Strong Turing Completeness of Continuous Chemical Reaction Networks

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Joint work with Olivier Bournez, François Fages, Guillaume Le Guludec and Daniel Graça

10 october 2018

Chemical Reaction Networks

A reaction system is a finite set of

- molecular species $y_1, \ldots, y_n$
- reactions of the form $\sum_i a_i y_i \xrightarrow{f} \sum_i b_i y_i \qquad (a_i, b_i \in \mathbb{N}, f = \text{rate})$

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$$2\text{H} \quad + \quad \text{O} \quad \rightarrow \quad \text{H}_2\text{O}$$

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$$y_i' = \sum_{\text{reaction } R} (b_i^R - a_i^R) f^R(y)$$

Example :

$$[H_2O]' = f(H_2O)$$

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Example :

$$[\text{H}_2\text{O}]' = [\text{O}][\text{H}]^2$$

⇝ Polynomial ODE !

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$$
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Not limited to simple chemical reactions :

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- protein reactions

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Implementing CRNs is a recent and active research field.

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Some reactions are unrealistic :

$$y_1 + 26y_2 + 7y_3 \to 13y_4 + y_5$$

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Only consider elementary reactions : at most two reactants

- $A + B \xrightarrow{k} C$
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- $A \xrightarrow{k} B$
- $A \xrightarrow{k} \varnothing$
- $\varnothing \xrightarrow{k} A$

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Example : $A + B \xrightarrow{k} C$

$$A' = -kAB \qquad B' = -kAB \qquad C' = kAB$$

$\rightsquigarrow$ Quadratic ODE !

Can we use CRNs to compute ?

Chemical Reaction Networks : what can we compute ?

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It depends a lot on how we define computability, in particular :

- rate : dependent/independent
- semantics : discrete/stochastic/differential
- kinetics : mass action/Michaelis/...
- species : finite/unbounded/infinite
- encoding : molecule count/concentration/digits
- more : robust, stable, ...

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Extreme examples :

rate-independent, differential, any kinetics, finite species, value is concentration, stable

$\rightsquigarrow$ piecewise linear functions

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Extreme examples :

rate-independent, differential, any kinetics, finite species, value is concentration, stable

$\rightsquigarrow$ piecewise linear functions

rate-dependent, stochastic, Markov, finite species, value is molecule count (must be small)

$\rightsquigarrow$ probabilistic Turing machine

Chemical Reaction Networks : main result

A reaction is elementary if it has at most two reactants
⇒ can, in principle, be implemented with DNA, RNA or proteins

Theorem (CMSB 2017)

Elementary mass-action-law reaction system on finite universes of molecules are Turing-complete under the differential semantics.

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Note : in fact the following elementary reactions suffice :

$$\emptyset \xrightarrow{k} x \qquad x \xrightarrow{k} x + z \qquad x + y \xrightarrow{k} x + y + z \qquad x + y \xrightarrow{k} \emptyset$$

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We can even say something about the complexity :

$f \in$ FPTIME $\Rightarrow$ CRN computes f in
- polynomial time&space

or equivalently
- polynomial length

Chemical Reaction Networks : mathematics

mass-action-law reaction system on finite universes of molecules under the differential semantics

$$\Updownarrow$$

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Polynomial ODE :

$$\begin{cases} y_1' = p_1(y_1, \dots, y_n) \\ \vdots \\ y_n' = p_n(y_1, \dots, y_n) \end{cases}$$

with constraints :

- nonnegative values (concentration)
- restricted negative feedback : $x' = -xyz$

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value encoding : $y = y^+ - y^-$

Polynomial ODE : $y' = p(y)$

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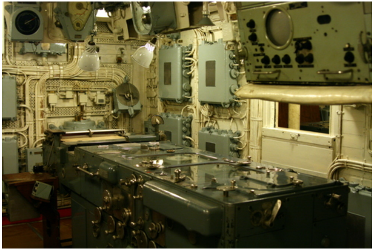
What can we compute with polynomial ODEs ?

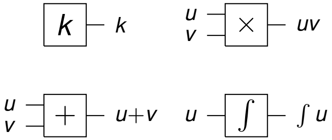
Analog Computers

Differential Analyser
“Mathematica of the 1920s”



Admiralty Fire Control Table
British Navy ships (WW2)

Polynomial Differential Equations



General Purpose
Analog Computer

Differential Analyzer

Newton mechanics

Reaction networks :

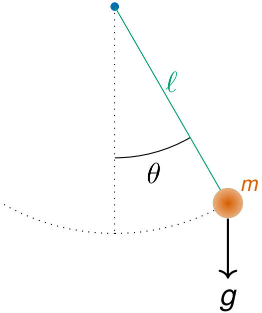
- chemical
- enzymatic

polynomial differential equations :

$$\begin{cases} y(0) = y_0 \\ y'(t) = p(y(t)) \end{cases}$$

- Rich class
- Stable $(+, \times, \circ, /, \mathrm{ED})$
- No closed-form solution

