DEWS CENTER OF EXCELLENCE

BEA SMART

Smart Technologies for Biomedical and Environmental Applications
A joint DEWS@UNIVAQ – IASI@CNR Laboratory

Model-based control of plasma glycemia: in quest of robustness

The symbolic approach: a tool to tame the complexity of models and specifications

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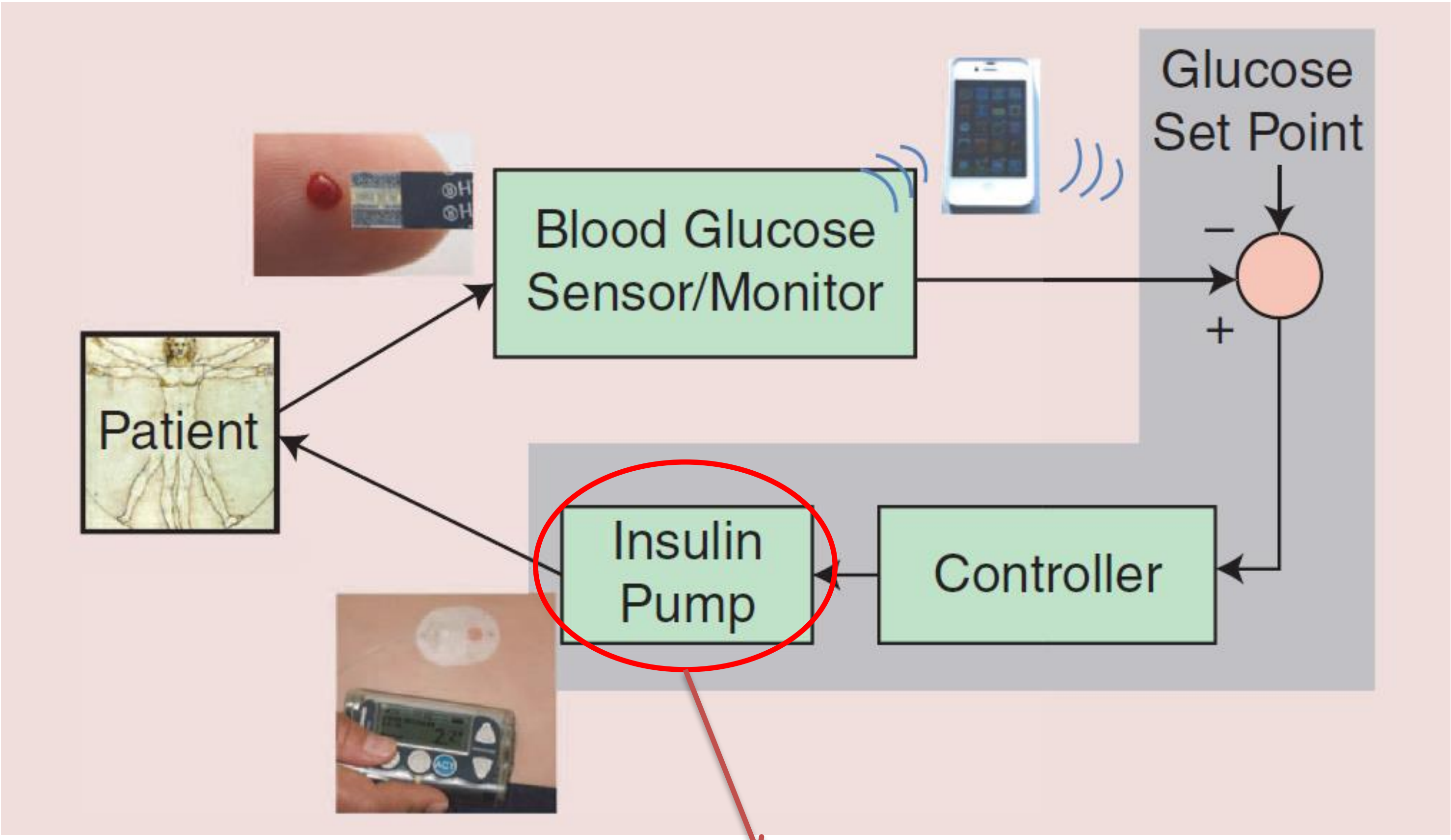
AP control loop



it delivers continuous subcutaneous insulin therapy

Single-delay model

Model equations Adapted from Panunzi et al. (2007), Palumbo et al. (2007)

Insulin input

Glycemia [mM] $$\frac{dG(t)}{dt} = -k_{xgi}\mathrm{G(t)I(t)} + \frac{T_{gh}}{V_G}$$

Insulinemia [pM] $$\frac{dI(t)}{dt} = -k_{xi}\mathrm{I(t)} + \frac{T_{iGmax}}{V_I}\varphi\left(G\left(t-\tau_g\right)\right) + u(t)$$

$$\varphi(x) = \frac{\left(\frac{x}{G^*}\right)^\gamma}{1+\left(\frac{x}{G^*}\right)^\gamma}$$

Init conditions

$G(t) = G_b \quad \forall t < 0$ $\qquad I(t) = I_b \quad \forall t < 0$

$G(0) = G_b + G_\Delta$ $\qquad I(0) = I_b + I_{\Delta G}G_\Delta$

Equilibrium constraints: $T_{gh} = k_{xgi}G_bI_bV_g$ $\qquad T_{iGmax} = k_{xi}I_bV_i$

Challenges in glucose regulation via insulin

Challenges

- From a control-theoretic viewpoint, insulin is a **non-negative input**
- **Food** as a source of **uncertainty**
- Random variations (hormones, stress, physical activity…)
- The **subcutaneous compartment** introduces filtering/delay effects
- I/O **sampling and quantization**
- Actuation **lags**

Time-varying control targets

TABLE I

CONTROL TARGETS

Target	**Range** $[mM]$
Very good fasting glycemia	$3.9 \leq G(t) < 5.6$
Good fasting glycemia	$5.6 \leq G(t) < 6.5$
Satisfactory pre-prandial state	$4.4 \leq G(t) < 7.2$
Very good post-prandial (2 hours after meal) state	$G(t) < 7.8$
Good post-prandial (2 hours after meal) state	$7.8 \leq G(t) < 10$

Targets established according to current clinical practice recommendations and guidelines of the American Diabetes Association (ADA) for the diabetes care and treatment.

Control based on SDM

«Classical» nonlinear state/output feedback control:

- (semiglobal, practical) stabilization can be imposed, but the other guarantees need to be «a-posteriori» checked

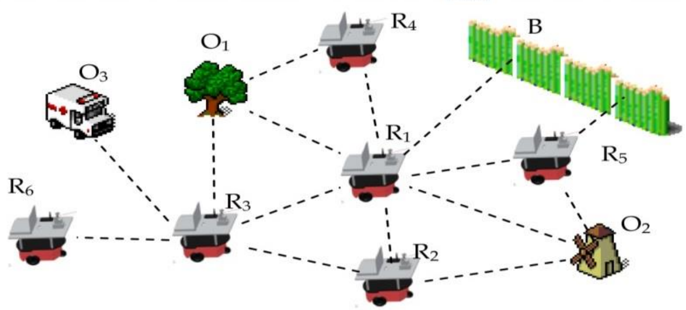
How to deal systematically with:

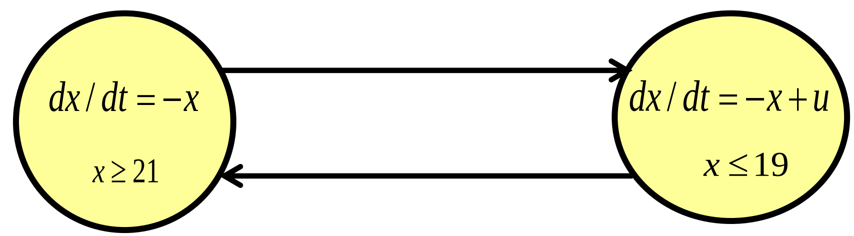
- complex specifications?
- positive inputs?
- (possibly given) quantization parameters (CGM sampling time, insulin units) and non-idealities arising in a digital environment?

A possible answer: **formal methods**.

Formal Methods in Control

- **Formal methods** are mathematically based techniques for the specification, development and verification of software and hardware systems
- **Mathematical analysis** contributes to the **reliability** and **robustness** of a design
- Combination of **discrete, continuous, heterogeneous and distributed** systems



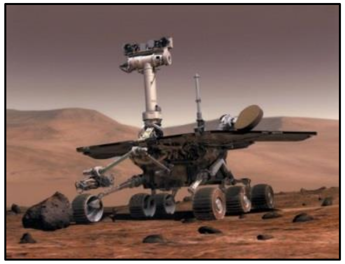


Formal Methods in Control

Modern systems are characterized by tight interaction of many distributed, real-time computing systems and physical systems
(the so-called **Cyber-Physical Systems, CPS**)

Examples: Airplanes, cars, buildings with advanced HVAC controls, manufacturing plants, power plants

- Computational systems, but not stand alone computers, interfacing sensors and actuators, reactive to physical environment stimuli, designed to perform one or a few dedicated functions, often with real-time computing constraints.
- Coordination between physical process and computing/communication components.



A. Borri (2011): Hybrid Control of Cyber-Physical Systems, PhD Thesis

CPS for healthcare: Cyber-Medical Systems

Features of Cyber-Medical Systems (CMS) L. Kovács (2017)

- Mathematical algorithms able to be personalized on the patients' need and physiology
- Control engineering methods and real-time computation to fasten and intensify a "knowledge-based" intelligent decision support
- Artificial Intelligence and big data analysis for feature extraction

Artificial Pancreas is a CMS involving technological advances in diabetes treatment:

  - Continuous Glucose Monitors (CGMs)
  - Insulin pumps

Formal methods: a tool to tame the complexity of CPS and to deal with logic requirements and complex specifications.

"Complex" specifications

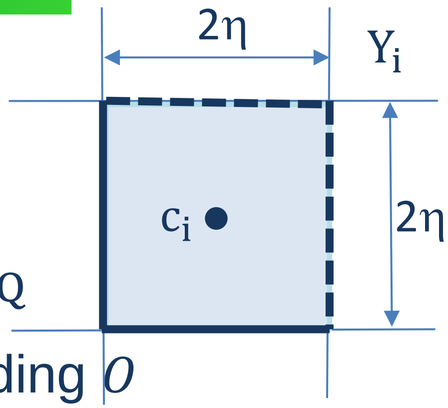
Logic/temporal specifications

- **Stay**: trajectories start in the target set Z and remain in Z.
- **Reach**: trajectories enter the target set Z in finite time.
- **Reach and Stay**: trajectories enter the target set Z in finite time and remain within Z thereafter.
- **Reach and Stay while Stay**: trajectories enter the target set Z in finite time and remain within Z thereafter while always remaining within the constraint set W.

Language specifications

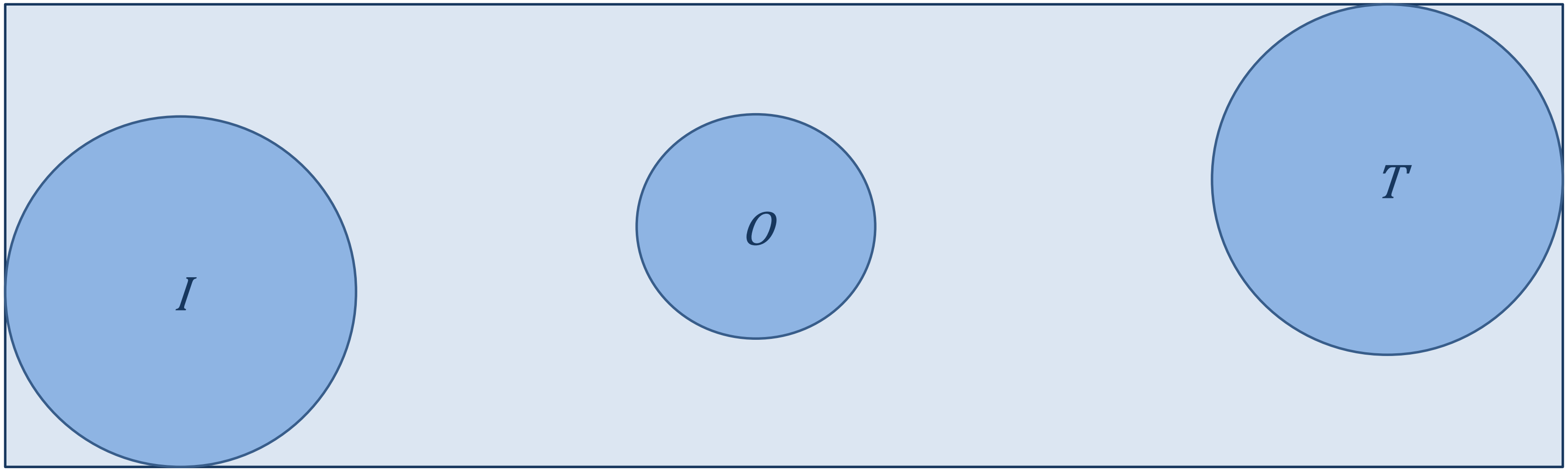
- A **word** is a finite sequence of "output" symbols (it may encode a sampled trajectory)
- A **language** is a collection of words (it may encode good trajectories)

Language specifications



- Consider a collection Y of left-closed right-open hyper-cubes Y_i of $\mathbb{R}^n$
- We consider a specification expressed as a language L_Q

Example Starting from I reach T in finite time while avoiding O



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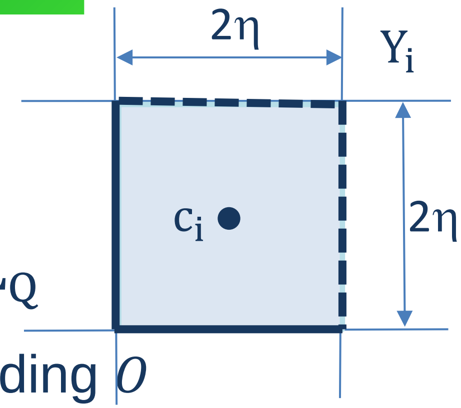

