Pacific Northwest
NATIONAL LABORATORY

ChemComp: Compiling and Computing with Chemical Reaction Networks

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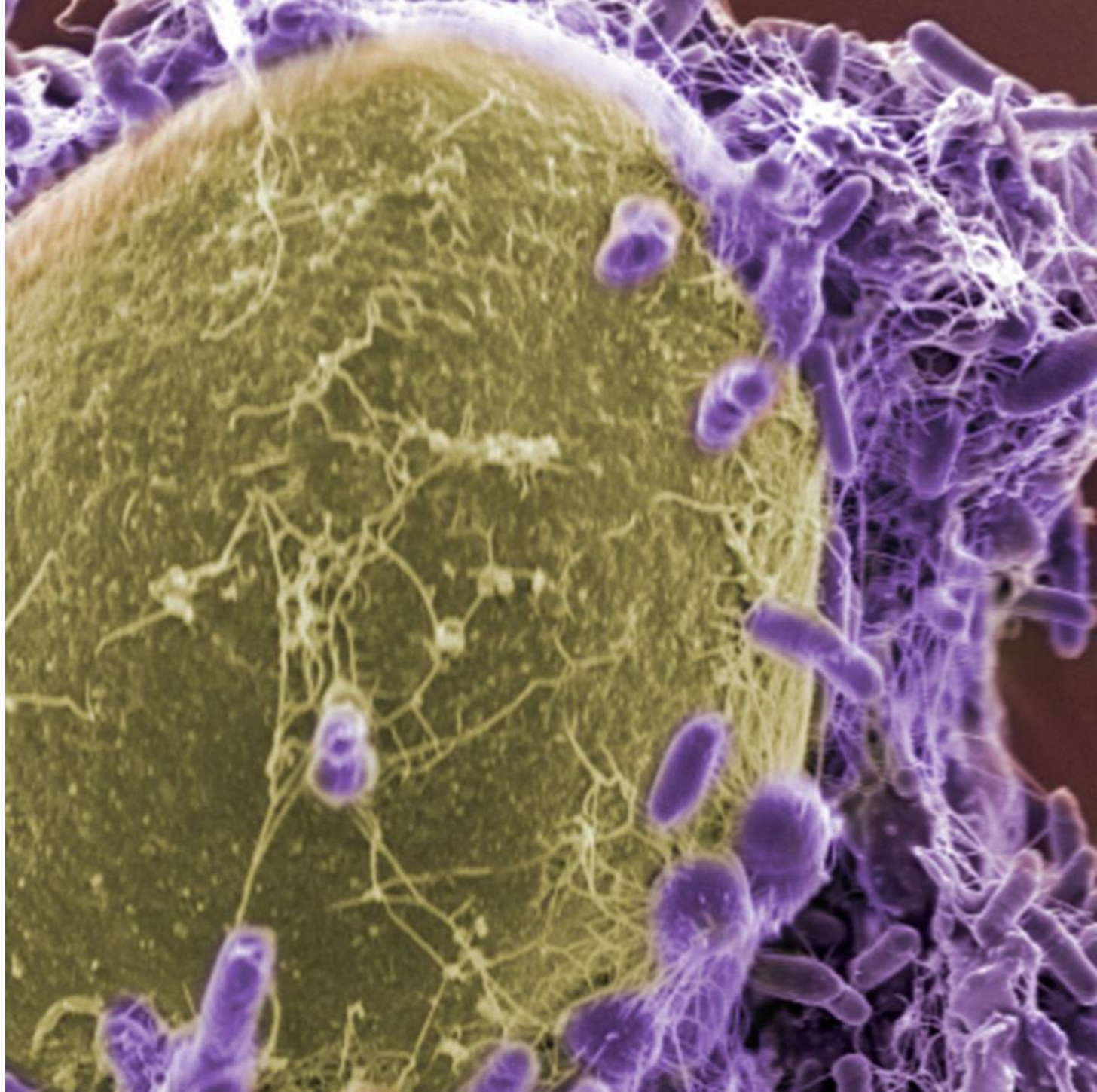