Example of dynamical system



$$\ddot{\theta} + \frac{g}{\ell}\sin(\theta) = 0$$

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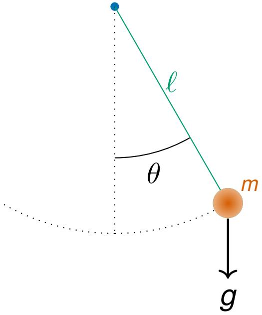

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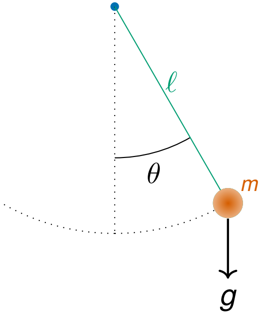

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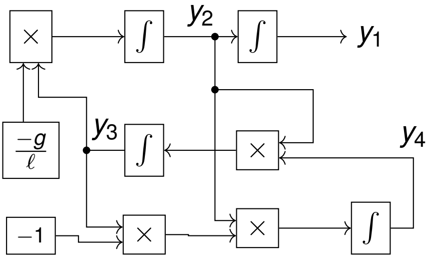

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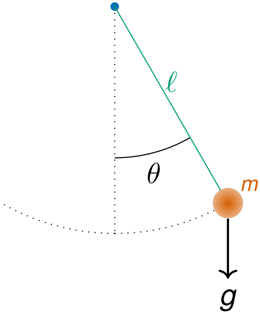

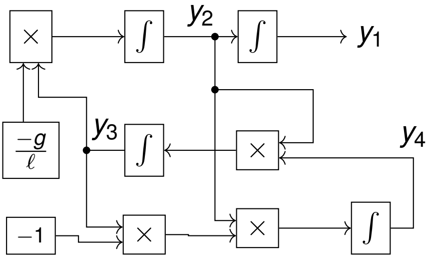

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Historical remark : the word “analog”

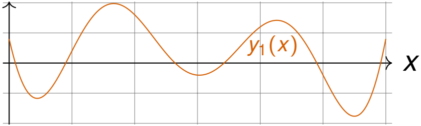
The pendulum and the circuit have the same equation. One can study one using the other by analogy.

Computing with differential equations

Generable functions

$$\begin{cases} y(0) = y_0 \\ y'(x) = p(y(x)) \end{cases} \qquad x \in \mathbb{R}$$

$$f(x) = y_1(x)$$



Shannon's notion

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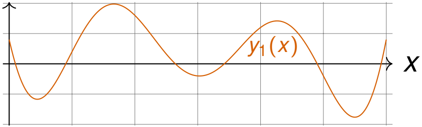

Shannon's notion

$\sin, \cos, \exp, \log, \ldots$

Strictly weaker than Turing machines [Shannon, 1941]

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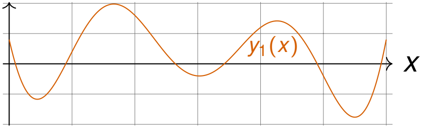

Shannon's notion

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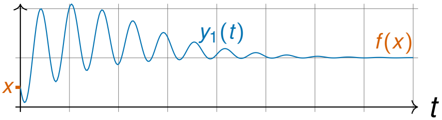
Computable

$$\begin{cases} y(0) = q(x) \\ y'(t) = p(y(t)) \end{cases} \qquad \begin{matrix} x \in \mathbb{R} \\ t \in \mathbb{R}_+ \end{matrix}$$

$$f(x) = \lim_{t \to \infty} y_1(t)$$



Modern notion

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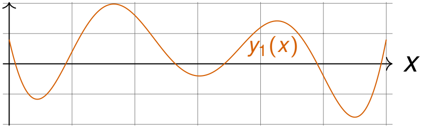

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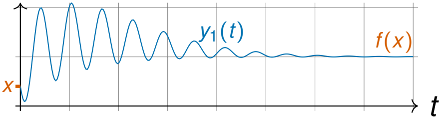


Modern notion

sin, cos, exp, log, Γ, ζ, ...

Turing powerful [Bournez et al., 2007]

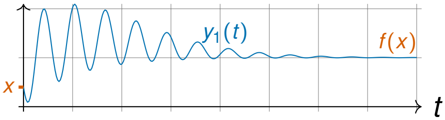
Equivalence with computable analysis

Definition (Bournez et al, 2007)

f **computable by GPAC** if $\exists p$ polynomial such that $\forall x \in [a,b]$

$$y(0) = (x, 0, \dots, 0) \qquad y'(t) = p(y(t))$$

satisfies $|f(x) - y_1(t)| \leqslant y_2(t)$ et $y_2(t) \xrightarrow[t\to\infty]{} 0$.