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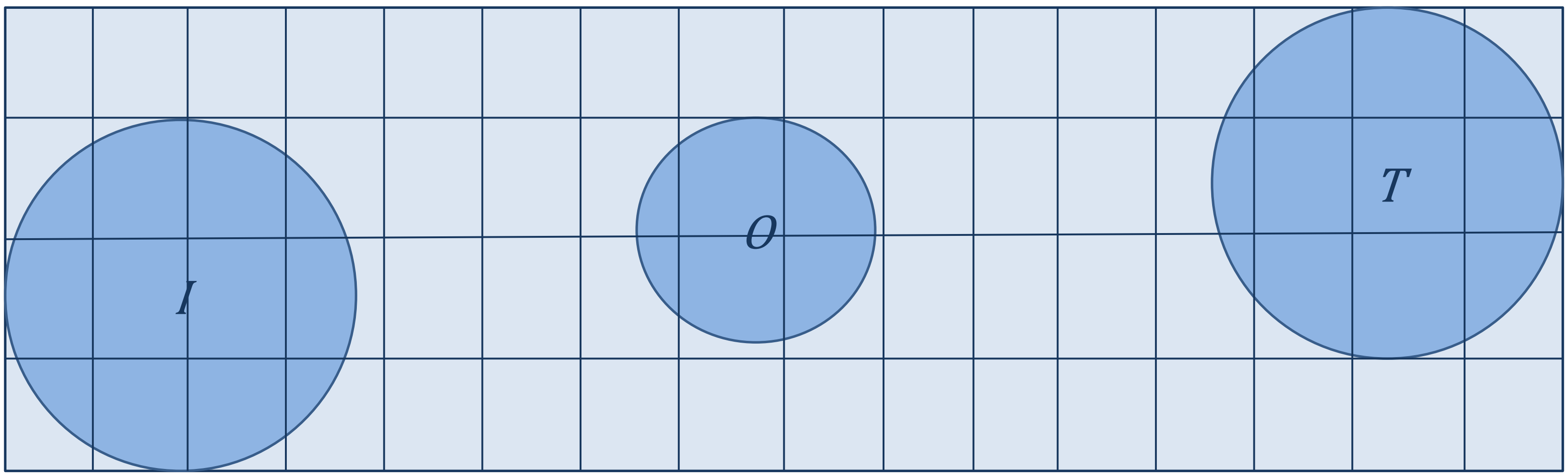
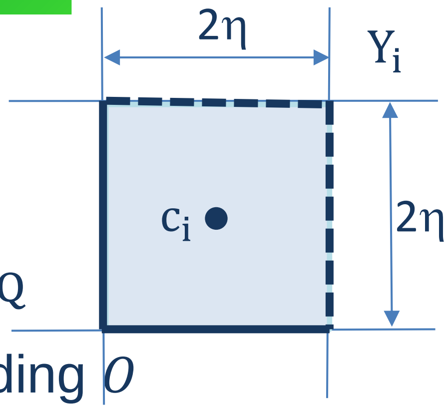


Language specifications



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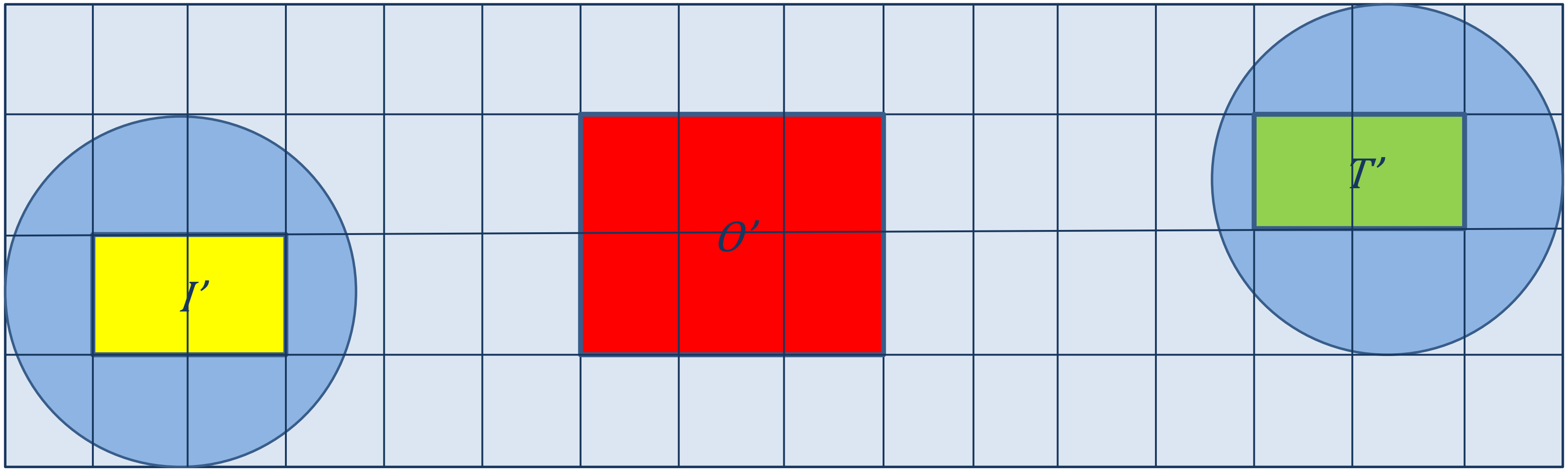
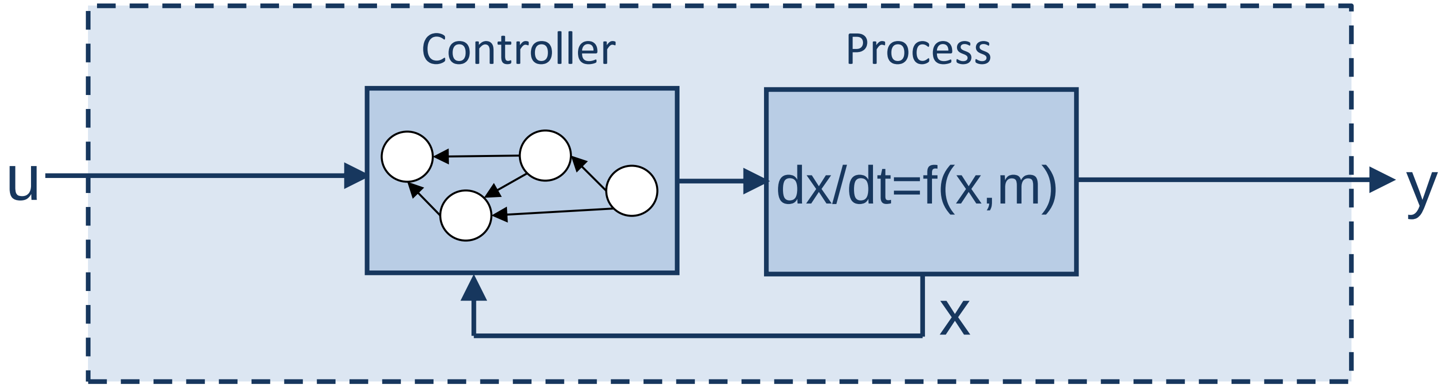
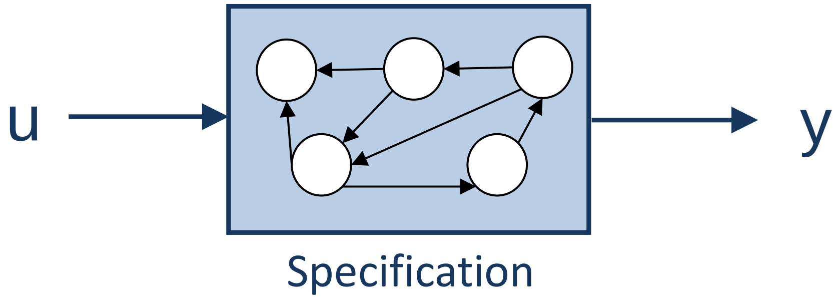


L_Q = collection of words starting with [yellow square], ending with [green square] and with no [red square]

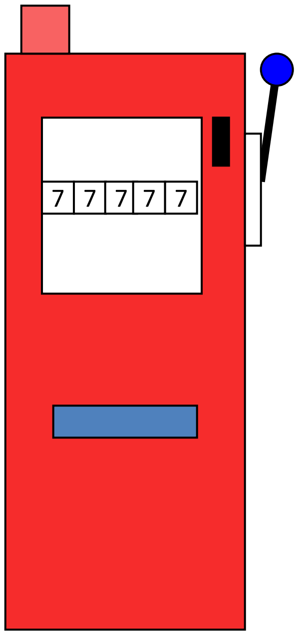
Logic specifications expressed by finite state machines





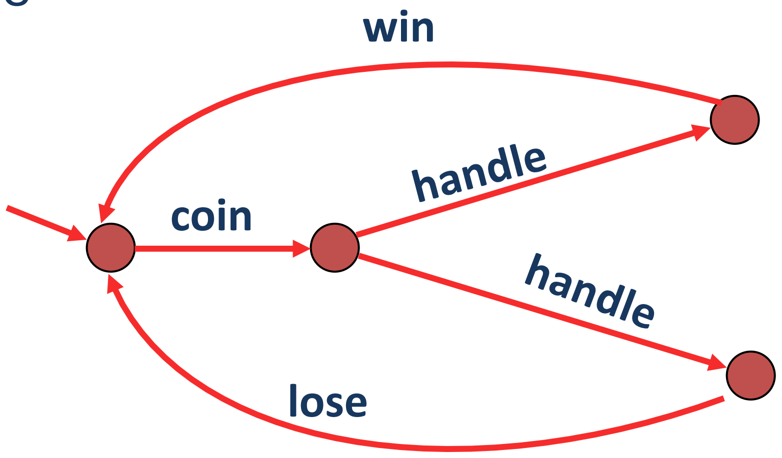
Finite state machines also encode logic and language specifications

Purely discrete systems: finite state machines or automata



Slot machine

1. Insert coin
2. Pull handle
3. Win if the combination is good, otherwise lose



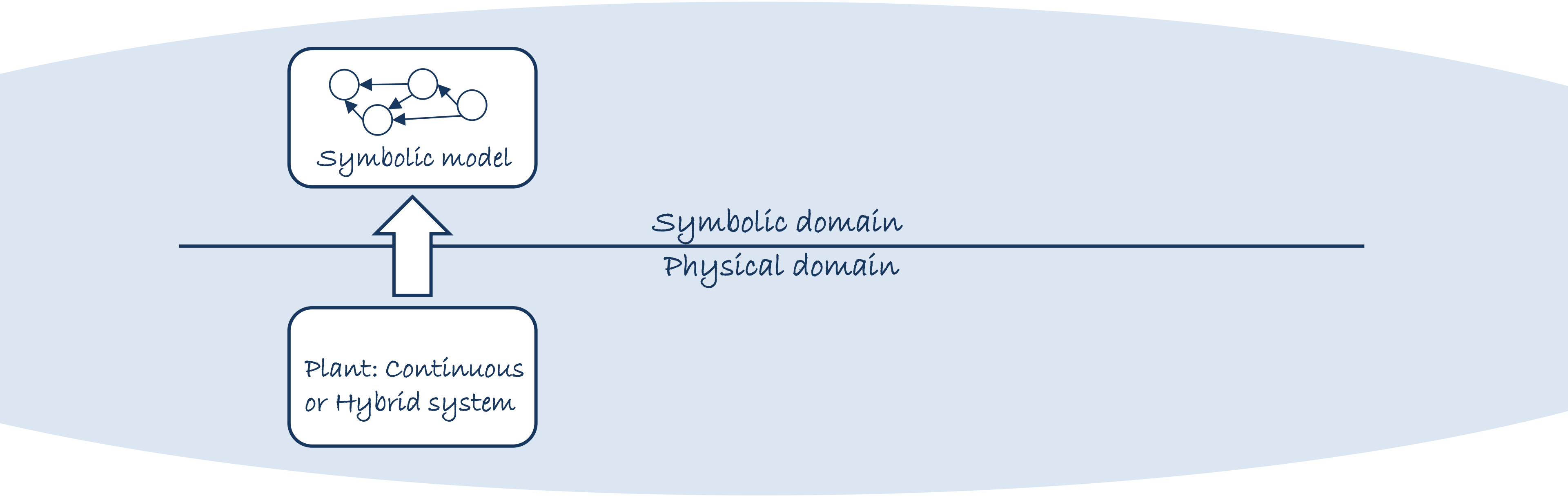
Features: events may be time-abstract, possible non-determinism