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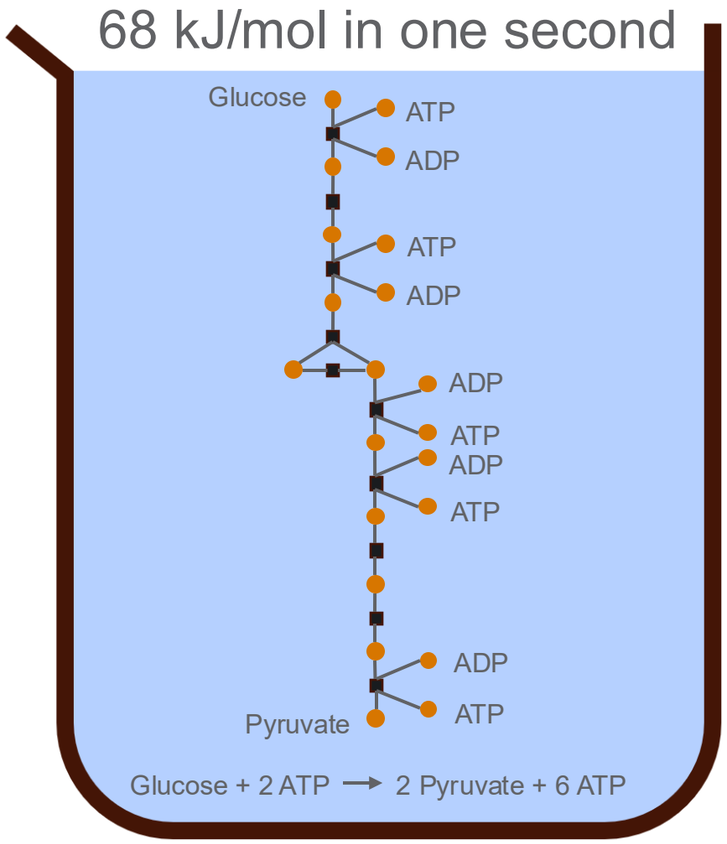
Chemistry conveys a “chemical advantage” for computation



Rules are ‘simple’ compared to biology

Potential of Biochemical Pathway
OPS: ~10^23
Energy/s: ~68 kW

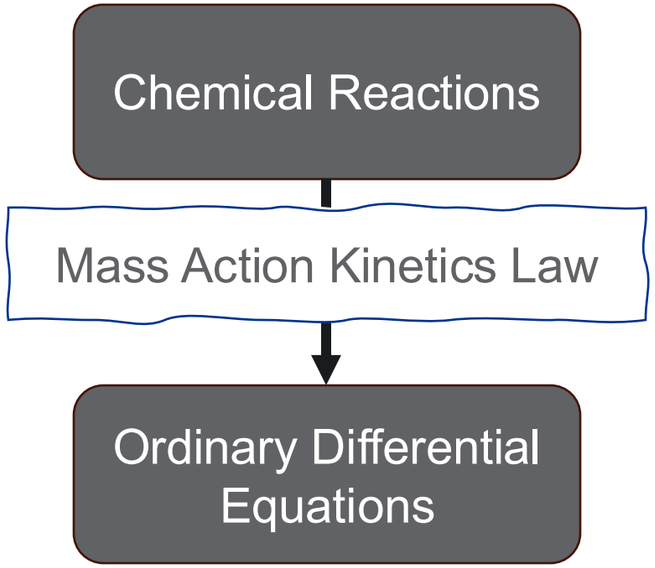
Frontier (ORNL, 2021)
FLOPS: ~10^18
Energy/s: ~29,000 kW