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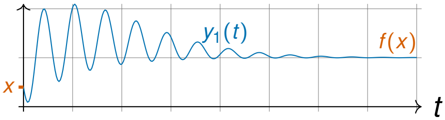

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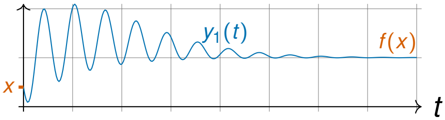

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1. In Computable Analysis, a standard model over reals built from Turing machines.

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Tentative definition

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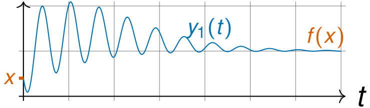

Complexity of analog systems

- Turing machines : $T(x) =$ number of steps to compute on x
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Tentative definition

$T(x, \mu) =$

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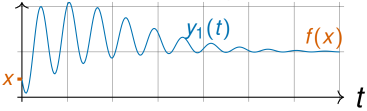

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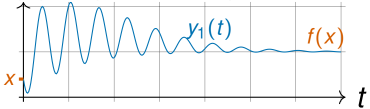

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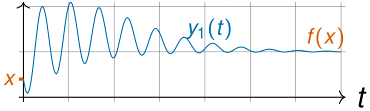
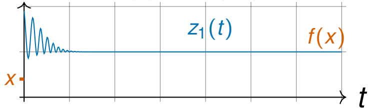


$\rightsquigarrow$

$z(t) = y(e^t)$



Complexity of analog systems

- Turing machines : $T(x) =$ number of steps to compute on x
- GPAC :

Tentative definition

$T(x,\mu) =$ first time t so that $|y_1(t) - f(x)| \leqslant e^{-\mu}$

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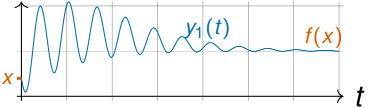

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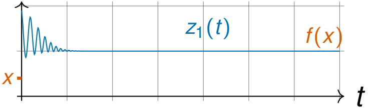
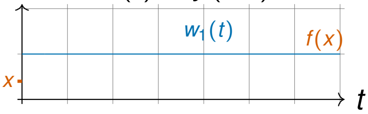


$w(t) = y(e^{e^t})$



Complexity of analog systems

- Turing machines : $T(x)$ = number of steps to compute on x
- GPAC : time contraction problem $\rightarrow$ **open problem**

Tentative definition

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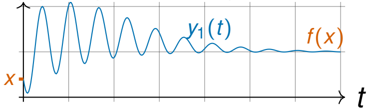

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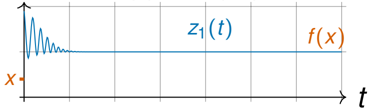

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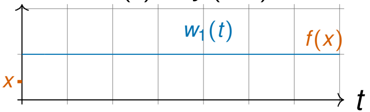
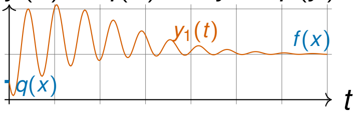


Something is wrong...

All functions have constant time complexity.

Time-space correlation of the GPAC

$y(0) = q(x) \qquad y' = p(y)$



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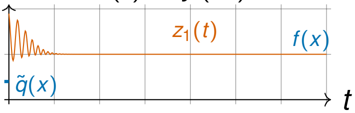

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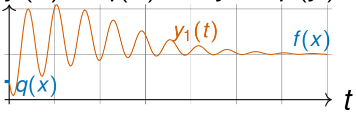

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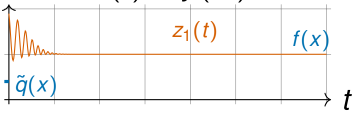
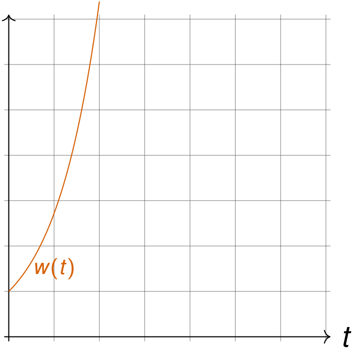


extra component : $w(t) = e^t$



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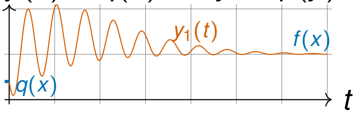

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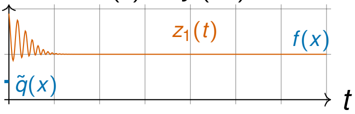

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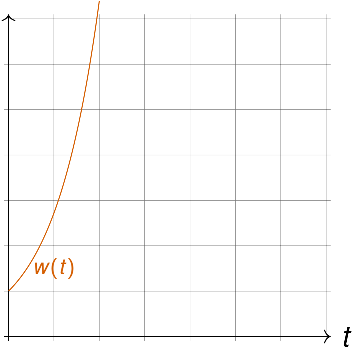


Observation

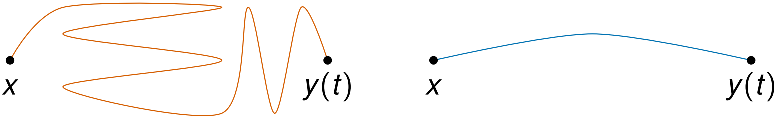
Time scaling costs “space”.