Control based on formal methods

Symbolic domain

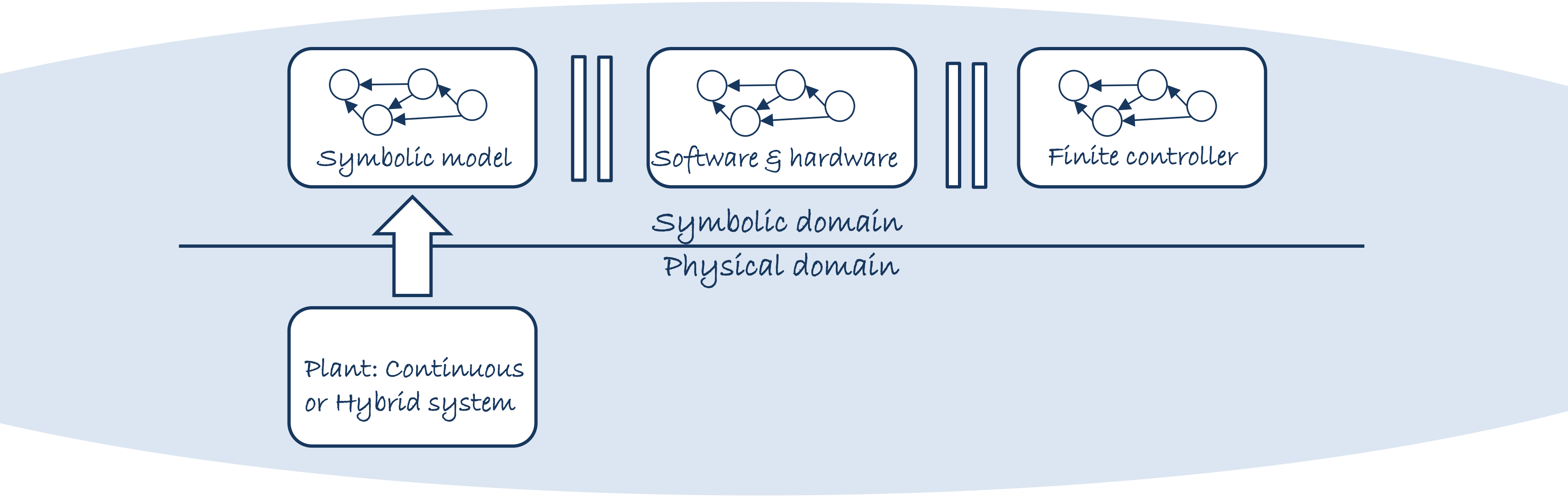
Physical domain

#1. Construct the finite/symbolic model T approximating the plant system P



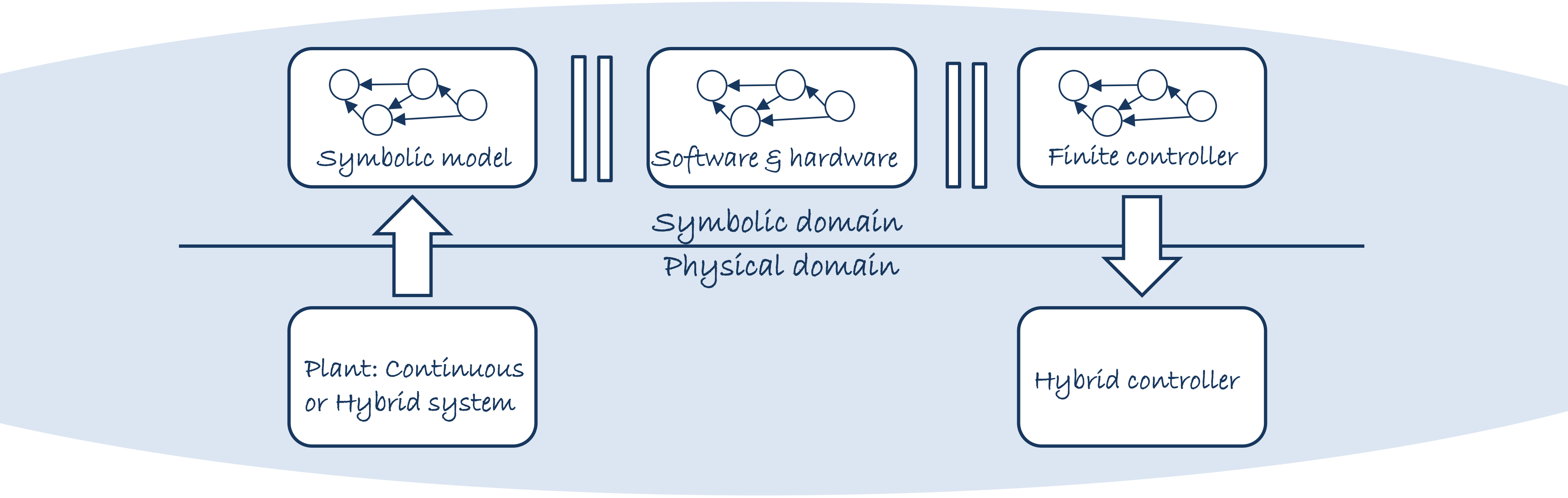
Control based on formal methods

#1. Construct the finite/symbolic model T approximating the plant system P
#2. Design a finite/symbolic controller C that solves the specification S for T



Control based on formal methods

#1. Construct the finite/symbolic model T approximating the plant system P
#2. Design a finite/symbolic controller C that solves the specification S for T
#3. Refine the controller C to the controller C' to be applied to P



Correct-by-design embedded control software synthesis

Control based on formal methods

#1. Construct the finite/symbolic model T approximating the plant system P
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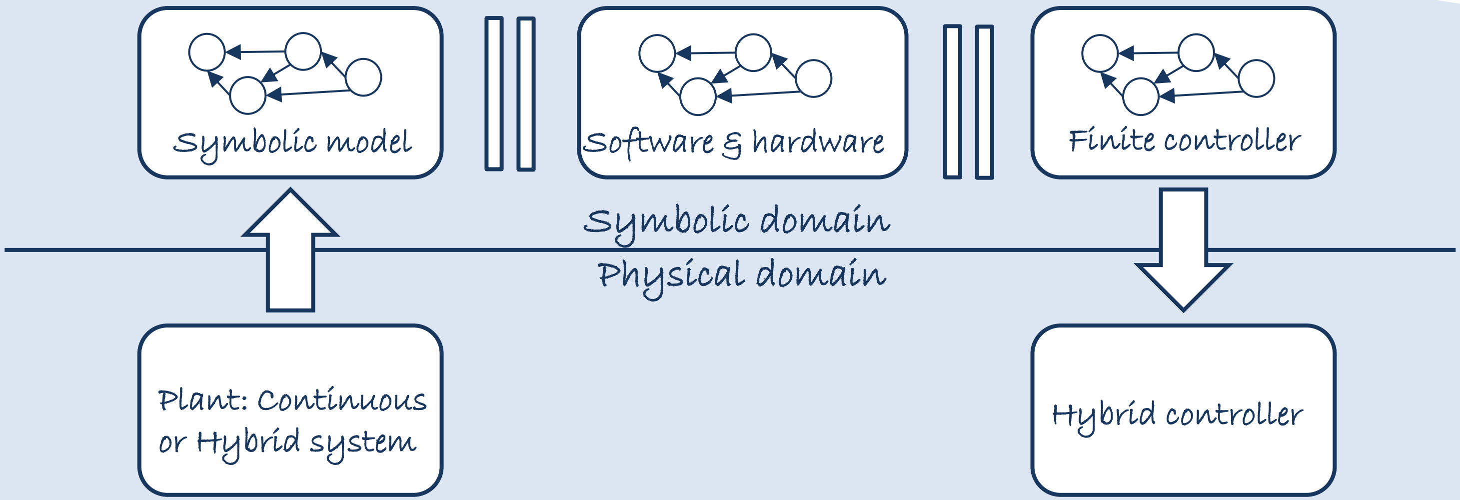


- Integration of SW/HW constraints in the control design of continuous processes
- Logic specifications can be addressed

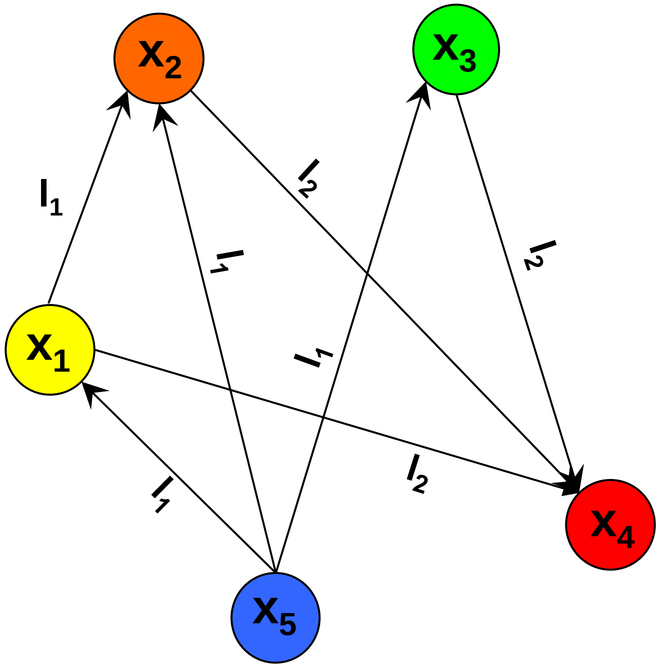
A unified framework for continuous and discrete systems

Definition A **transition system** is a tuple:

$$T = (X, X_0, L, \longrightarrow, X_m, Y, H),$$

consisting of:

- a set of states X
- a set of initial states $X_0 \subseteq X$
- a set of inputs L
- a transition relation $\longrightarrow \subseteq X \times L \times X$
- a set of marked states $X_m \subseteq X$
- a set of outputs Y
- an output function $H: X \rightarrow Y$



T is said countable if X and L are countable sets
T is said symbolic/finite if X and L are finite sets
T is metric if the output set is equipped with a metric

We will follow standard practice and denote $(x, l, x') \in \longrightarrow$ by $x \xrightarrow{l} x'$

A unified framework for continuous and discrete systems

A **nonlinear control system** Σ

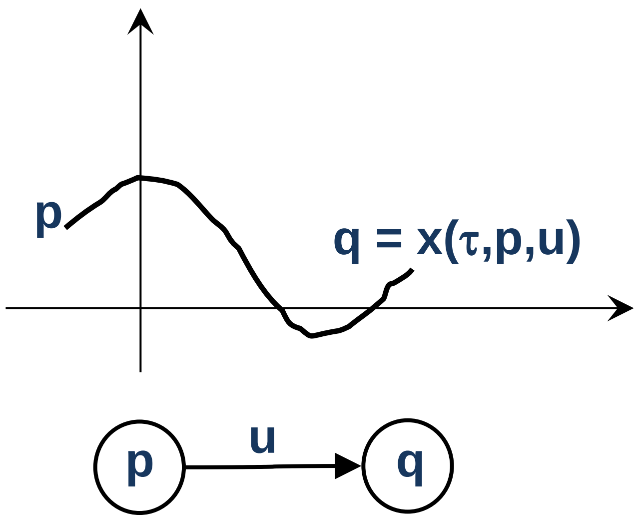
$$dx/dt = f(x,u),\ x \in X \subseteq R^n,\ u \in U \subseteq R^m$$

can be modeled by the transition system

$$T(\Sigma) = (X, X_0, \mathcal{U}, \longrightarrow, X_m, Y, H),$$

where:

- $X_0 = X$
- $\mathcal{U}$ is the collection of control signals $u : R \to U$
- $p \xrightarrow{u} q$, if $x(\tau,p,u) = q$ for some $\tau \geq 0$
- $X_m = X$
- $Y = X$
- H is the identity function



$T(\Sigma)$ captures the information contained in Σ but it is not a symbolic model because X and U are infinite sets!

Exact equivalence notions

[Milner & Park, 1981]

Given $T_1 = (X_1, X_{01}, L_1, \longrightarrow_1, X_{m1}, Y_1, H_1)$ and $T_2 = (X_2, X_{02}, L_2, \longrightarrow_2, X_{m2}, Y_2, H_2)$ with $Y_1 = Y_2$, a relation

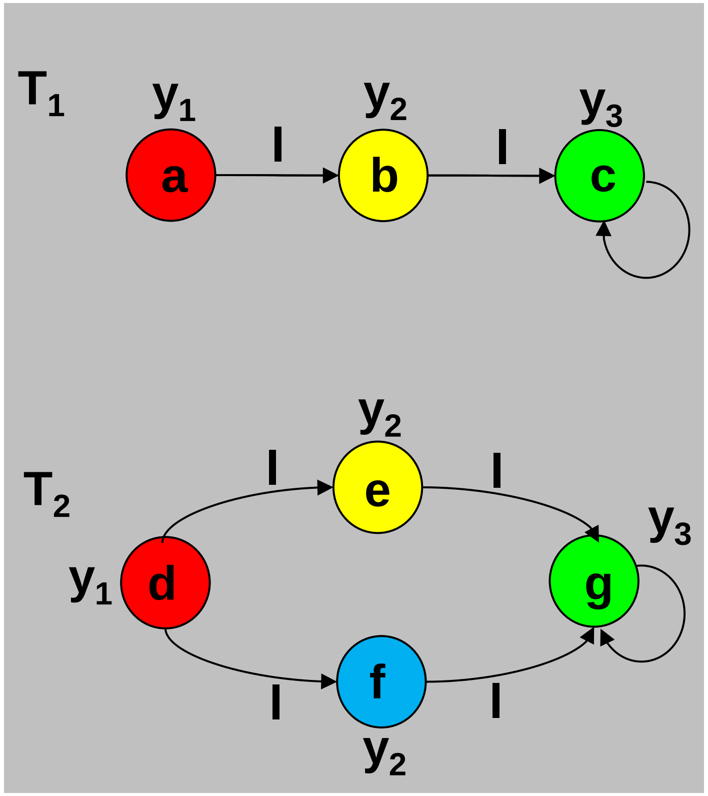
$$R \subseteq X_1 \times X_2$$

is a ***simulation relation*** from T_1 to T_2 if

- $\forall x_1 \in X_{01}, \exists\, x_2 \in X_{02}$ s.t. $(x_1, x_2) \in R$
- $\forall x_1 \in X_{m1}, \exists\, x_2 \in X_{m2}$ s.t. $(x_1, x_2) \in R$
- $\forall (x_1, x_2) \in R$, $H_1(x_1) = H_2(x_2)$
- $\forall (x_1, x_2) \in R$, if $x_1 \xrightarrow{l_1}_1 p_1$ then there exists

  $x_2 \xrightarrow{l_2}_2 p_2$ such that $(p_1, p_2) \in R$

Transition system T_1 is *simulated* by T_2 ($T_1 \preccurlyeq T_2$) if there exists a *simulation relation* from T_1 to T_2



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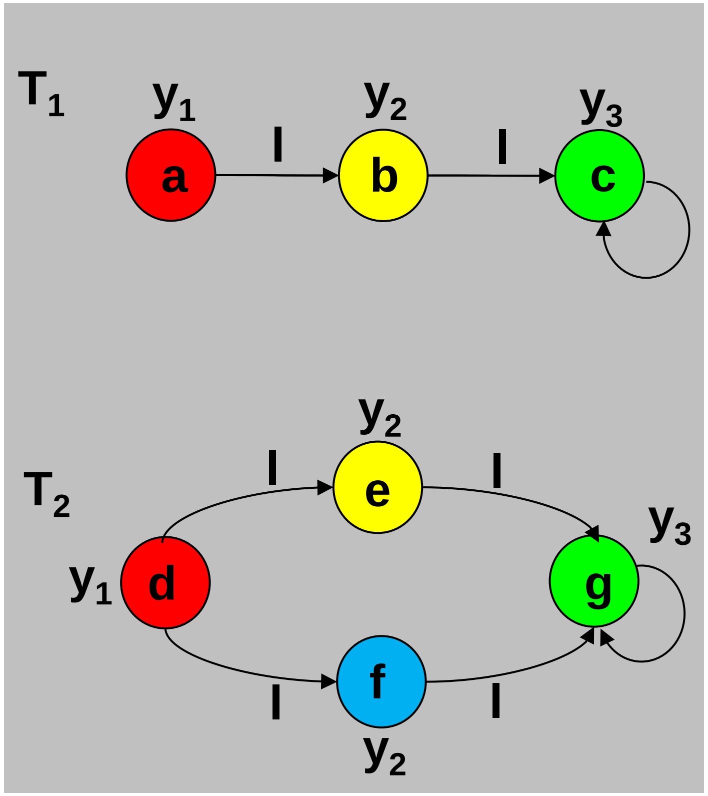
Note that T_2 is **not** *simulated* by T_1!