Potential Gain in OPS/W
~4x10^7 x

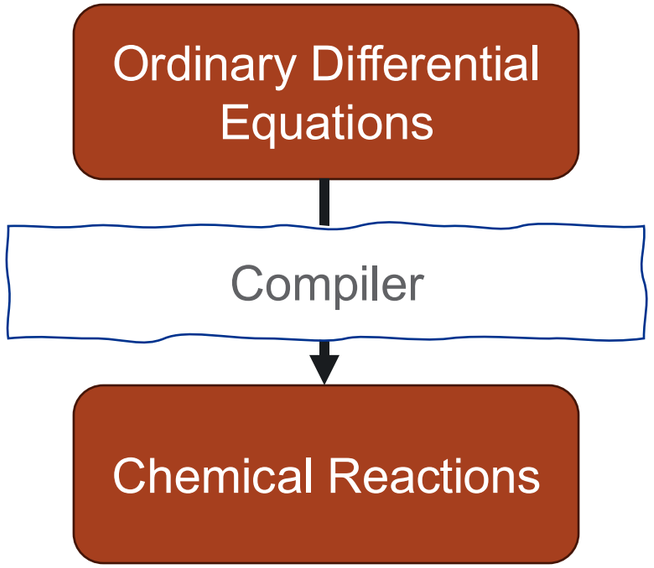
“Chemical advantage” meets the high-performance requirements for scientific workflows:
- Scalable
- Massively concurrent
- Continuous (time) representation
- “Low” energy

Beneficial to applications:
- Continuous systems such as ODEs as natural representation
- Neural networks/NLP as massively concurrent inference

Chemical reactions can be used for useful computation



D. Soloveichik, et.al. - Turing completeness [Natural Computing 2008]
M. Matejak, et.al. – Modelic Lib of Chem Processes [Modelica Conf 2015]
W. Poole, et.al. - BioCRNpyler [PLOS Computational Biology 2022]
R. Rendal, et.al. - Chemilang [Github 2023]



S. Shah, et.al. - CCompiler [arXiv 2008]
M. Vasic, et.al. - CRN++ [Natural Computing 2020]

RW does not consider:
- Concrete chemical reactions
- Tracking species over time

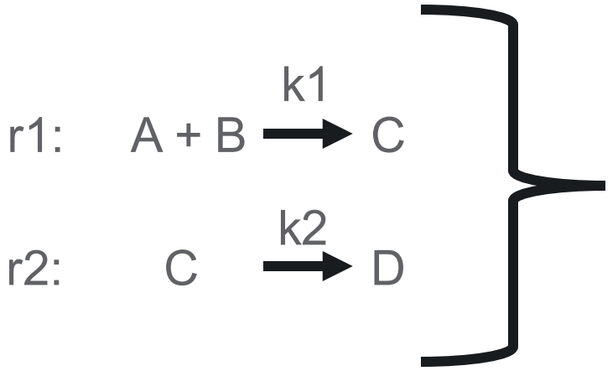
Chemical reaction can be mapped to ODEs

Using the Law of Mass Action kinetics:

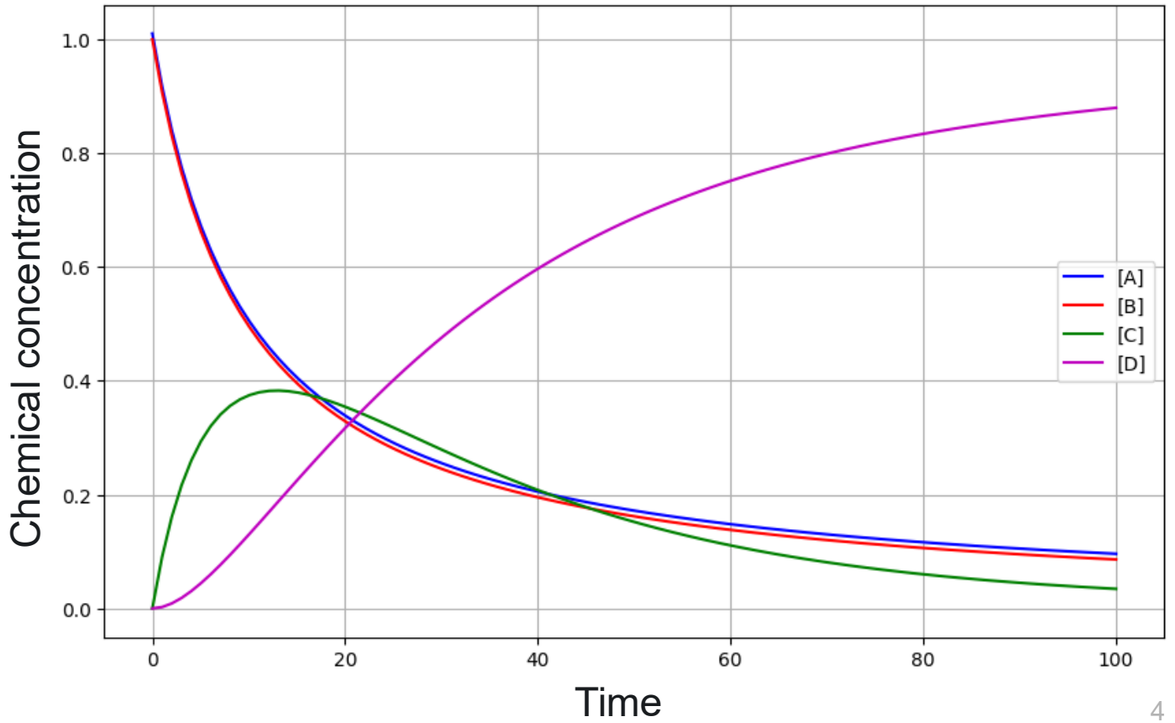
$$\sum_i I_i^r X_i \xrightarrow{p_r(x)} \sum_i O_i^r X_i$$

$$\frac{dX_i}{dt} = \sum_i (O_i^r - I_i^r) p_r(X)$$

I_i^r : Number of input species i in reaction r
O_i^r : Number of output species i in reaction r
$p_r(x)$: Propensity or Rate of the reaction r

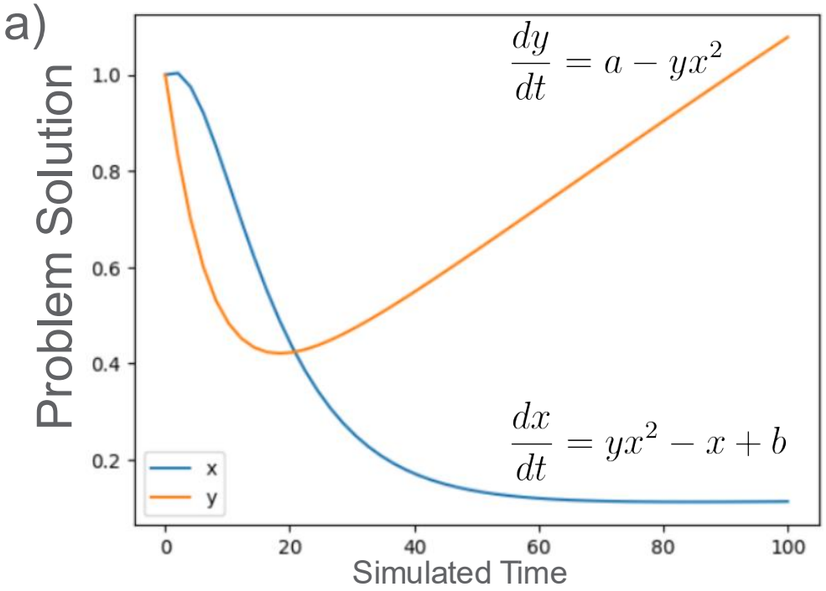


$$\frac{d[A]}{dt} = -k_1[A][B]$$
$$\frac{d[B]}{dt} = -k_1[A][B]$$
$$\frac{d[C]}{dt} = k_1[A][B] - k_2[C]$$
$$\frac{d[D]}{dt} = k_2[C]$$