$\leadsto$

Time complexity for the GPAC must involve time and space !

Complexity of solving polynomial ODEs

$$y(0) = x \qquad y'(t) = p(y(t))$$



Complexity of solving polynomial ODEs

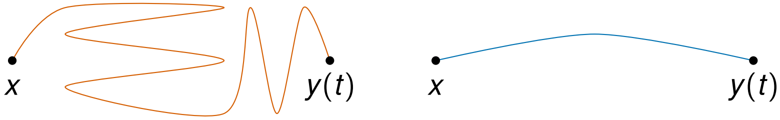
$$y(0) = x \qquad y'(t) = p(y(t))$$

Theorem

If $y(t)$ exists, one can compute p, q such that $\left|\frac{p}{q} - y(t)\right| \leqslant 2^{-n}$ in time

$$\operatorname{poly}(\textit{size of } x \textit{ and } p, n, \ell(t))$$

where $\ell(t) \approx$ length of the curve (between x and $y(t)$)

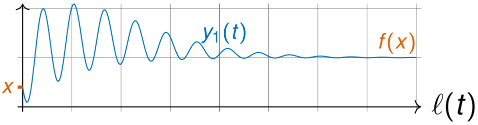


length of the curve = complexity = ressource

Characterization of real polynomial time

Definition : $f : [a,b] \to \mathbb{R}$ in ANALOG-P$_{\mathbb{R}}$ $\Leftrightarrow \exists p$ polynomial, $\forall x \in [a,b]$

$$y(0) = (x, 0, \ldots, 0) \qquad y' = p(y)$$



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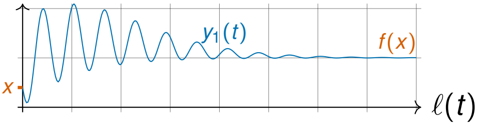
satisfies :

1. $|y_1(t) - f(x)| \leqslant 2^{-\ell(t)}$

   «greater length $\Rightarrow$ greater precision»

2. $\ell(t) \geqslant t$

   «length increases with time»



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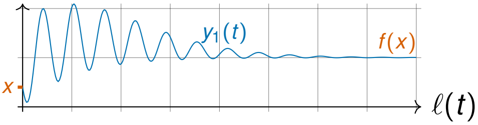


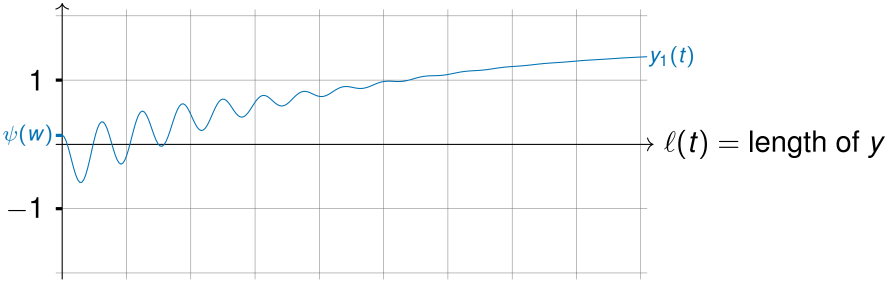
Theorem

$f : [a,b] \to \mathbb{R}$ computable in polynomial time $\Leftrightarrow f \in$ ANALOG-P$_{\mathbb{R}}$.

Characterization of polynomial time

Definition : $\mathcal{L} \in$ ANALOG-PTIME $\Leftrightarrow \exists p$ polynomial, $\forall$ word w

$$y(0) = (\psi(w), |w|, 0, \ldots, 0) \qquad y' = p(y) \qquad \psi(w) = \sum_{i=1}^{|w|} w_i 2^{-i}$$



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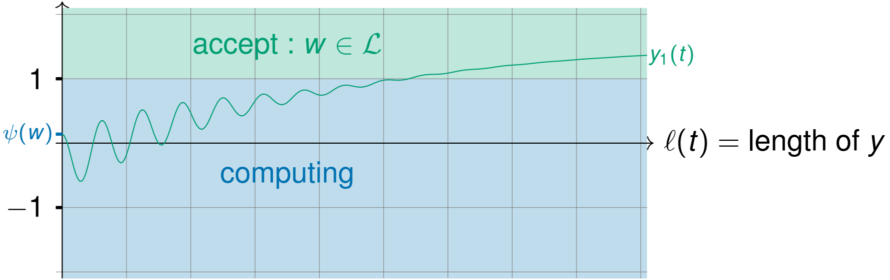

