Real-Time Equivalence of Chemical Reaction Networks and Analog Computers

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August 7th, 2019

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Motivation & Introduction

Computability/Complexity of Real Numbers

Which (real) numbers can we compute?

Given a (new) computational model, this is a simple yet profound question to ask.

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- Yamada (1962): Do that fast, please. (Real-time computability)
- Hartmanis & Stearns (1965): no can do, square root of two. (open conjecture)

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- Better yet, give theoretical boundary of the computational model. (Identify “mission impossible”.)

Today, we are going to advance our knowledge of the complexity of real numbers in the analog chemical reaction networks (CRNs) model.

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Hydrazine Combustion

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Abstract CRN

$$3A \longrightarrow 4B + C$$
$$A \longrightarrow C + 2D$$
$$4B + A \longrightarrow 3C + 8D$$
$$2D + E \longrightarrow 2F$$

The General Purpose Analog Computer (GPAC) is an analog computer model first introduced in 1941 by Claude Shannon.

For simplicity, we can view both GPACs and CRNs as polynomial initial value problems (PIVPs):

GPAC/ODE

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = x_i' = p_i(x_1, \cdots, x_n),$$

for $i = 1, 2, \cdots, n$,

where p_i's are polynomials.

[1] Vera Hars and János Tóth: On the Inverse Problem of Reaction Kinetics, 1979.

CRNs and GPACs In A Nutshell

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CRN/ODE[1]

$$x_i' = p_i(x_1, \cdots, x_n) - q_i(x_1, \cdots, x_n)\mathbf{x_i},$$

for $i = 1, 2, \cdots, n$,

where p_i's and q_i's are polynomials with **positive** coefficients.

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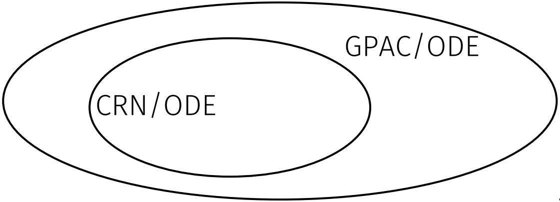
By the previous definition, CRNs are restricted GPACs. In terms of ODEs that they induce, we have



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CRN

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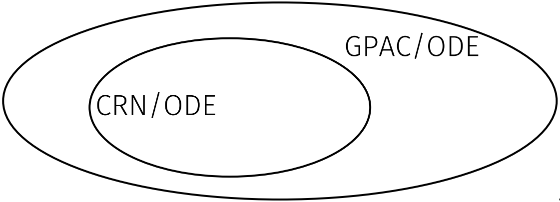

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CRN

$$x' = 1 - x.$$

GPAC but not CRN

$$x' = 1 - x,$$
$$y' = 1 - \boxed{x}.$$

The intuition: for CRNs, no participation $\Rightarrow$ no destruction.

Computable Real Numbers

Computable real numbers in **discrete** models:

1. In Turing's revolutionary 1936 paper, he defined a notion of a computable real number.
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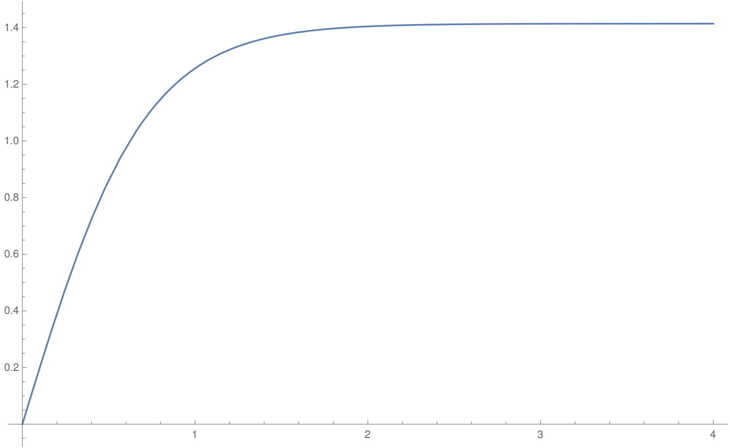
Inspired by the above notion, in analog models (GPAC/CRN), we can designate a variable x, such that

$$\lim_{t \to \infty} x(t) = \alpha.$$

And then we say x **computes** α.

GPAC/CRN computable numbers

Compute $\sqrt{2}$ in the limit:



But how **fast** does it converge to $\sqrt{2}$?

In 1962, Yamada introduced a notion of computing a number $\alpha \in \mathbb{R}$ in **real time.**[2]

[2]Yamada, Hisao. "Real-time computation and recursive functions not real-time computable." IRE Transactions on Electronic Computers 6 (1962): 753-760.