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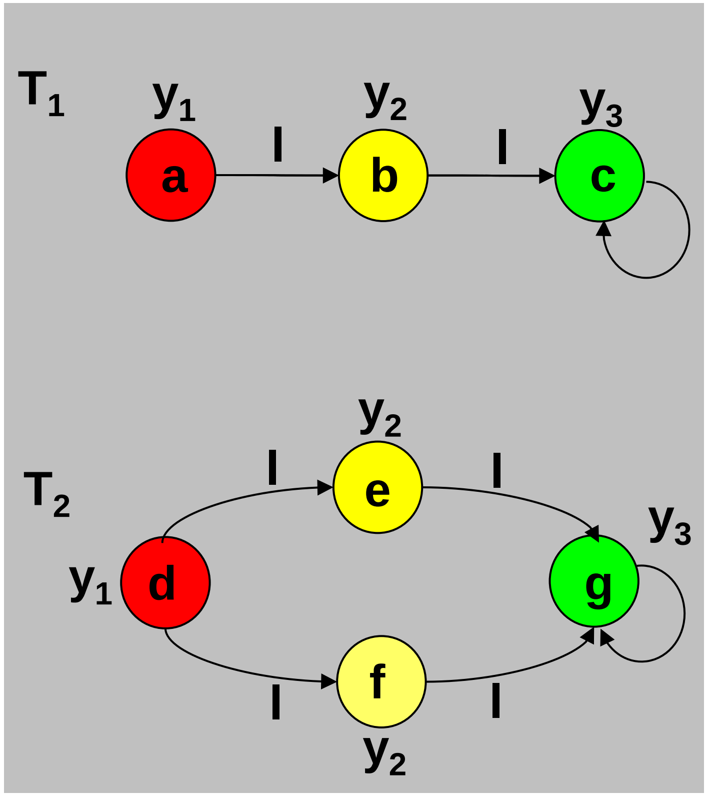
R is a **bisimulation relation** between T_1 and T_2 if

- R is a simulation relation from T_1 to T_2
- R^{-1} is a simulation relation from T_2 to T_1



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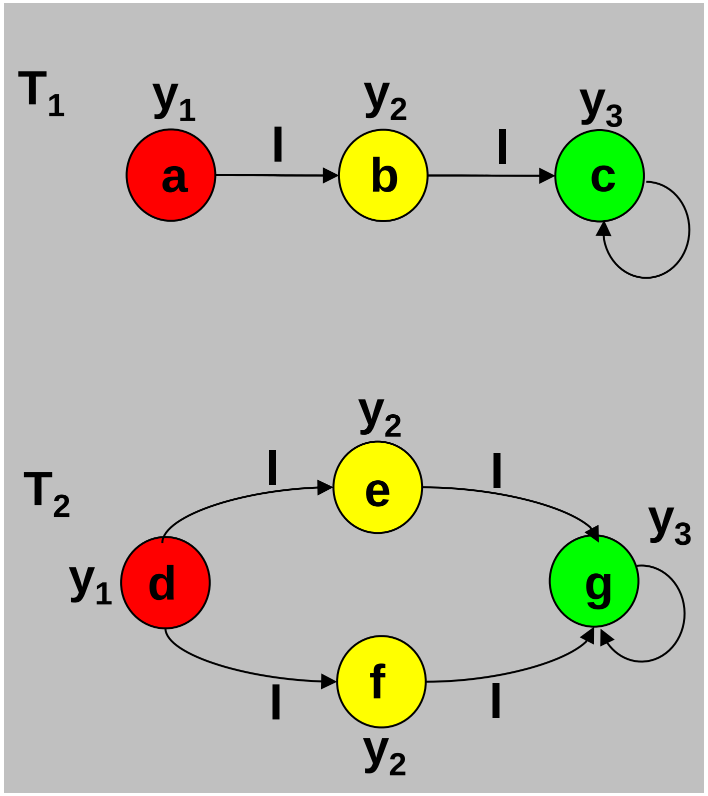
Transition systems T_1 and T_2 are *bisimilar* (denoted by $T_1 \cong T_2$) if there exists a *bisimulation relation* between T_1 and T_2



Approximate equivalence notions

[Girard & Pappas, 2007] "A bridge between computer science and control theory"

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- $\forall (x_1, x_2) \in R$, $d(H_1(q_1), H_2(q_2)) \leq \varepsilon$
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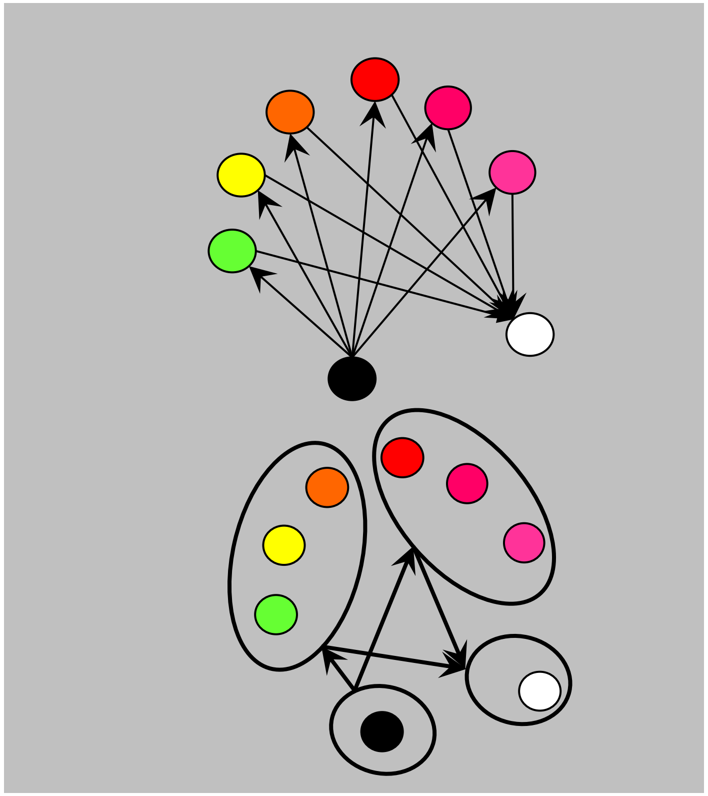

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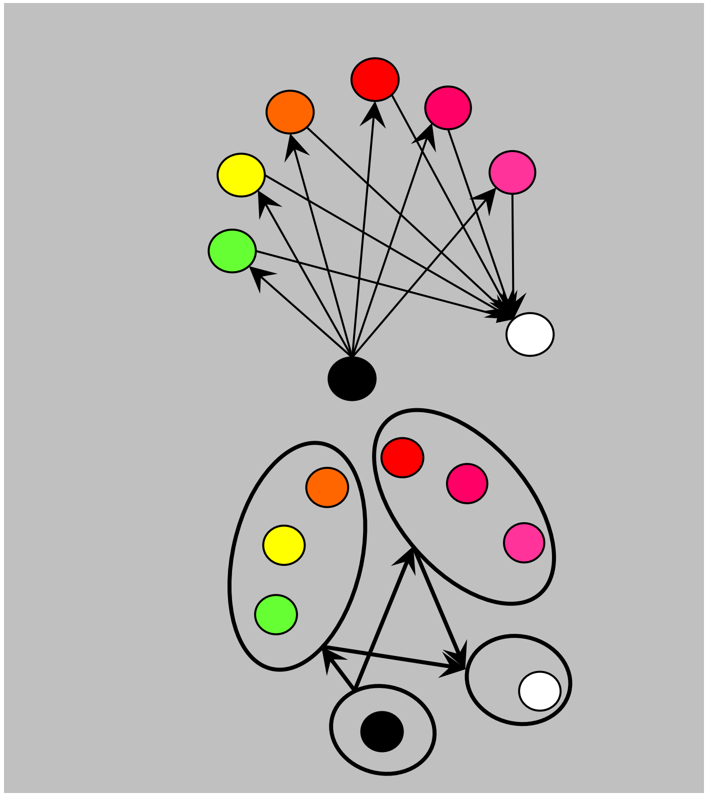


Construction of symbolic models

We consider digital control systems, i.e. control systems where input signals are piecewise constant.

Consider a nonlinear digital control system

$$T(\Sigma) = (X, X_0, \mathcal{U}, \longrightarrow, X_m, O, H),$$

and given some $\tau > 0$, define the transition system

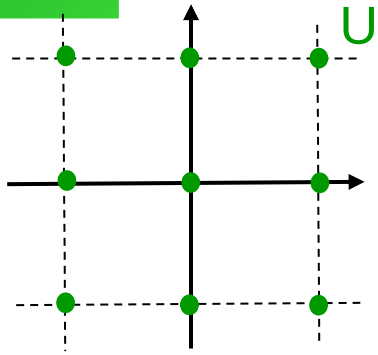
$$T_\tau(\Sigma) = (X, X_0, \mathcal{U}_\tau, \longrightarrow_\tau, X_m, O, H),$$

where:

- $\mathcal{U}_\tau$ is the collection of constant input functions $u : [0,\tau] \rightarrow R^m$
- $p \xrightarrow{u}_\tau q$ if $x(\tau,p,u) = q$

Construction of symbolic models

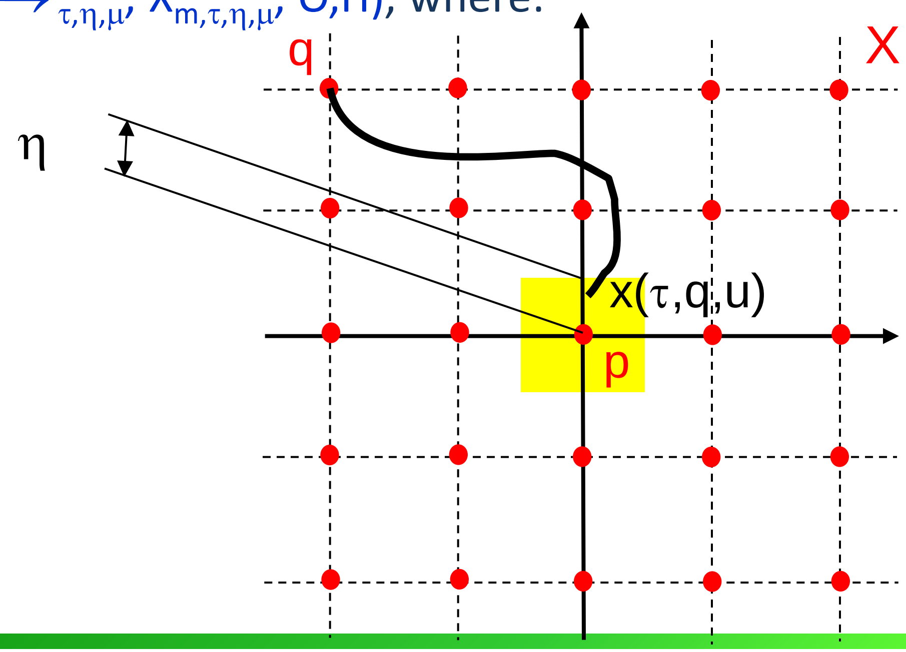
Consider the following parameters:



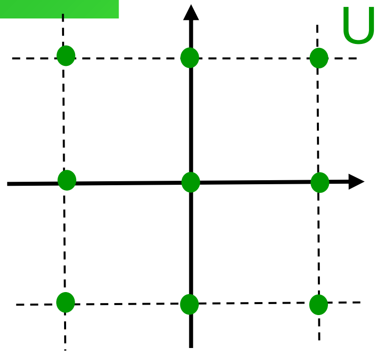
- $\tau > 0$ sampling time
- $\eta > 0$ state space quantization
- $\mu > 0$ input space quantization

and define $T_{\tau,\eta,\mu}(\Sigma) = (X_{\tau,\eta,\mu}, X_{0,\tau,\eta,\mu}, U_{\tau,\eta,\mu}, \longrightarrow_{\tau,\eta,\mu}, X_{m,\tau,\eta,\mu}, O, H)$, where:

- $X_{\tau,\eta,\mu} = [X]_{2\eta}$
- $X_{0,\tau,\eta,\mu} = X_{\tau,\eta,\mu} \cap X_0$
- $U_{\tau,\eta,\mu} = [U]_{2\mu}$
- $q \xrightarrow{u}_{\tau,\eta,\mu} p$, if $|x(\tau,q,u) - p| \leq \eta$
- $X_{m,\tau,\eta,\mu} = X_{\tau,\eta,\mu} \cap X_m$
- $O = X$
- H is the identity function