satisfies

1. if $y_1(t) \geqslant 1$ then $w \in \mathcal{L}$

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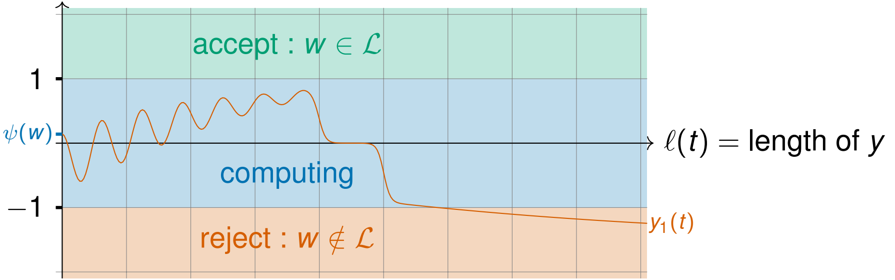

satisfies

2. if $y_1(t) \leqslant -1$ then $w \notin \mathcal{L}$

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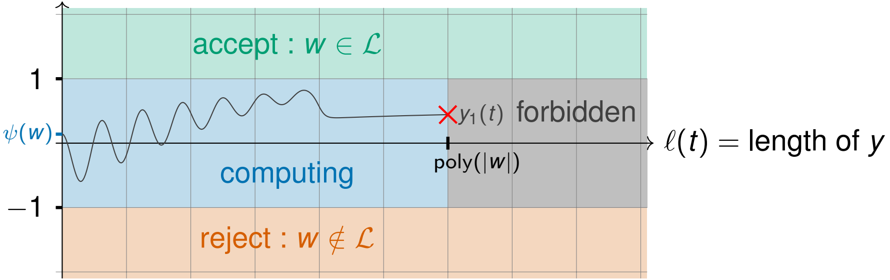

satisfies

3. if $\ell(t) \geqslant \text{poly}(|w|)$ then $|y_1(t)| \geqslant 1$

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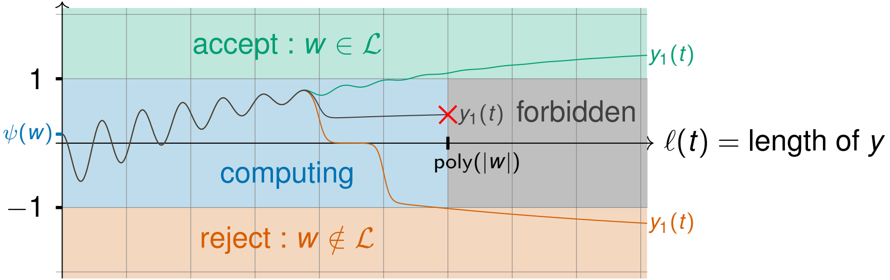
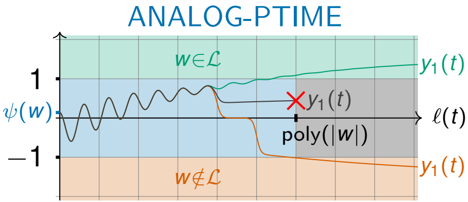
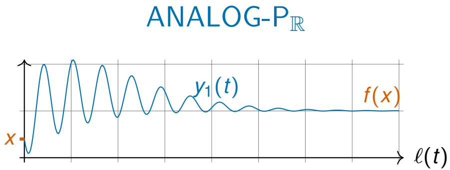


Theorem

PTIME = ANALOG-PTIME

Summary





Theorem

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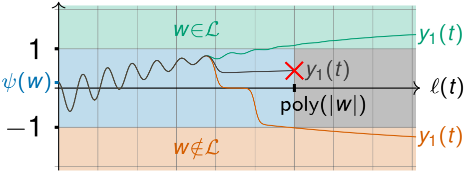
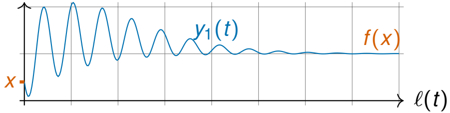
- Analog complexity theory based on length
- Time of Turing machine $\Leftrightarrow$ length of the GPAC
- Purely continuous characterization of PTIME

Summary

ANALOG-PTIME



ANALOG-$P_{\mathbb{R}}$



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- Analog complexity theory based on length
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- Purely continuous characterization of PTIME
- Only rational coefficients needed

Back to Chemical Reaction Networks

Theorem (CMSB 2017)

Elementary mass-action-law reaction system on finite universes of molecules are Turing-complete under the differential semantics.

Is this really realistic ?

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"Integer" encoding :

- exponential growth
- very robust : $|e| \leqslant 1$

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- somewhat robust : if $|e| \leqslant e^{-N^c}$ can do $SPACE(\mathcal{O}(N))$

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2. Disclaimer : not in the paper, I haven't checked the details.