[3]Lipton RJ (2017) Why the Hartmanis–Stearns conjecture is still open, 2012. Blog post. Retrieved 3 Feb from https://rjlipton.wordpress.com/2012/06/15/why-the-hartmanis-stearns-conjecture-is-still- open/

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Similarly, in CRNs/GPACs, to define real-time computability, we can require our designated variable $x(t)$ such that

$$|x(t) - \alpha| < O(2^{-t}).$$

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Real-Time CRN Computable Reals

$\alpha \in \mathbb{R}$ is **real-time CRN-computable** (resp., **GPAC-computable**), and we write $\alpha \in \mathbb{R}_{RTCRN}$ (resp., $\alpha \in \mathbb{R}_{RTGPAC}$), if there exist an (**integral**) PIVP problem induced by a CRN (resp. GPAC) and a variable $x(t)$ in the system with the following properties:

1. (**zero initial values**). For all variable $x(t)$, $x(0) = 0$. (This can be relaxed to integral values.)

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$$x(t) \leq \beta.$$
3. (**real-time convergence**).
$$|x(t) - |\alpha|| \leq O(2^{-t}).$$

Previous Results

We[4] previously showed that

Theorem
All algebraic real numbers are in $\mathbb{R}_{RTCRN}$.

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Theorem
Some transcendental numbers are in $\mathbb{R}_{RTCRN}$.

- Two (ugly) numbers u,v, such that $u - v = e$.
- Did not know how to prove **subtraction** can be done in **real time**.
- Did not know $\mathbb{R}_{RTCRN}$ is a field. Hard to compute real numbers in general because of lack of field structure.

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2. $\mathbb{R}_{RTCRN}$ is equivalent to the class $\mathbb{R}_{RTGPAC}$ of real-time computable real numbers by **general purpose analog computers** (**GPACs**).
3. $\mathbb{R}_{RTCRN}$ contains the transcendental numbers e and π.

Implications

1. $\mathbb{R}_{RTCRN}$ is a field:
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   - It greatly simplifies the proof that a number $\alpha \in \mathbb{R}_{RTCRN}$.

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   - It greatly simplifies the proof that a number $\alpha \in \mathbb{R}_{RTCRN}$.
3. e, $\pi \in \mathbb{R}_{RTCRN}$: the field $\mathbb{R}_{RTCRN}$ is not boring.

$\mathbb{R}_{RTCRN}$ is a Field

Closure Under Addition, Multiplication

Lemma (Addition)
If $\alpha, \beta \in \mathbb{R}_{RTCRN}$*, then* $\alpha + \beta \in \mathbb{R}_{RTCRN}$*.*

Lemma (Multiplication)
If $\alpha, \beta \in \mathbb{R}_{RTCRN}$*, then* $\alpha\beta \in \mathbb{R}_{RTCRN}$*.*

Subtraction Is Hard

Assume $A(t)$, $B(t)$ computes α, β, resp. Then $C(t)$ in the following CRN/ODE[5], [6] computes $\alpha - \beta$.

Subtraction CRN

$$A \longrightarrow A + C$$
$$B \longrightarrow B + H$$
$$C \longrightarrow \emptyset$$
$$C + H \longrightarrow \emptyset$$

Subtraction ODE

$$C' = A - CH - C \qquad (1)$$
$$H' = B - CH \qquad (2)$$

However, it is hard to prove exponential rate of convergence.

[5] Buisman, H.J. et al.: Computing algebraic functions with biochemical reaction networks, 2009.

[6] Marko Vasic, David Soloveichik, and Sarfraz Khurshid: CRN++: Molecular Programming Language, 2018.

Let $f(t)$ be a function that converges to $\alpha \in \mathbb{R}$ **exponentially fast**, that is, there exist constants τ and γ such that for all $t \in [\tau, \infty)$

$$|f(t) - \alpha| \leq e^{-\gamma t}$$

Lemma (Reciprocal Convergence)
If $x(t)$ is a function that satisfies

$$\frac{dx}{dt} = 1 - f(t) \cdot x,$$

then $x(t)$ converges to $\frac{1}{\alpha}$ exponentially fast.

Lemma (Reciprocal)
If $\alpha \in \mathbb{R}_{RTCRN}$, then $\frac{1}{\alpha} \in \mathbb{R}_{RTCRN}$.

Lemma (Subtraction)
If $\alpha, \beta \in \mathbb{R}_{RTCRN}$ *and* $\alpha > \beta > 0$, *then* $\alpha - \beta \in \mathbb{R}_{RTCRN}$.

Proof Sketch
Let x, y computes α, β in real time.

Construct an CRN/ODE for a new variable z such that

$$z' = 1 - (x - y)z$$

Let $f(t) = x(t) - y(t)$, apply **reciprocal** convergence lemma, and use closure under **reciprocal**.