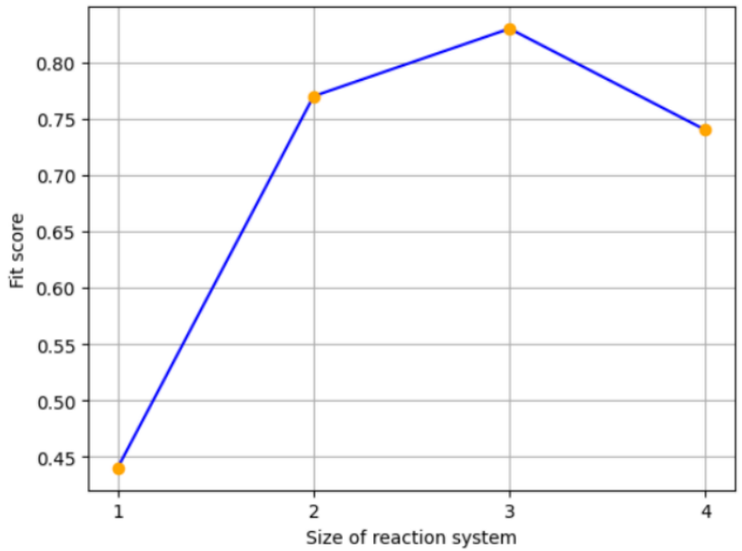


Fitting mathematical patterns into concrete CRs

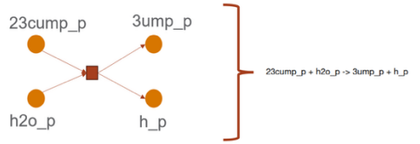
a)

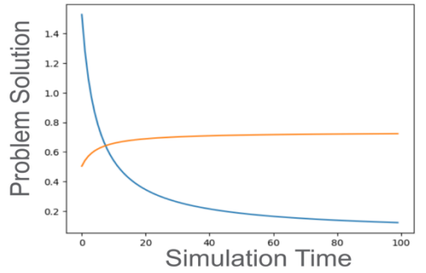


c)