Future work

Reaction networks :

- chemical
- enzymatic

$$y' = p(y)$$

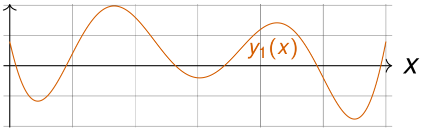
?

$$y' = p(y) + e(t)$$

- Finer time complexity (linear)
- Nondeterminism
- Robustness
- « Space» complexity
- Other models
- Stochastic

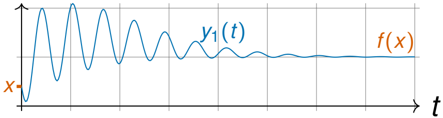
Universal differential equations

Generable functions



subclass of analytic functions

Computable functions



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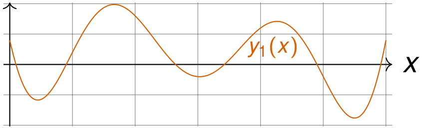

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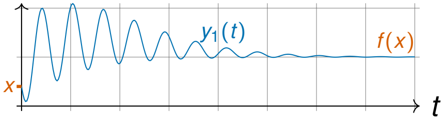

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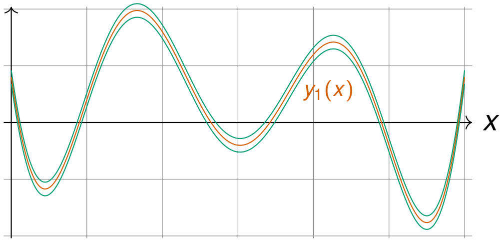
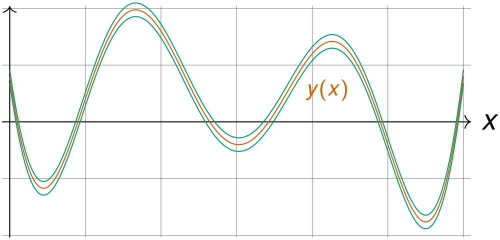


Universal differential algebraic equation (DAE)



Theorem (Rubel, 1981)

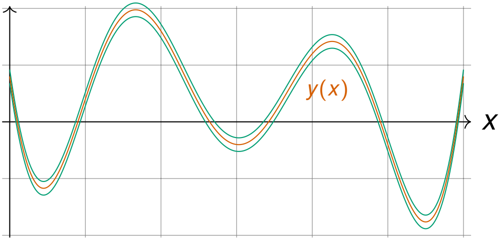
For any continuous functions f and ε, there exists $y : \mathbb{R} \to \mathbb{R}$ solution to

$$\begin{aligned} 3y'^4 y'' y''''^2 & -4y'^4 y'''^2 y'''' + 6y'^3 y''^2 y''' y'''' + 24y'^2 y''^4 y'''' \\ & -12y'^3 y'' y'''^3 - 29y'^2 y''^3 y'''^2 + 12y''^7 \qquad = 0 \end{aligned}$$

such that $\forall t \in \mathbb{R}$,

$$|y(t) - f(t)| \leqslant \varepsilon(t).$$

Universal differential algebraic equation (DAE)



Theorem (Rubel, 1981)

*There exists a **fixed** polynomial p and $k \in \mathbb{N}$ such that for any continuous functions f and ε, there exists a solution $y : \mathbb{R} \to \mathbb{R}$ to*

$$p(y, y', \ldots, y^{(k)}) = 0$$

such that $\forall t \in \mathbb{R}$,

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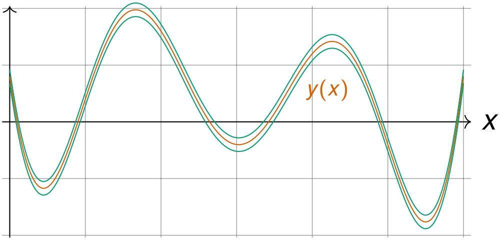

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Problem : this is «weak» result.

The problem with Rubel's DAE

The solution y is not unique, **even with added initial conditions** :

$$p(y, y', \ldots, y^{(k)}) = 0, \quad y(0) = \alpha_0, y'(0) = \alpha_1, \ldots, y^{(k)}(0) = \alpha_k$$

In fact, this is fundamental for Rubel's proof to work !

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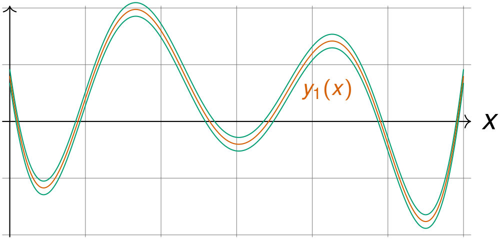
In fact, this is fundamental for Rubel's proof to work !