Moreover, z is **solvable** and easy to **analyze**.

$\mathbb{R}_{RTCRN}$ is a Field

Theorem
$\mathbb{R}_{RTCRN}$ is a field.

Proof.
This follows immediately by closure under addition, subtraction, multiplication, and reciprocal. $\square$

$$\mathbb{R}_{RTCRN} = \mathbb{R}_{RTGPAC}$$

Proof that $\mathbb{R}_{RTCRN} = \mathbb{R}_{RTGPAC}$

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Proof ($\subseteq$).
CRNs are special forms of GPACs. $\square$

The backward direction is the non-trivial direction. We need to use a **soup-up version** of the following theorem.

Simulating a GPAC with a CRN

Theorem (Difference Encoding[7])
Given a GPAC $\mathcal{A}$, there is a CRN $\mathcal{N}$ that for each variable x in $\mathcal{A}$, there are two variables x_1 and x_2 in $\mathcal{N}$ such that

$$x(t) = x_1(t) - x_2(t) \quad \textbf{pointwise for every t} \geq \mathbf{0}.$$

This means we can compile a GPAC into a CRN.

We use a similar construction. Moreover, we also show that **if $x(t)$ is bounded, then x_1 and x_2 are also bounded**.

[7] François Fages, Guillaume Le Guludec, Olivier Bournez, and Amaury Pouly. "Strong turing completeness of continuous chemical reaction networks and compilation of mixed analog-digital programs." International Conference on Computational Methods in Systems Biology. Springer, Cham, 2017.

Example: Difference Encoding

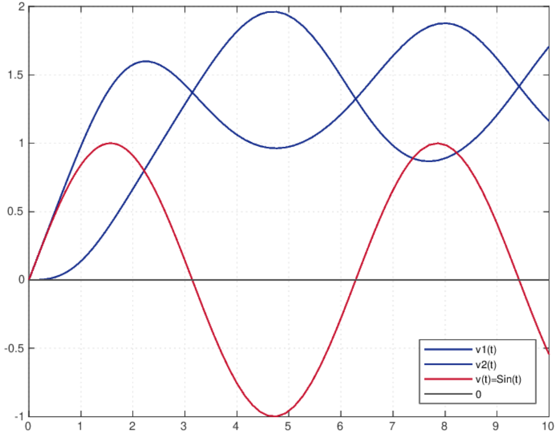
The function $v(t) = \sin(t)$ can be implemented by the top-left GPAC/ODE, and encoded by $v_1(t) - v_2(t)$ in the bottom-left CRN/ODE.

GPAC/ODE

$$u' = v$$
$$v' = 1 - u$$

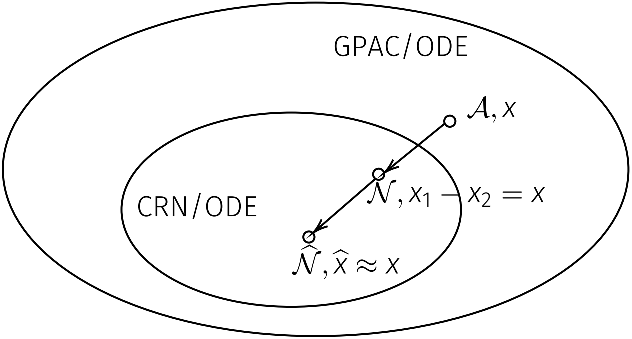
CRN/ODE

$$u_1' = v_1 - u_1 u_2$$
$$u_2' = v_2 - u_1 u_2$$
$$v_1' = 1 + u_2 - v_1 v_2$$
$$v_2' = u_1 - v_1 v_2$$



Plot: $\sin(t) = v_1(t) - v_2(t)$

The Rest of The Proof



- Let x in $\mathcal{A}$ computes α in real time.
- Now the CRN $\mathcal{N}$ encodes x by **two** variables $x_1 - x_2$.

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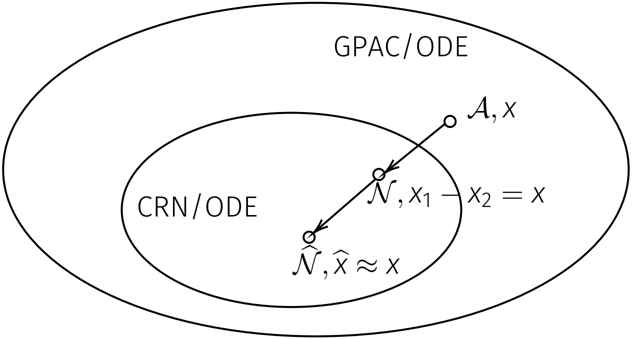