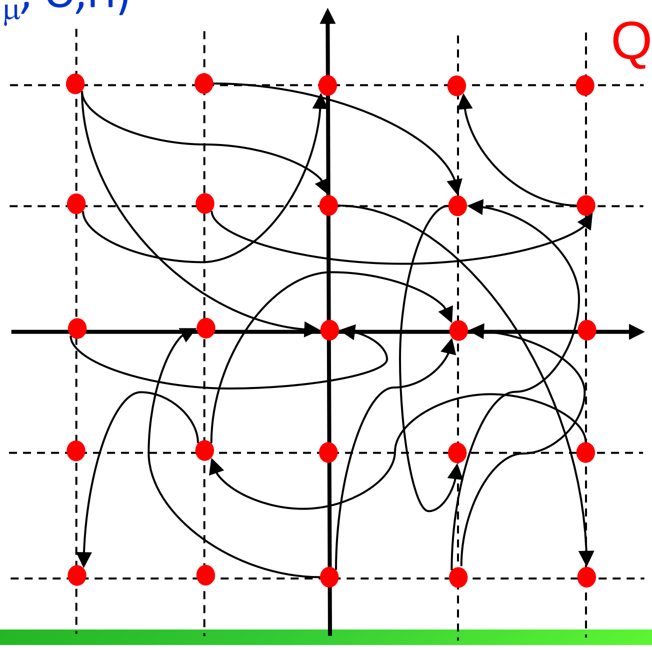
Construction of symbolic models



Consider the following parameters:

- $\tau > 0$ sampling time
- $\eta > 0$ state space quantization
- $\mu > 0$ input space quantization

and define $T_{\tau,\eta,\mu}(\Sigma) = (X_{\tau,\eta,\mu}, X_{0,\tau,\eta,\mu}, U_{\tau,\eta,\mu}, \xrightarrow{\quad}_{\tau,\eta,\mu}, X_{m,\tau,\eta,\mu}, O, H)$



Theorem If Σ is δ-ISS, for any desired accuracy $\varepsilon > 0$ and for any $\tau, \eta, \mu > 0$ satisfying

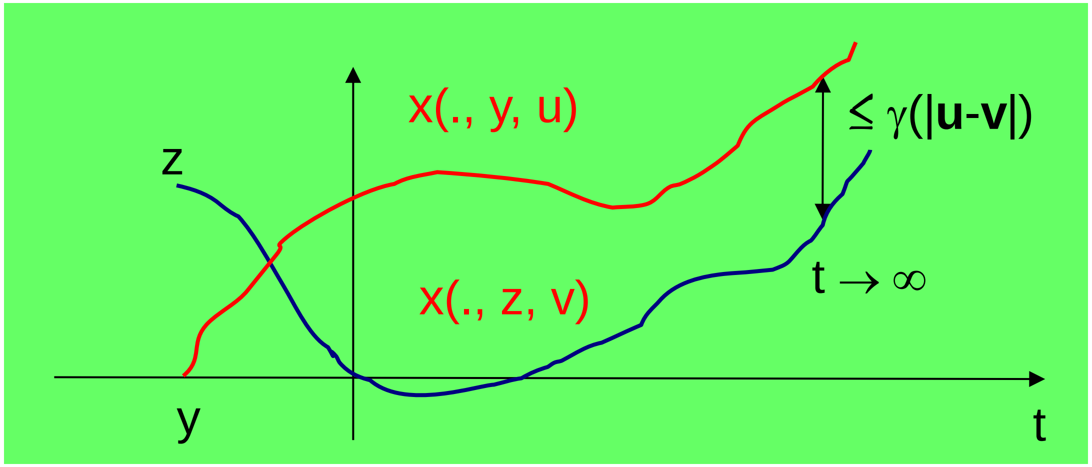
$$\beta(\varepsilon,\tau) + \eta + \gamma(\mu) \leq \varepsilon$$

then $T_\tau(\Sigma)$ and $T_{\tau,\eta,\mu}(\Sigma)$ are ε-bisimilar

Pola et al. (Automatica 2008) *Approximately bisimilar symbolic models for nonlinear control systems*

Incremental stability

The δ-ISS property (incremental input-to-state stability) is a fairly strong assumption, but it enables the construction of deterministic symbolic models.

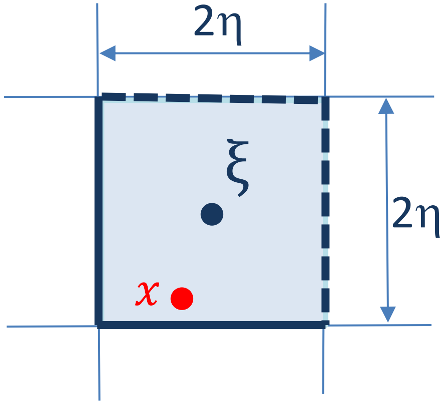


$$| x(t,y,u) - x(t,z,v) | \leq \beta(|y - z|, t) + \gamma(|u - v|)$$

Dealing with unstable systems

The δ-ISS property (incremental input-to-state stability) is a fairly strong assumption, but it enables the construction of deterministic symbolic models.

We remove the stability assumption…



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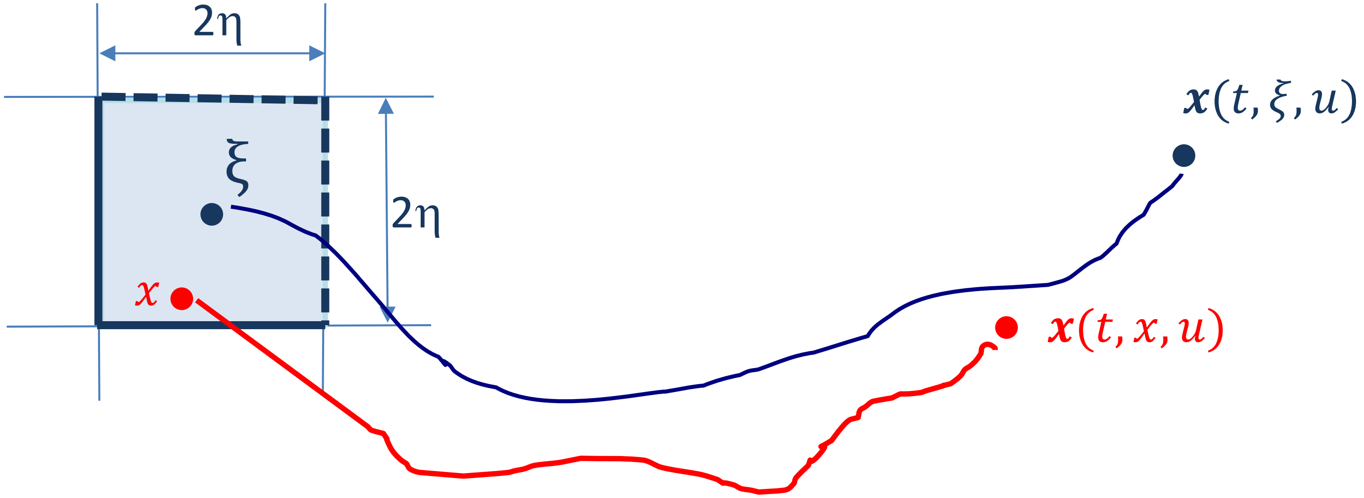

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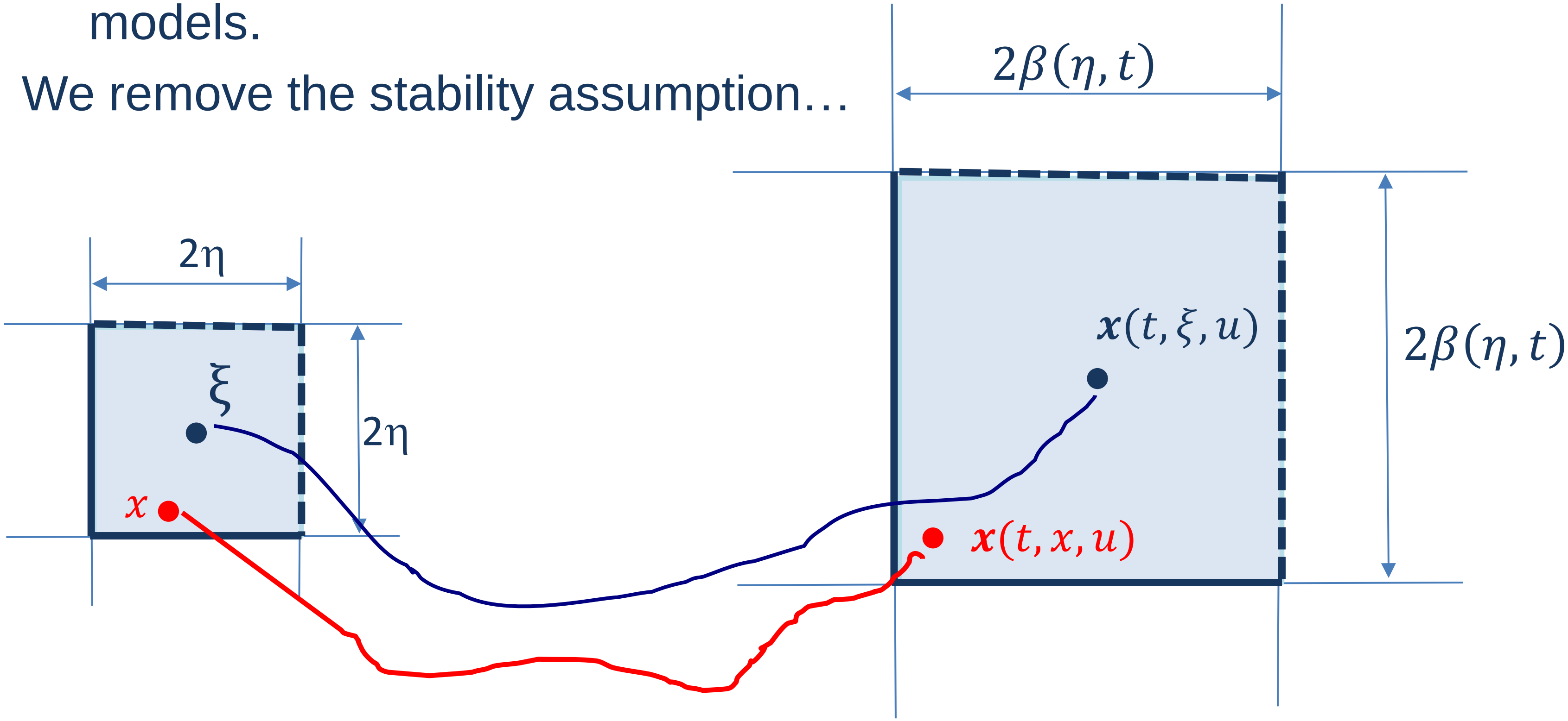

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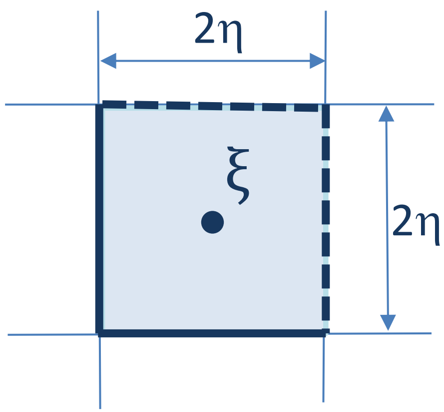