- Rubel's statement : this DAE is universal
- More realistic interpretation : this DAE allows almost anything

Open Problem (Rubel, 1981)

Is there a universal ODE $y' = p(y)$?
Note : explicit polynomial ODE $\Rightarrow$ unique solution

Universal initial value problem (IVP)



Theorem

There exists a ***fixed*** *(vector of) polynomial p such that for any continuous functions f and* ε*, there exists* $\alpha \in \mathbb{R}^d$ *such that*

$$y(0) = \alpha, \qquad y'(t) = p(y(t))$$

has a ***unique solution*** $y : \mathbb{R} \to \mathbb{R}^d$ *and* $\forall t \in \mathbb{R}$,

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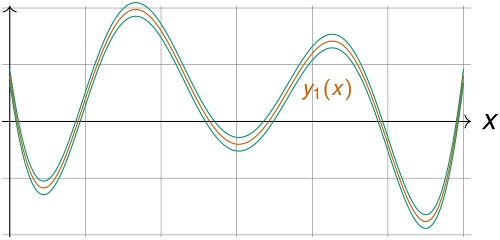

Notes :

- **system** of ODEs,
- y is analytic,
- we need $d \approx 300$.

Theorem

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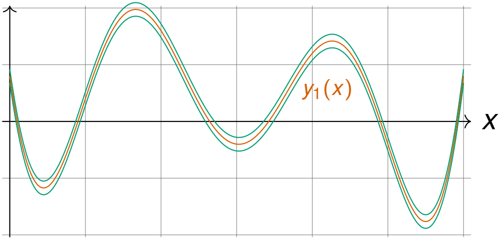
Universal initial value problem (IVP)



Notes :

- **system** of ODEs,
- y is analytic,
- we need $d \approx 300$.

Theorem

*There exists a **fixed** (vector of) polynomial p such that for any continuous functions f and ε, there exists $\alpha \in \mathbb{R}^d$ such that*

$$y(0) = \alpha, \qquad y'(t) = p(y(t))$$

*has a **unique solution** $y : \mathbb{R} \to \mathbb{R}^d$ and $\forall t \in \mathbb{R}$,*

$$|y_1(t) - f(t)| \leqslant \varepsilon(t).$$

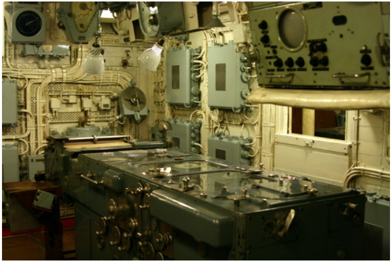
Remark : α is usually transcendental, but computable from f and ε

What is a computer?

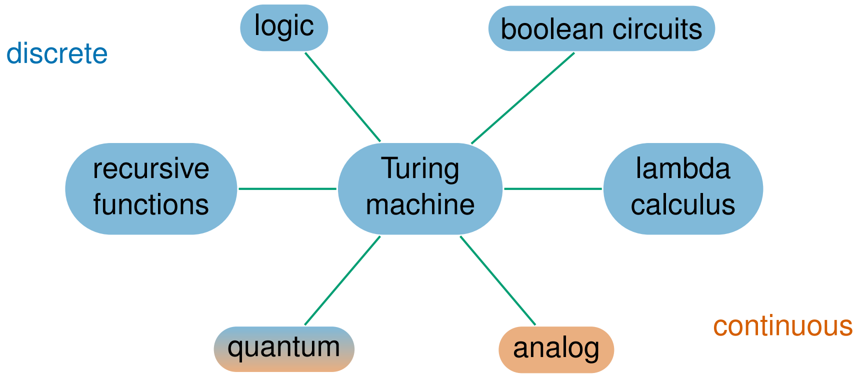
What is a computer ?

What is a computer ?

VS



Computability

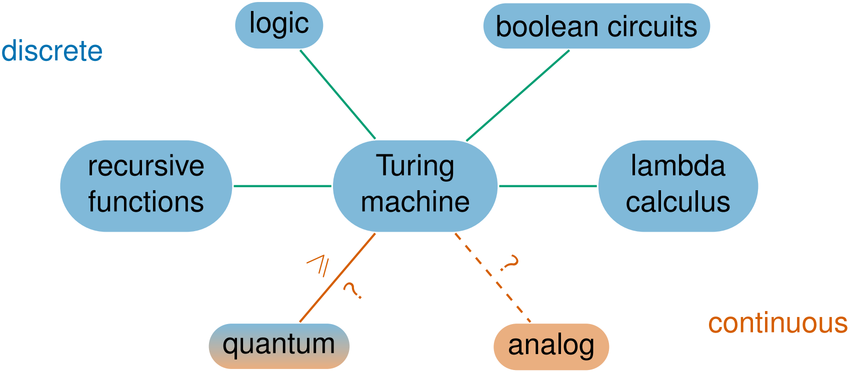


Church Thesis

All **reasonable** models of computation are equivalent.

Church Thesis

Complexity



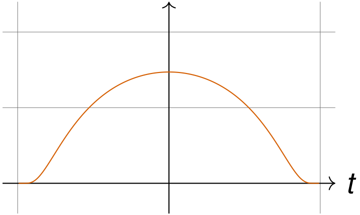
Effective Church Thesis

All **reasonable** models of computation are equivalent for complexity.