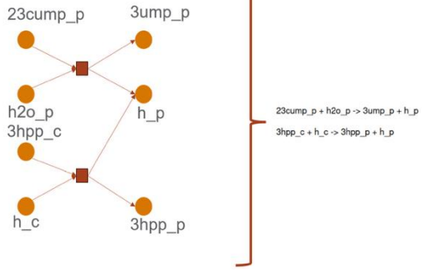


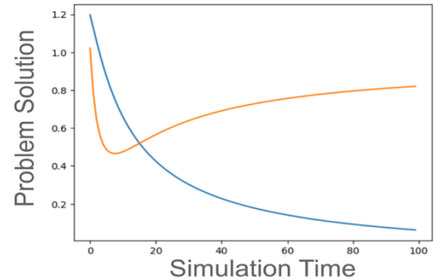
b) One reaction



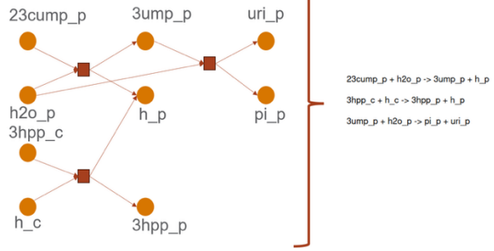


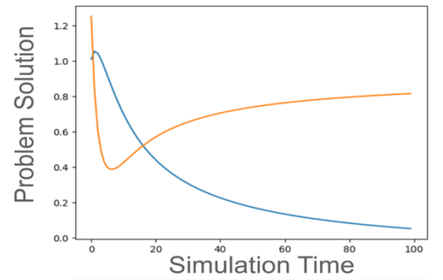
Two reactions



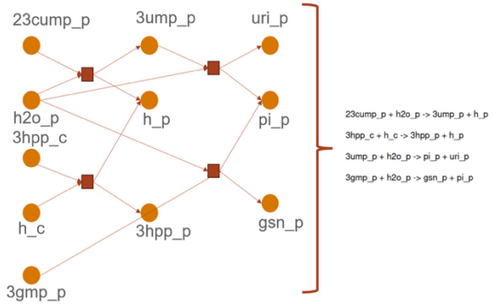


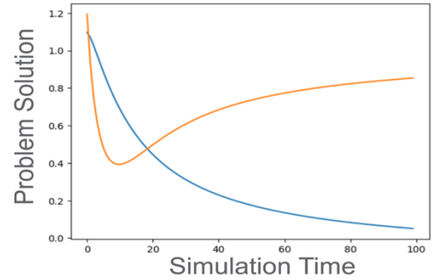
Three reactions



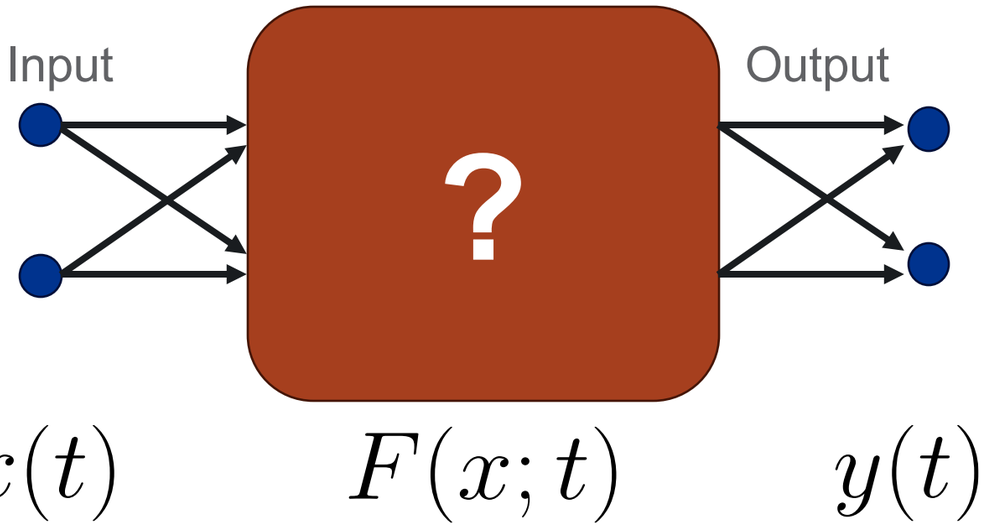


Four reactions





Reservoir computing can harness real world systems for computation and forecasting



- Provide problem as input signal
- Map the signal onto a higher dimension physical system
- Dynamical system performs some process function
- Perform measurements of system states and form weighted combination of measurements
- Use linear least squares optimization of output weights

A range of dynamical systems have been considered:

- Optofluidic systems (Gao et al., 2022)
- Water waves (Maksymov and Pototsky, 2023)
- Ecosystems of Unicellular organisms (Ushio et al., 2023)
- Ferromagnetic materials (Everschor-Sitte et al., 2024)
- Formose reaction network (Baltussen et al., 2024)

ChemComp: A Compilation Framework for Computing with Chemical Reaction Networks

Approach

- Develop a compiler using MLIR [1] to capture ODE and realistic chemical and biological processes
- Create a compilation flow to convert ODEs into chemical operations from a curated database of known motifs
- Implement CRNCMs, leveraging the BiGG [2] database and respective mass action kinetics

Input: ODEs

$$dy_0/dt = \alpha_0 \sin(\beta_0 t + \theta_0) + \lambda_0$$
$$dy_1/dt = \alpha_1 \sin(\beta_1 t + \theta_1) + \lambda_1$$
$$dy_2/dt = \alpha_2 \sin(\beta_2 t + \theta_2) + \lambda_2$$