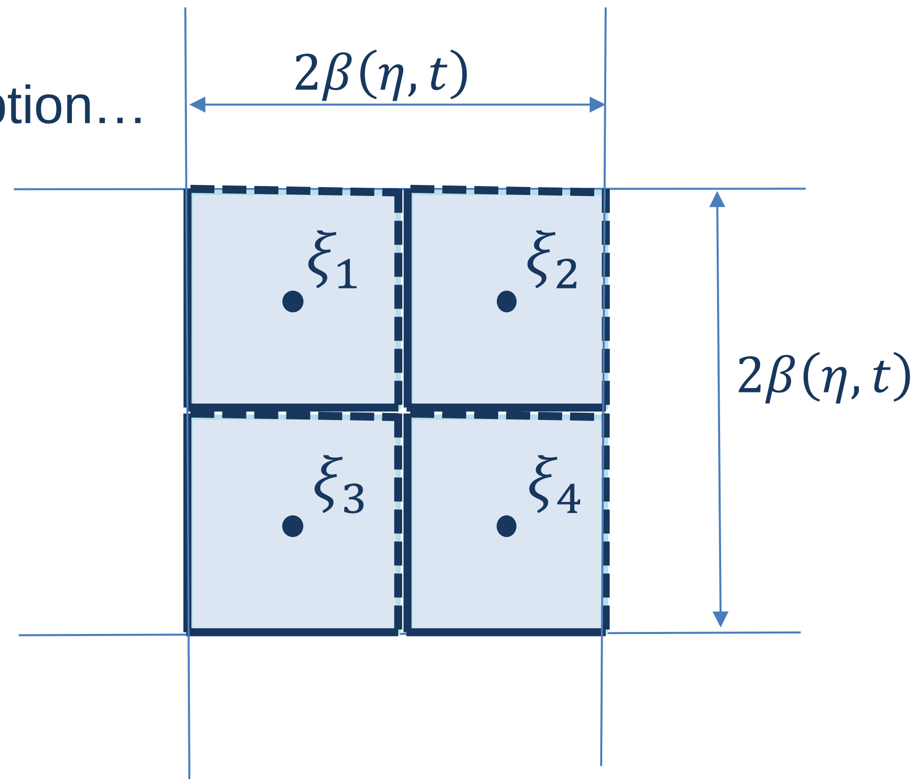

Dealing with unstable systems

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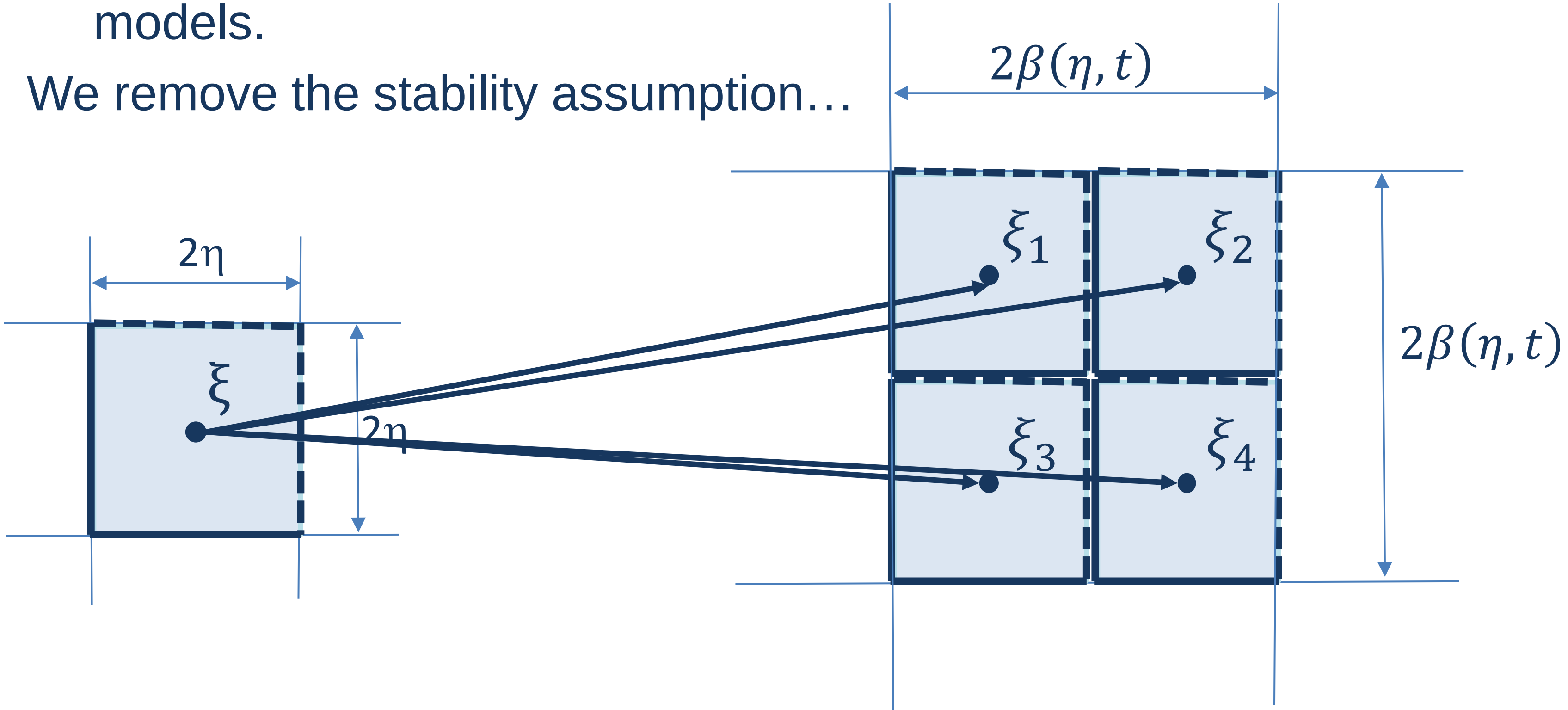
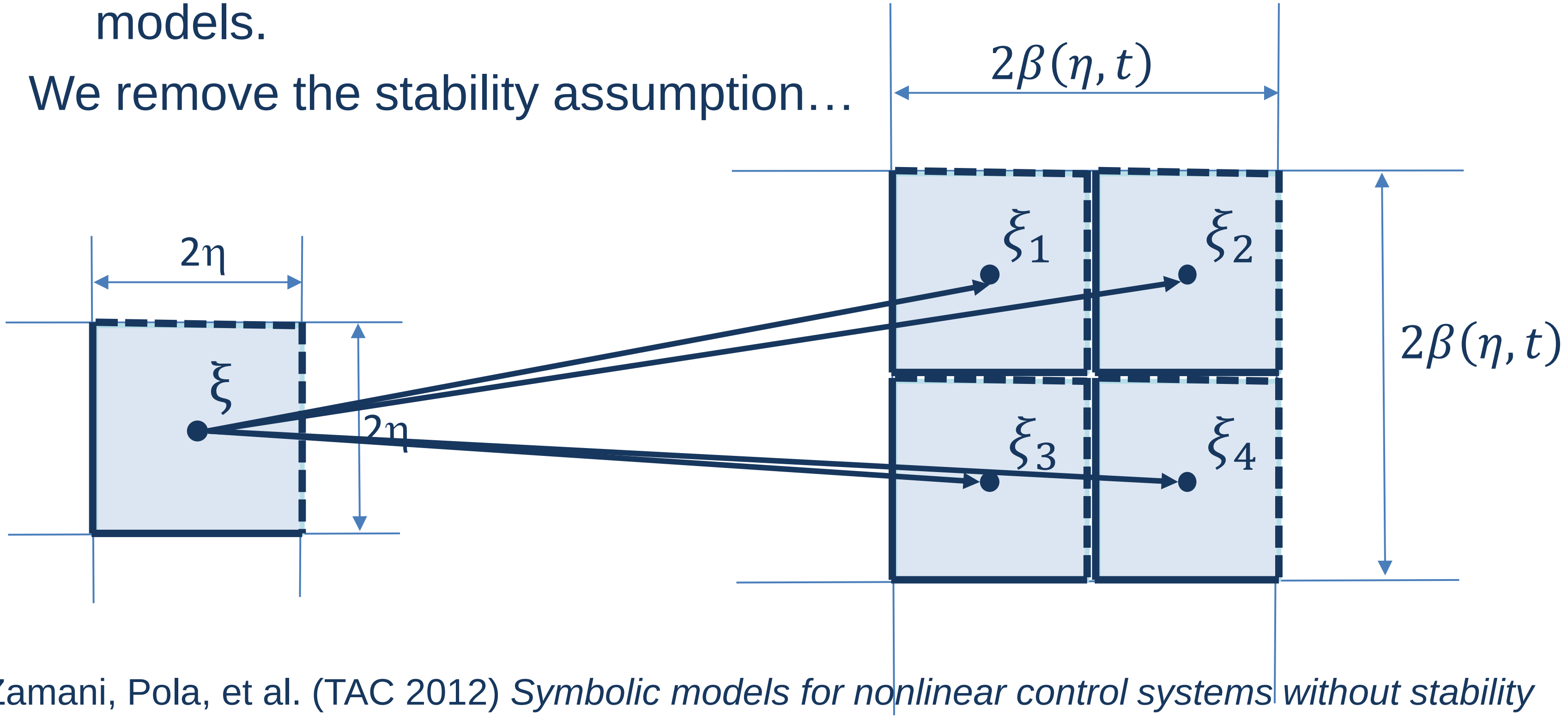


… translating instability into nondeterminism in the symbolic model!

Dealing with unstable systems

The δ-ISS property (incremental input-to-state stability) is a fairly strong assumption, but it enables the construction of deterministic symbolic models.

We remove the stability assumption…



Zamani, Pola, et al. (TAC 2012) *Symbolic models for nonlinear control systems without stability assumptions*.

Spline approximation of functional spaces

Approximation error:

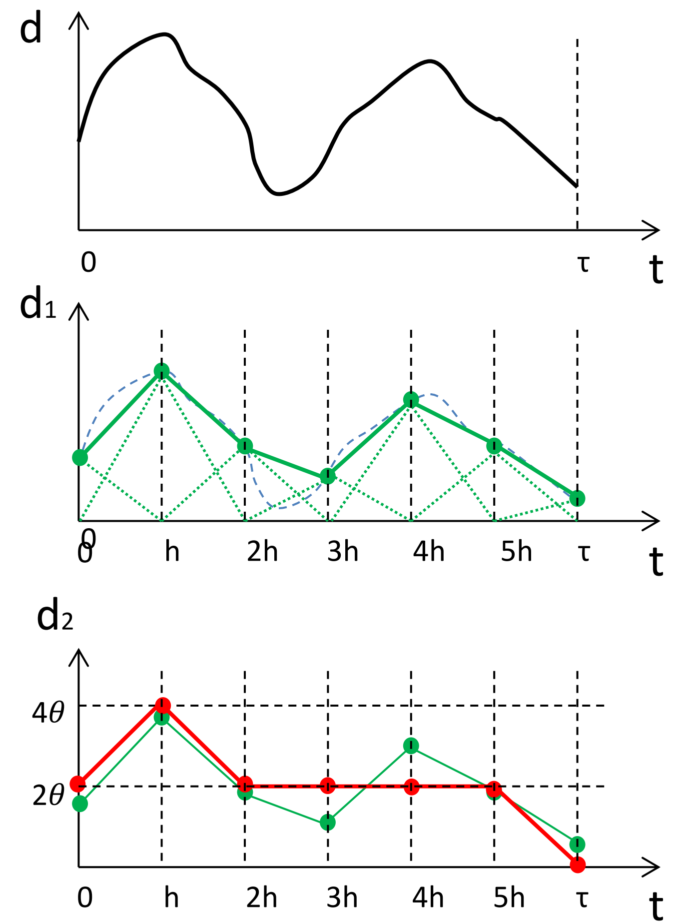
$$\Lambda\,(N,\theta,M) = h^2 M/8 + (N+2)\theta$$

where

- N is the number of time samples
- M is the infinity-norm bound on the second derivative
- θ is the space quantization

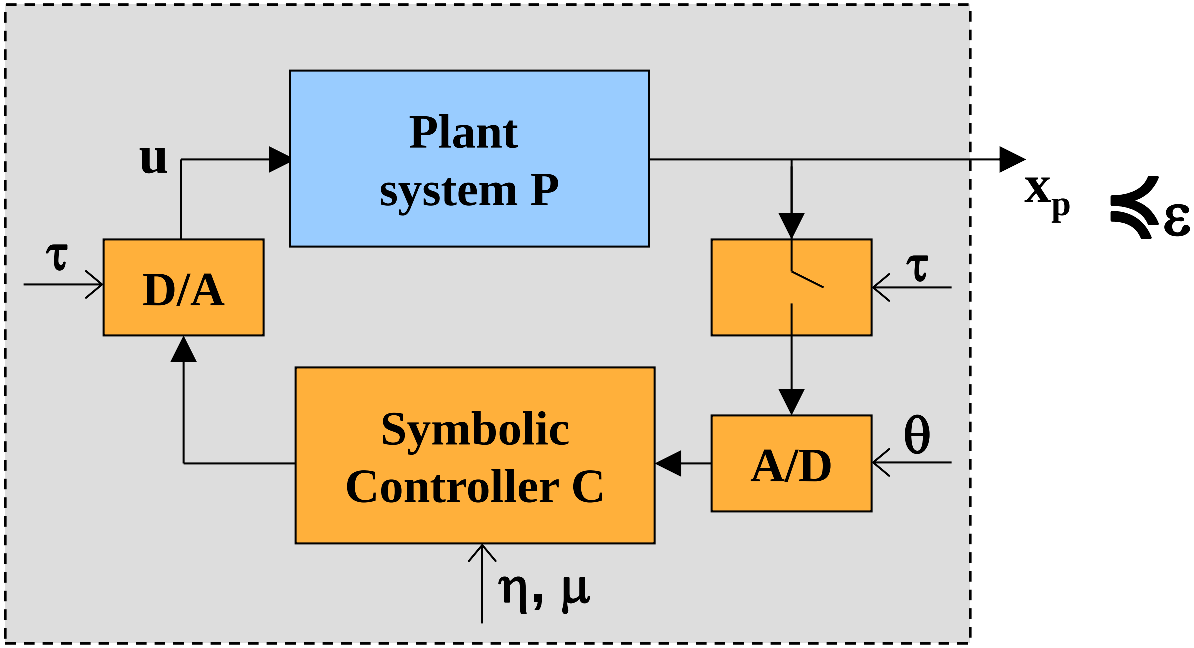
Lemma 1: For any λ, M, there always exist N and θ s.t. $\Lambda\,(N,\theta,M) \leq \lambda$

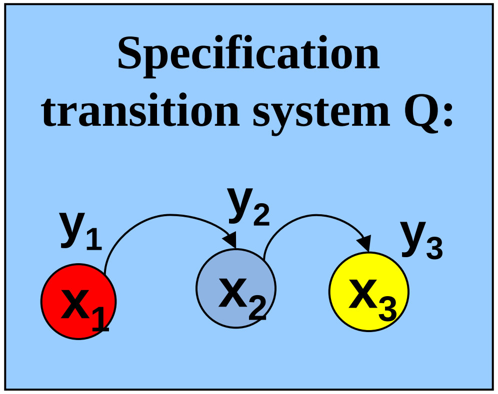
Lemma 2: If the original functions are bounded, the set of approximating functions is symbolic (finite).



Problem: Specifications given as deterministic transition systems

Given a plant P, a deterministic specification Q and a desired accuracy $\varepsilon > 0$, find a symbolic controller that implements Q up to the accuracy ε and that is alive when interacting with P.