Rubel's proof in one slide

- Take $f(t) = e^{\frac{-1}{1-t^2}}$ for $-1 < t < 1$ and $f(t) = 0$ otherwise.

It satisfies $\quad (1-t^2)^2 f''(t) + 2tf'(t) = 0.$



Rubel's proof in one slide

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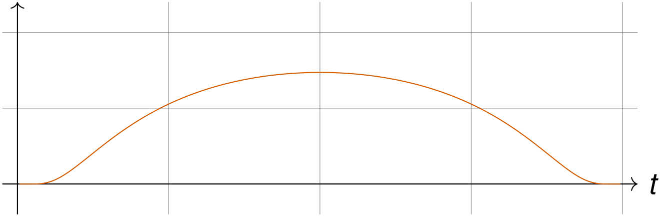
  It satisfies $\quad (1-t^2)^2 f''(t) + 2tf'(t) = 0.$
- For any $a, b, c \in \mathbb{R}$, $y(t) = cf(at+b)$ satisfies

$$\begin{aligned} 3y'^4 y'' y''''^2 \quad & -4y'^4 y''^2 y'''' + 6y'^3 y''^2 y''' y'''' + 24 y'^2 y''^4 y'''' \\ & -12 y'^3 y'' y'''^3 - 29 y'^2 y''^3 y'''^2 + 12 y''^7 = 0 \end{aligned}$$

Translation and rescaling :



Rubel's proof in one slide

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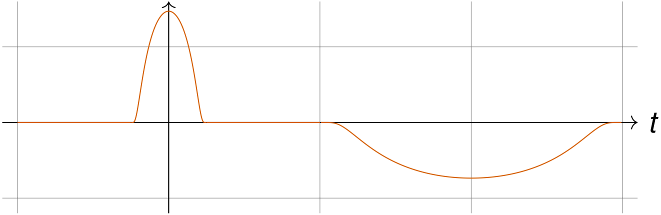
- For any $a, b, c \in \mathbb{R}$, $y(t) = cf(at + b)$ satisfies

  $$3y'^4y''y''''^2 - 4y'^4y''^2y'''' + 6y'^3y''^2y'''y'''' + 24y'^2y''^4y'''' - 12y'^3y''y'''^3 - 29y'^2y''^3y'''^2 + 12y''^7 = 0$$
- Can glue together arbitrary many such pieces



Rubel's proof in one slide

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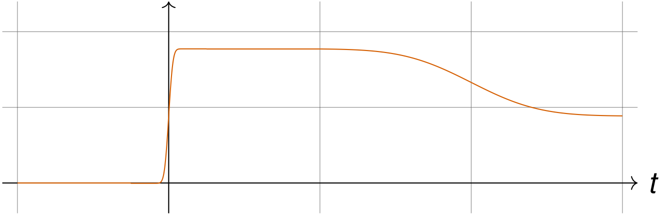
- Can glue together arbitrary many such pieces
- Can arrange so that $\int f$ is solution : piecewise pseudo-linear



Rubel's proof in one slide

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- For any $a, b, c \in \mathbb{R}$, $y(t) = cf(at+b)$ satisfies

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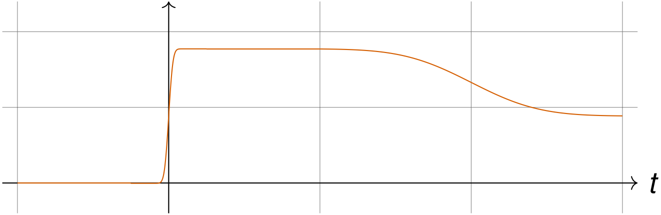
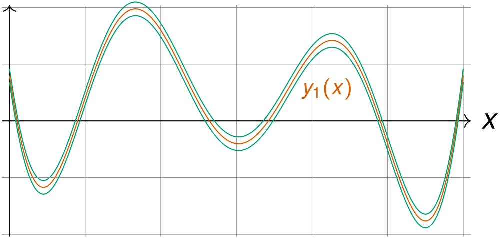


Conclusion : Rubel's equation allows any piecewise pseudo-linear functions, and those are **dense in** C^0

Universal DAE revisited



Theorem

*There exists a **fixed** polynomial p and* $k \in \mathbb{N}$ *such that for any continuous functions f and* ε*, there exists* $\alpha_0, \ldots, \alpha_k \in \mathbb{R}$ *such that*

$$p(y, y', \ldots, y^{(k)}) = 0, \quad y(0) = \alpha_0, y'(0) = \alpha_1, \ldots, y^{(k)}(0) = \alpha_k$$

*has a **unique analytic solution** and this solution satisfies such that*

$$|y(t) - f(t)| \leqslant \varepsilon(t).$$