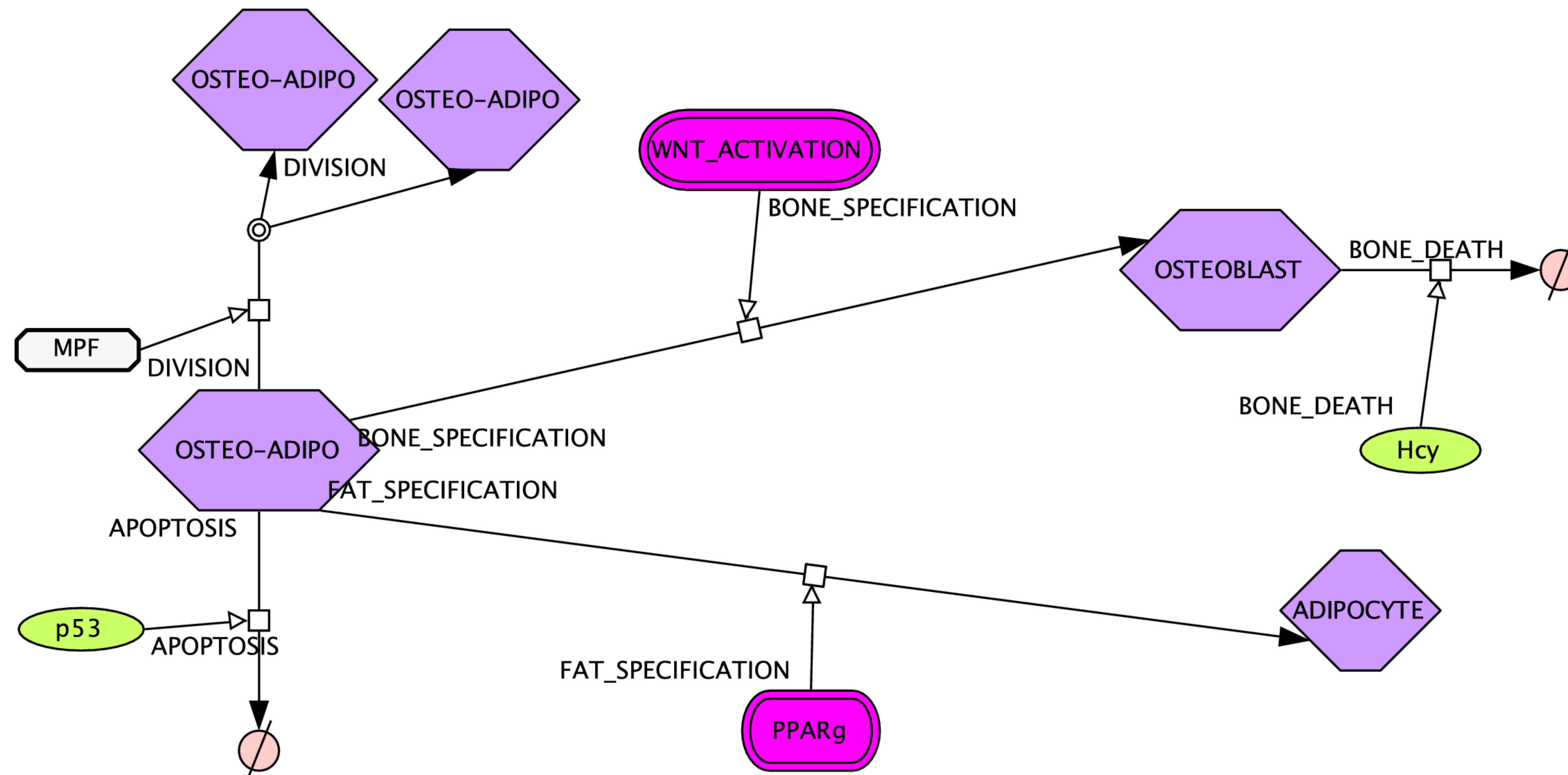


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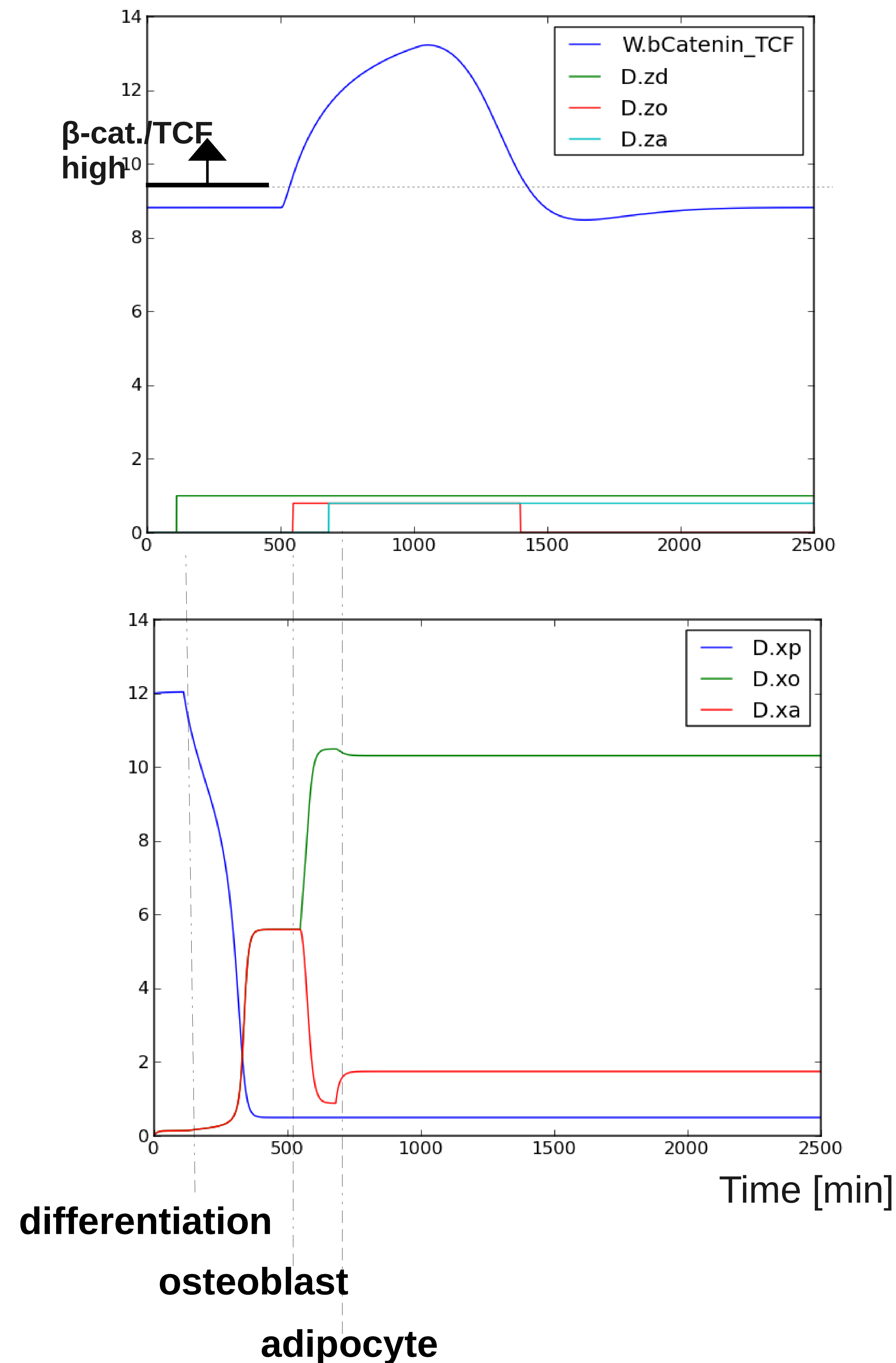


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External stimuli :

- Osteogenic : Wnt pathway (model by [Kim et al., 2007]),
- Adypogenic : *PPAR γ* activation [stochastic model],
- Apoptotic : increase of *homocysteine* [Kim et al., 2006].
- Division : kinetics of maturation promoter factor.

Results



- Stimulus signals
 - β -catenin production stimulates osteoblast lineage (*D.zo*)
 - Differentiation stimulus *D.zd*
 - Adipocyte lineage activation (*D.za*)
- Dynamics of cell commitments.

Conclusions and challenges

- First step to simulate physiological responses *in silico* to osteoporosis treatments.
- Towards treatments to enhance the bone mass
 - Exploring effect of regulatory signals (*Wnt* activation + ?).
 - Finding and validating treatments by simulating them.
- Including influence of epigenetic mechanisms
 - Information not included in the DNA,
 - Affecting expressions of biomarkers,
 - Provoking predisposition to specific lineages (osteobalsts, [Zaidi et al., 2010, Gordon et al., 2011]).

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Conclusions

- From processes modeled by just a simple model to others with many connected components,
- From processes with high information levels to others with poor information,
- From continuous models without changes over time to others with radical changes in their equations.

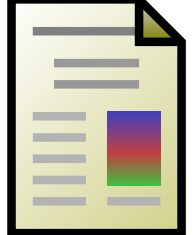
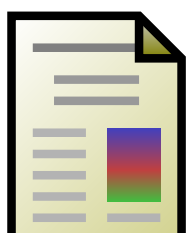
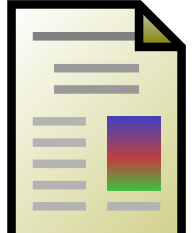
Applied to real problems :

- Reconciling wine fermentation kinetics,
- Reusing models for modeling cell fate in bone/fat formation.