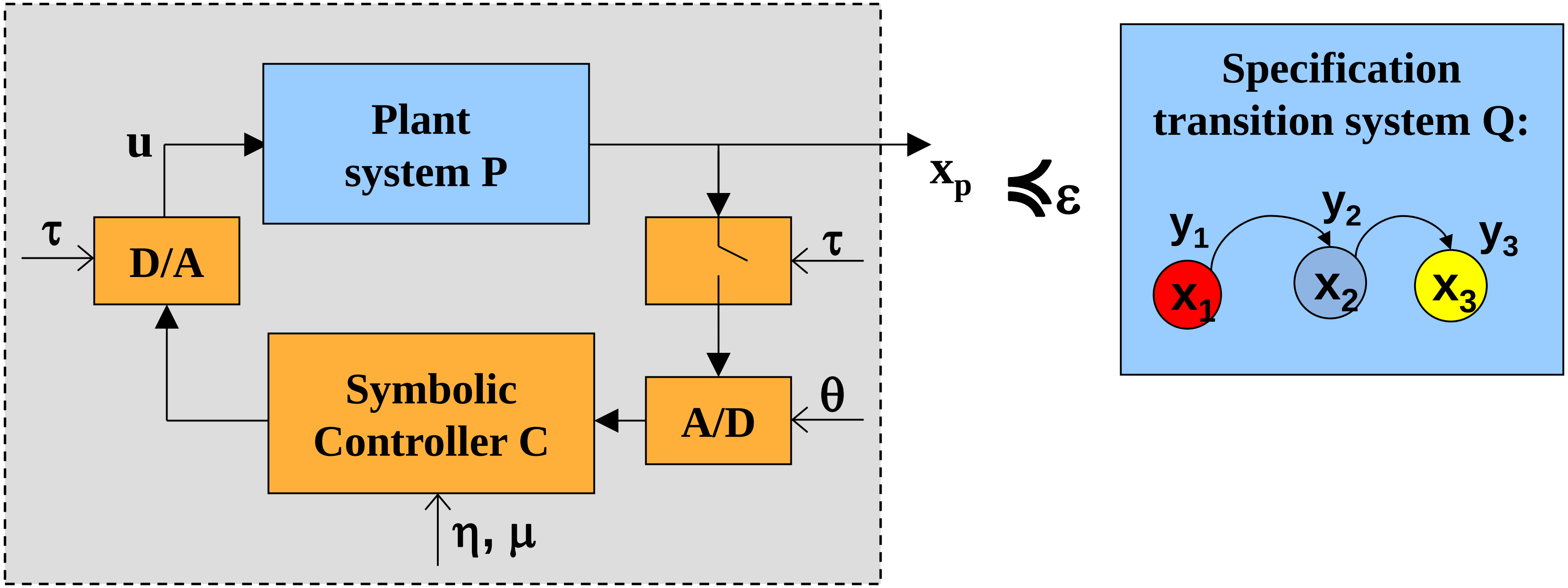


Design of symbolic controllers

Control problem

Given a plant P, a deterministic specification Q and a desired accuracy $\varepsilon > 0$, find a symbolic controller C such that

1. $T_\tau(P)||_\theta C \preccurlyeq_\varepsilon Q$
2. $T_\tau(P)||_\theta C$ is alive



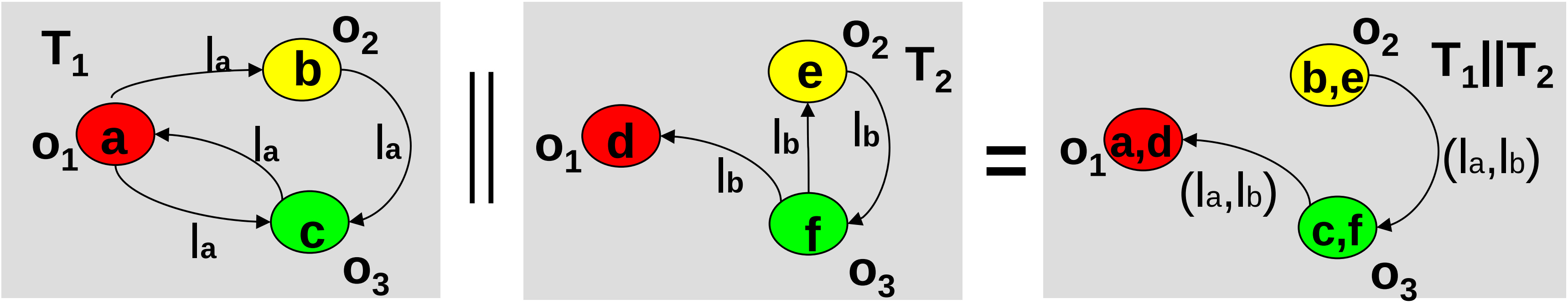
Approximate composition

[Tabuada IEEE TAC 08] Given $T_1 = (Q_1, Q_{01}, L_1, \longrightarrow_1, Q_{m1}, O_1, H_1)$ and $T_2 = (Q_2, Q_{02}, L_2, \longrightarrow_2, Q_{m2}, O_2, H_2)$, with $O_1 = O_2$, and an accuracy $\theta > 0$, the approximate composition of T_1 and T_2 is the system

$$T = T_1 \|_\theta T_2 = (Q, Q_0, L = L_1 \times L_2, \longrightarrow, Q_m, O = O_1, H)$$

where:

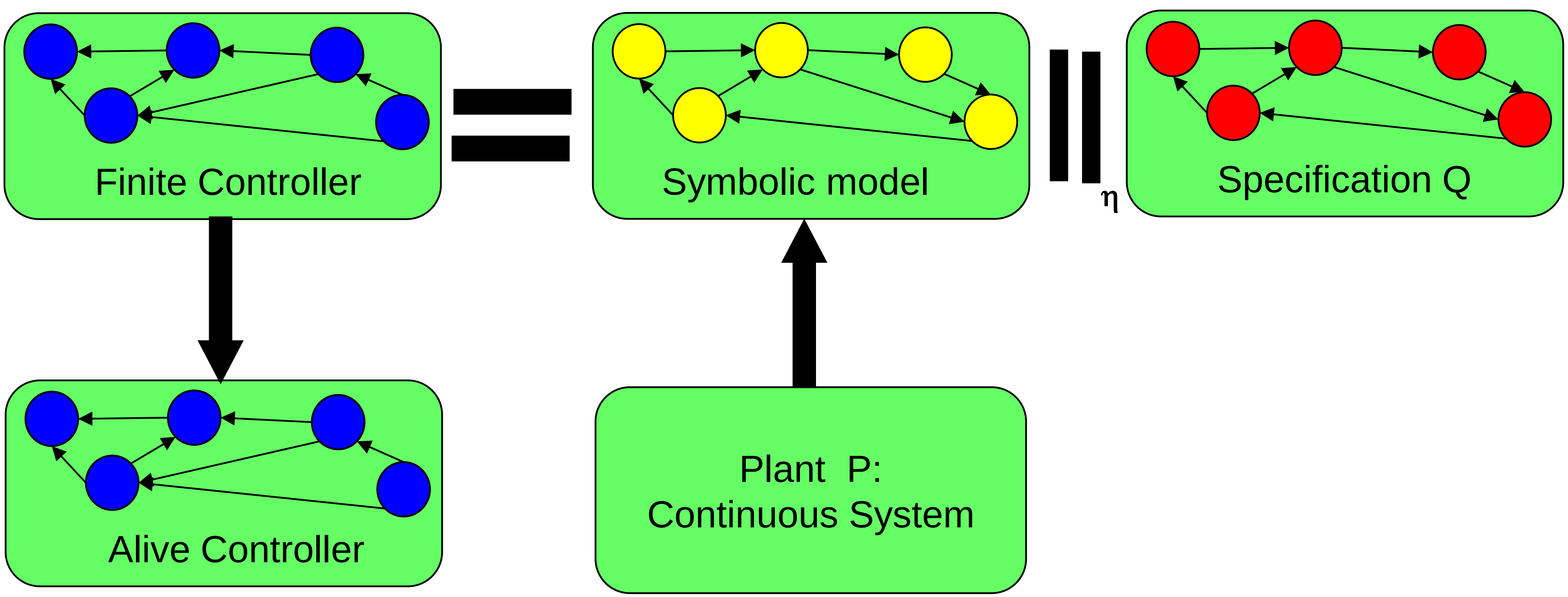
- $Q = \{(q_1, q_2) \in Q_1 \times Q_2 : d(H_1(q_1), H_2(q_2)) \leq \theta\}$
- $Q_0 = Q \cap (Q_{01} \times Q_{02})$
- $(q_1, q_2) \xrightarrow{(l_1, l_2)} (p_1, p_2)$, if $q_1 \xrightarrow{l_1} p_1$ and $q_2 \xrightarrow{l_2} p_2$
- $Q_m = Q \cap (Q_{m1} \times Q_{m2})$
- $H(q_1, q_2) = H_1(q_1)$



Design of symbolic controllers

Synthesis through a three-step process:

1. Compute the symbolic model $T_{\tau,\eta,\mu}(P)$ of P
2. Compute the symbolic controller $C^* = T_{\tau,\eta,\mu}(P) \,||_{\eta}\, Q$
3. Compute the alive part Alive(C*) of C*



Design of symbolic controllers

Synthesis through a three-step process:

1. Compute the symbolic model $T_{\tau,\eta,\mu}(P)$ of P
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3. Compute the alive part $Alive(C^*)$ of C^*

Theorem Suppose that P is δ–ISS and choose parameters $\tau, \eta, \mu, \theta > 0$ satisfying:

$$\beta(\theta,\tau) + \gamma(\mu) + 2\eta \leq \theta + \eta \leq \varepsilon$$

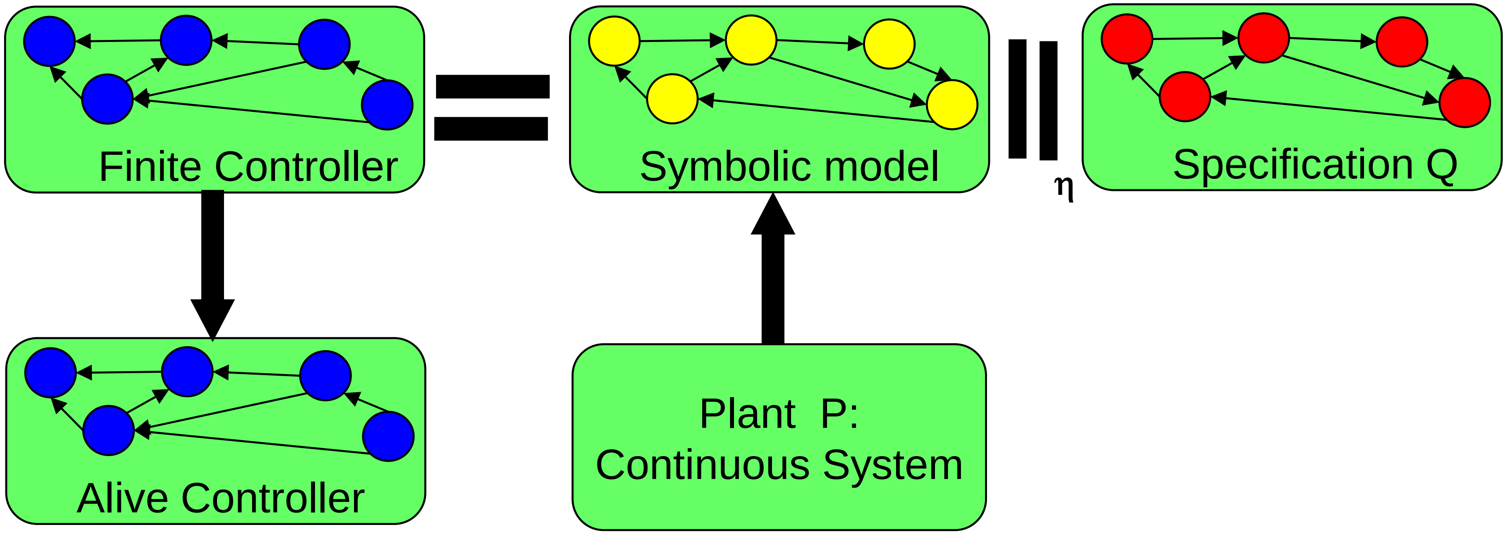
Then the symbolic controller $Alive(C^*)$ solves the control problem.

G. Pola, A. Borri, and M. D. Di Benedetto (IEEE TAC 2012)

Integrated control design

Basic ideas

1. It only considers the intersection of the accessible parts of P and Q
2. For any given source state x and target state y, it considers only one transition (x,u,y)
3. It eliminates blocking states as soon as they show up



G. Pola, A. Borri, and M. D. Di Benedetto (IEEE TAC 2012)

Extension to unstable TDS

Possibly unstable time-delay systems (TDS) in the form

$$\dot{x}(t) = f(x_t, u(t-r))$$
$$y(t) = [z(t)]_\lambda$$

- Incremental forward completeness (δ-FC) assumption on the TDS
- Quantized output and possibly delayed input (actuation lag)
- The δ-FC property can be checked by resorting to Lyapunov–Krasovskii-like functionals and related inequalities
- Symbolic models for TDS embedding symbolic approximations of the functional state space
- Strong alternating λ-approximate (AλA) simulation relation (Borri et al., IEEE TAC 2019) ensures robustness with respect to the non-determinism and enables refinement

Extension to unstable TDS

Possibly unstable time-delay systems (TDS) in the form

$$\dot{x}(t) = f(x_t, u(t-r))$$
$$y(t) = [z(t)]_\lambda$$

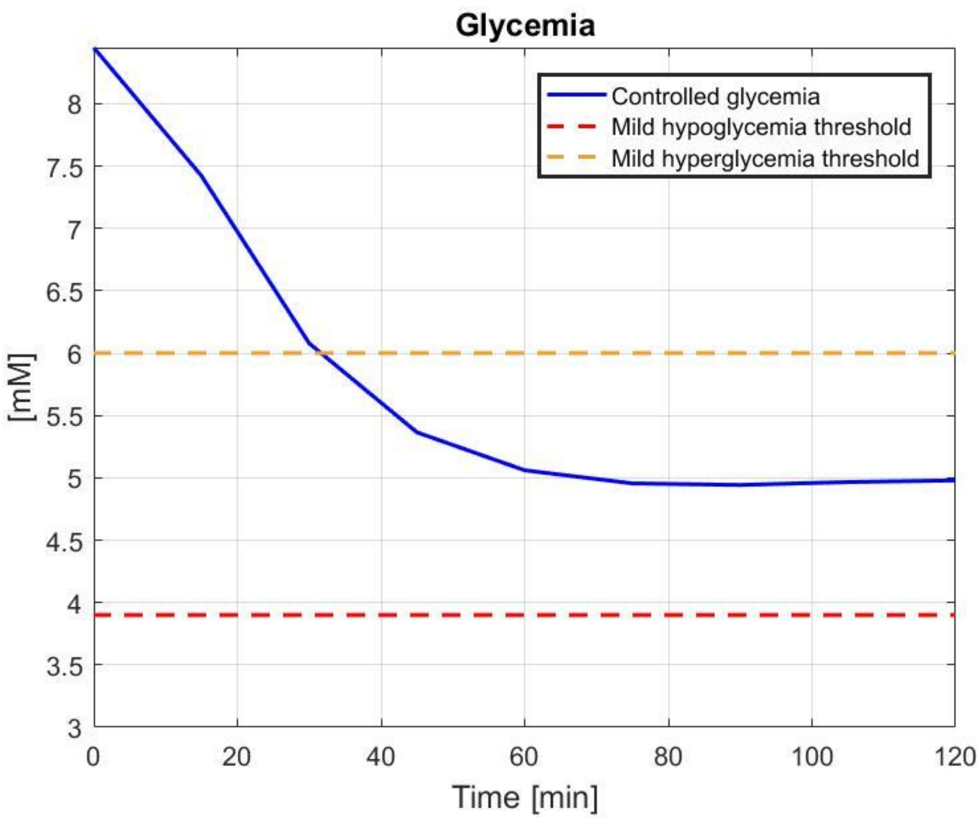
Main result (adapted) [Pola et al., ECC 2019]

Conditions:

- the TDS is δ-FC, with bounded state space X
- the functional f is Fréchet-differentiable, with Fréchet differential being continuous and bounded on bounded sets, so that a bound M is well defined
- for any λ, pick N and θ s.t. $\Lambda\,(N, \theta, M) \leq \lambda$

Then it is possible to build a symbolic model which approximates the original TDS in the sense of strong AλA simulation, where the approximation parameter λ can be made arbitrarily small (which affects complexity).