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- Can we do it in **one single variable**?
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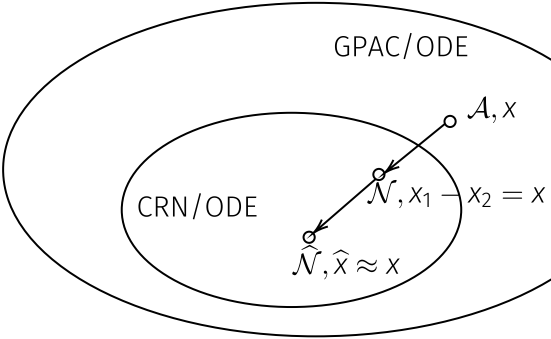

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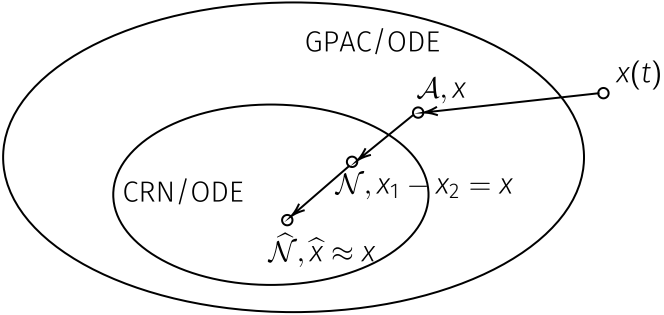
- Can we do it in **one single variable**?
  - Yes. By two applications of the reciprocal lemma, we get $\widehat{\mathcal{N}}$.
- By $\widehat{x} \approx x$, we mean it computes the same α in real time.

e and π are in $\mathbb{R}_{RTCRN}$

To Compute a number α in real time by CRN, we do

1. Pick a function $x(t)$ that converges to α **exponentially** fast. (creative)
2. Implement $x(t)$ by a GPAC. (creative)
3. Translate the GPAC into a CRN $\mathcal{N}$. (automatic)
4. Lastly, turn $\mathcal{N}$ into $\widehat{\mathcal{N}}$. (automatic)



π is in $\mathbb{R}_{RTCRN}$

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As a first attempt, we can use the fact that

$$\lim_{t\to\infty} \arctan(t) = \frac{\pi}{2}.$$

Let

$$x(t) = \arctan(t), \quad y(t) = \frac{1}{1+t^2}, \quad z(t) = \frac{t}{1+t^2}.$$

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Then we have

$$\begin{aligned} x' &= y \\ y' &= -2yz, \\ z' &= y^2 - z^2. \end{aligned}$$

with initial value $x(0) = z(0) = 0$ and $y(0) = 1$.

Unfortunately, $\operatorname{arctan}(t)$ does not converge to $\frac{\pi}{2}$ fast enough.

At the second attempt, we pick the function

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Since this function can be viewed as substituting t for $w(t) = 1 - e^{-t}$ in $\operatorname{arctan}(t)$, by **change of variable** and **chain rule**, we get the following PIVP

$$\begin{aligned} x' &= y \cdot w, \\ y' &= (-2yz) \cdot w, \\ z' &= (y^2 - z^2) \cdot w, \\ w' &= -w. \end{aligned}$$

with $x(0) = z(0) = w(0) = 0$, $y(0) = 1$.

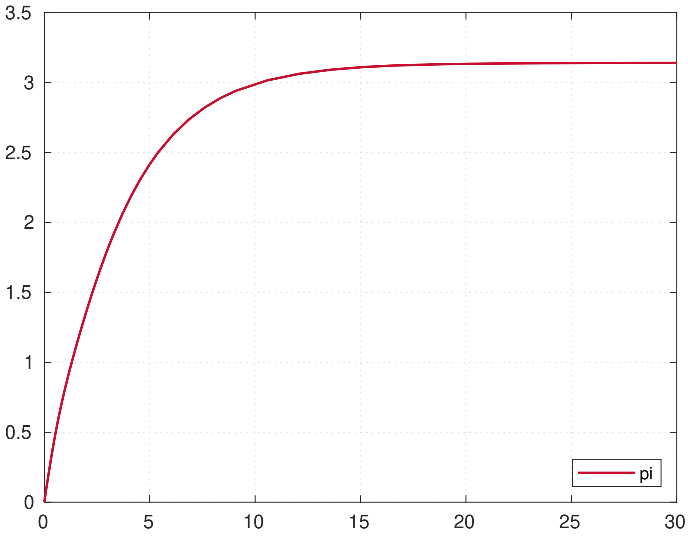

Figure 2: Plot of π. (CRN size: 10 species and 120 reactions.)

Thank you!