With methodological advantages :

- Adapted for reusing and combining different types of models,
- Reconciliation of competing models as particular case.
- With a theoretical support : hybrid systems.
- BioRica implementation.

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Hybrid systems : the idea

- Notation
 - **dependent variables** with continuous dynamics :
 $x = (x_1, \dots, x_n) \in \mathbb{R}^n$ called **state variables**,
 - **factor variables** with continuous dynamics :
 $u = (u_1, \dots, u_k) \in \mathbb{R}^k$,
 - **factor variables** with discrete dynamics :
 $mode \in M = \{1, \dots, M\}$ called **mode variables**.
- Two points of view in literature
 - Switched systems [Branicky, 1994, Shorten et al., 2005] : using differential equations. $\dot{x}(t) = F_{mode(t)}(x(t), u(t))$,
 $mode(t) = G(x(t), u(t), m(t^-))$.
 - Hybrid automata [Henzinger, 1996] : using automata theory.
 Guard conditions provoke mode changes.
- Here : using STS [De Alfaro, 1998] to describe mode changes
 - deterministic, non-deterministic and stochastic transitions,
 - different types of continuous models and interactions.

Ways of combining different types of models

- Using hybrid systems theory [Henzinger, 1996, Johansson, 2003] :
 - combining continuous, discrete, deterministic, stochastic and non-deterministic behaviors,
 - continuous variables evolve according to continuous models, but changes in mode values can change the definition of the continuous model.
- Using composition theory [De Alfaro et al., 2001] : building a model from the connection of two or more models :
 - allowing different types of composed models,
 - allowing different complexity levels and timescales