Symbolic glucose control (2D model)

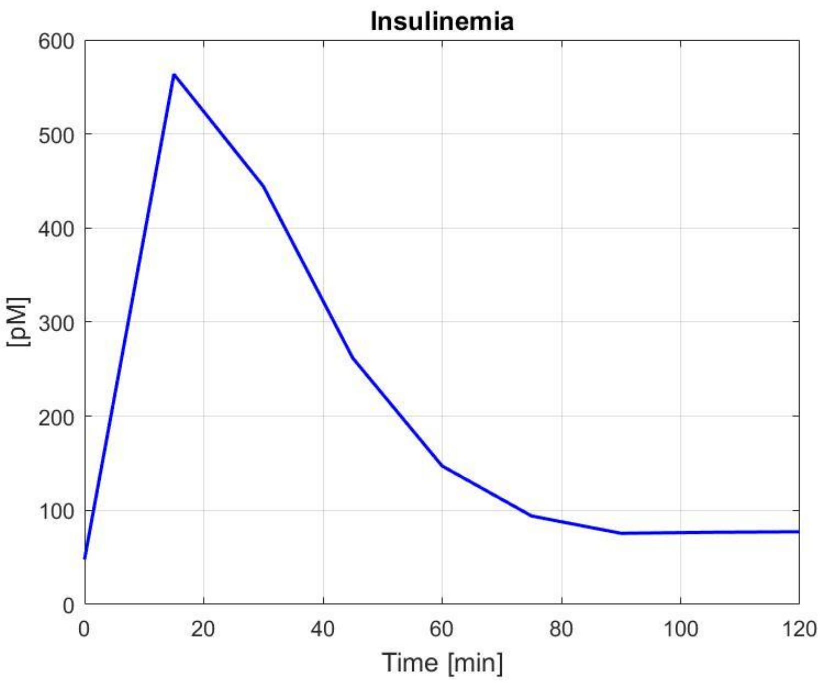


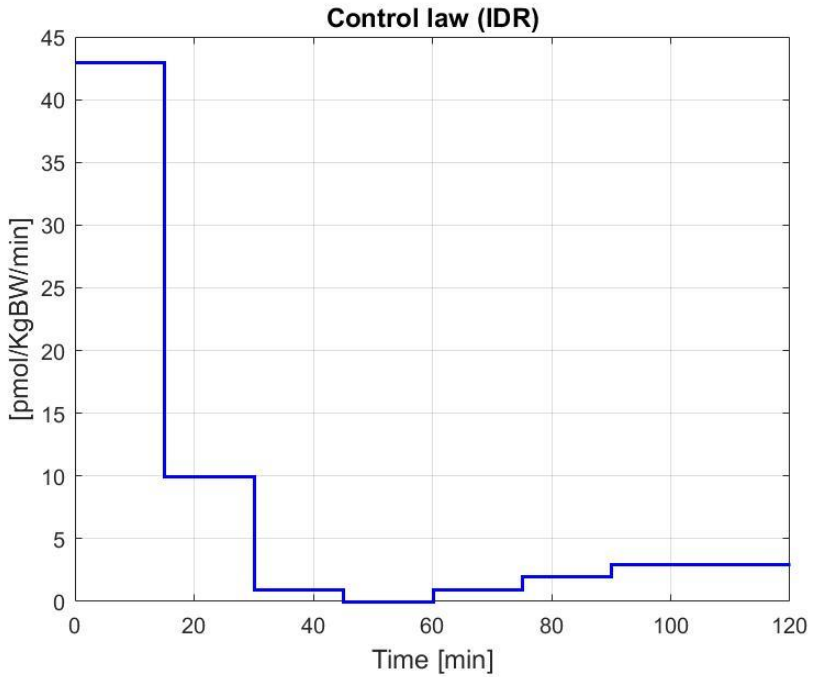
- Sampling time: $\tau = 15$ min
- Output quantization: 0.1 mM

- **Reach** in finite time (3h) **and stay** in a **safe** zone (between mild hypo- and mild hyper-glycemia)

G. Pola, A. Borri, P. Pepe, P. Palumbo, M.D. Di Benedetto, *Symbolic models approximating possibly unstable time–delay systems with application to the artificial pancreas*, European Control Conference (ECC 2019).

Symbolic glucose control (2D model)





G. Pola, A. Borri, P. Pepe, P. Palumbo, M.D. Di Benedetto, ECC 19

Ongoing work: Synchronization specifications

Considering the effect of meals and explicit (quantitative) time specifications

TABLE I

CONTROL TARGETS

Target	**Range** $[mM]$
Very good fasting glycemia	$3.9 \leq G(t) < 5.6$
Good fasting glycemia	$5.6 \leq G(t) < 6.5$
Satisfactory pre-prandial state	$4.4 \leq G(t) < 7.2$
Very good post-prandial (2 hours after meal) state	$G(t) < 7.8$
Good post-prandial (2 hours after meal) state	$7.8 \leq G(t) < 10$

Targets established according to current clinical practice recommendations and guidelines of the American Diabetes Association (ADA) for the diabetes care and treatment.

DEWS CENTER OF EXCELLENCE

Ongoing work: meals + subcutaneous compartment

$$\frac{dG(t)}{dt} = -k_{xgi}\mathrm{G(t)}I(t) + \frac{T_{gh}}{V_G} + \mathrm{d(t)}$$

$$\frac{dI(t)}{dt} = -k_{xi}\mathrm{I(t)} + \frac{T_{iGmax}}{V_I}\varphi\left(G(t-\tau_g)\right) + \frac{S_2(t)}{t_{max,I}V_I}$$

$$\frac{dS_1(t)}{dt} = -\frac{1}{t_{max,I}}S_1(t) + \mathrm{u(t)}$$

$$\frac{dS_2(t)}{dt} = \frac{1}{t_{max,I}}S_1(t) - \frac{1}{t_{max,I}}S_2(t)$$

Meal digestion model

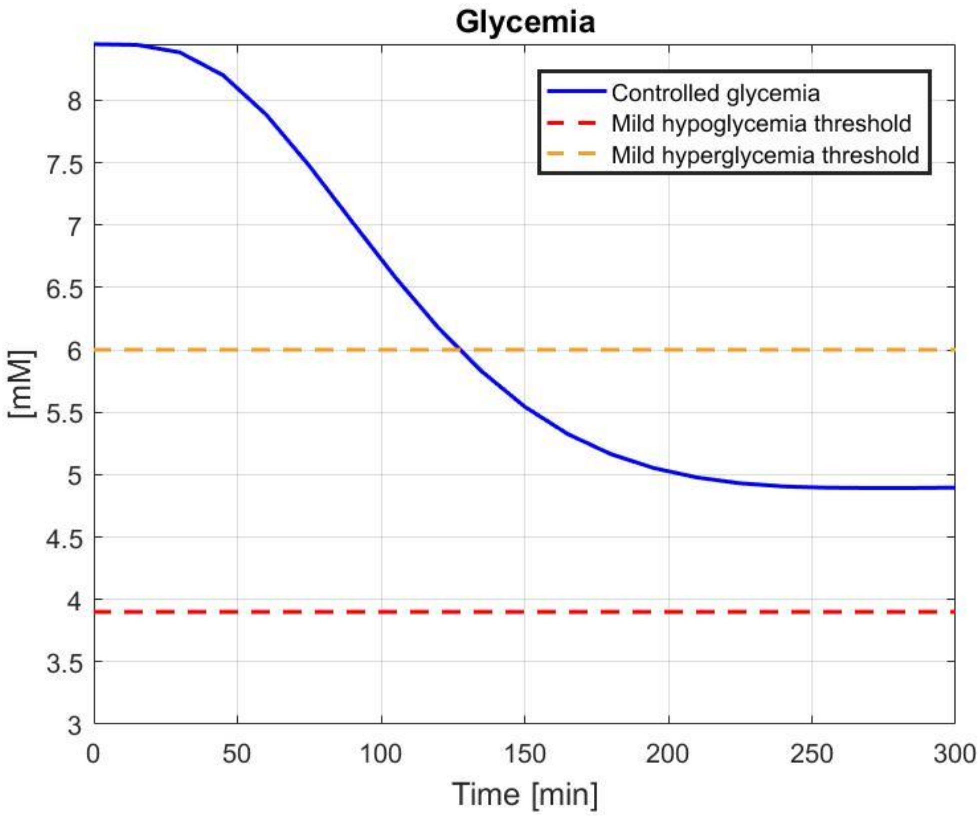
Magdelaine et al. (2015)

$$\varphi(x) = \frac{\left(\frac{x}{G^*}\right)^\gamma}{1+\left(\frac{x}{G^*}\right)^\gamma}$$

Subcutaneous compartment

Puckett et al. (1995)
Hovorka et al. (2004)

Symbolic glucose control (4D model)

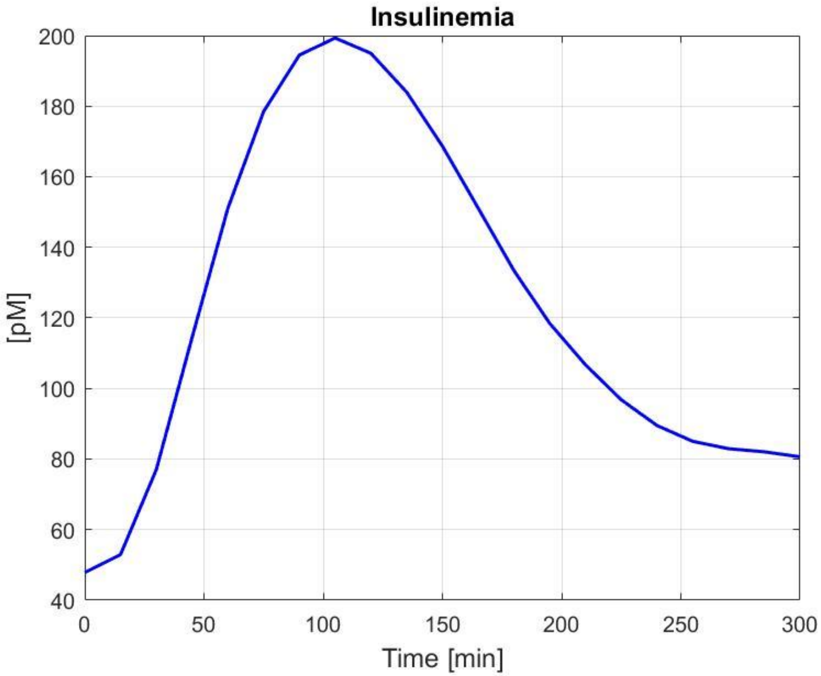


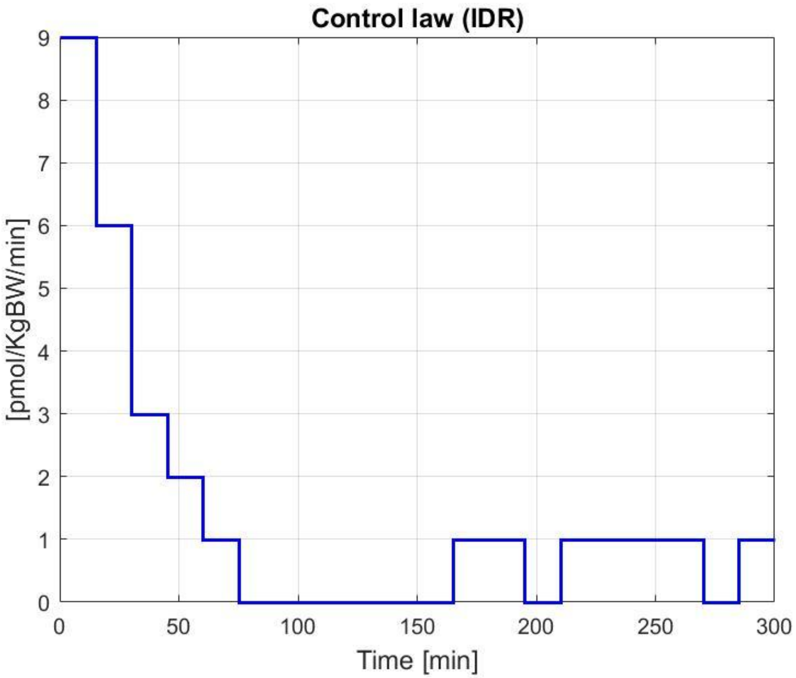
- Sampling time: $\tau = 15$ min
- Output quantization: 0.1 mM

- Takes into account the **subcutaneous compartment**

- **Higher settling time** (more realistic)

Symbolic glucose control (4D model)





- **Lower infusion rate**, applied for **longer time**
- The 2D model-based control law would lead the 4D system into **hypo**

Discussion

Ongoing/related work and future developments

- Meal uncertainties
- Big glucose – interactions among (most of the) players involved in glucose metabolism and homeostasis
- Modeling physical activity
- Validation on maximal models
- Long-term evolution of diabetes
- Ultra-rapid insulins
- Population models