Compiler

ODEs to CRN

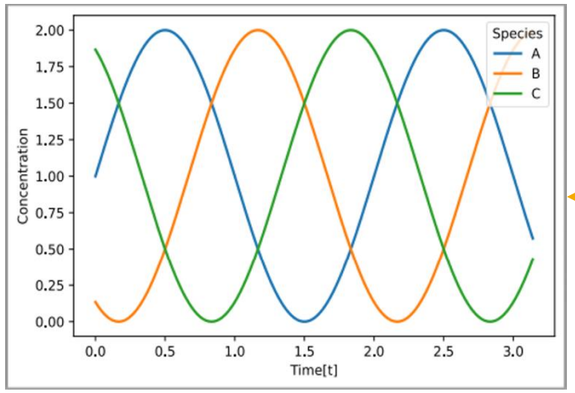
Abstractions

Configuration & Reaction Databases

CRN Modeling

Emulator

Output: Concentrations

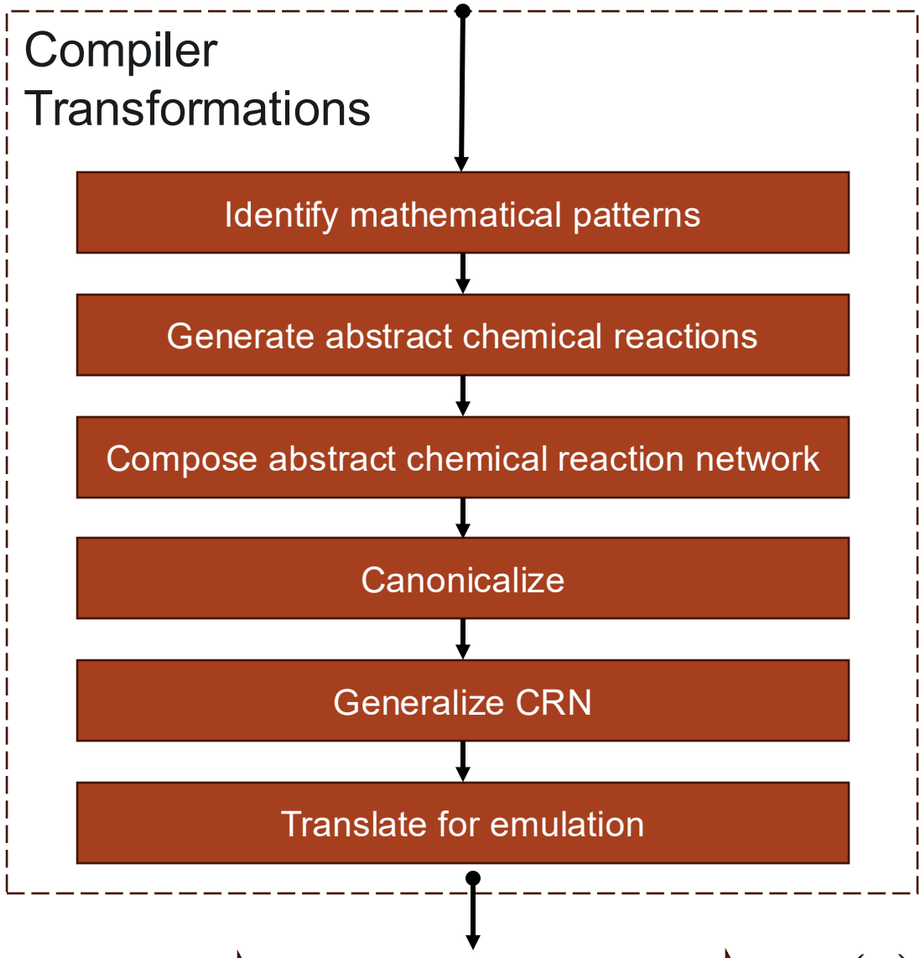


[1] C. Lattner, et al. "MLIR: Scaling compiler infrastructure for domain specific computation." 2021 IEEE/ACM International Symposium on Code Generation and Optimization (CGO). IEEE, 2021

[2] Z. A. King, et al., "BiGG Models: A platform for integrating, standardizing and sharing genome-scale models, Nucleic Acids Research", Volume 44

Approach to compiler support

- Introduce a new dialect to represent chemical reactions
- Using MLIR, implement lowerings of mathematical patterns to abstract chemical reactions
- Incorporate concrete chemical reactions in the flow

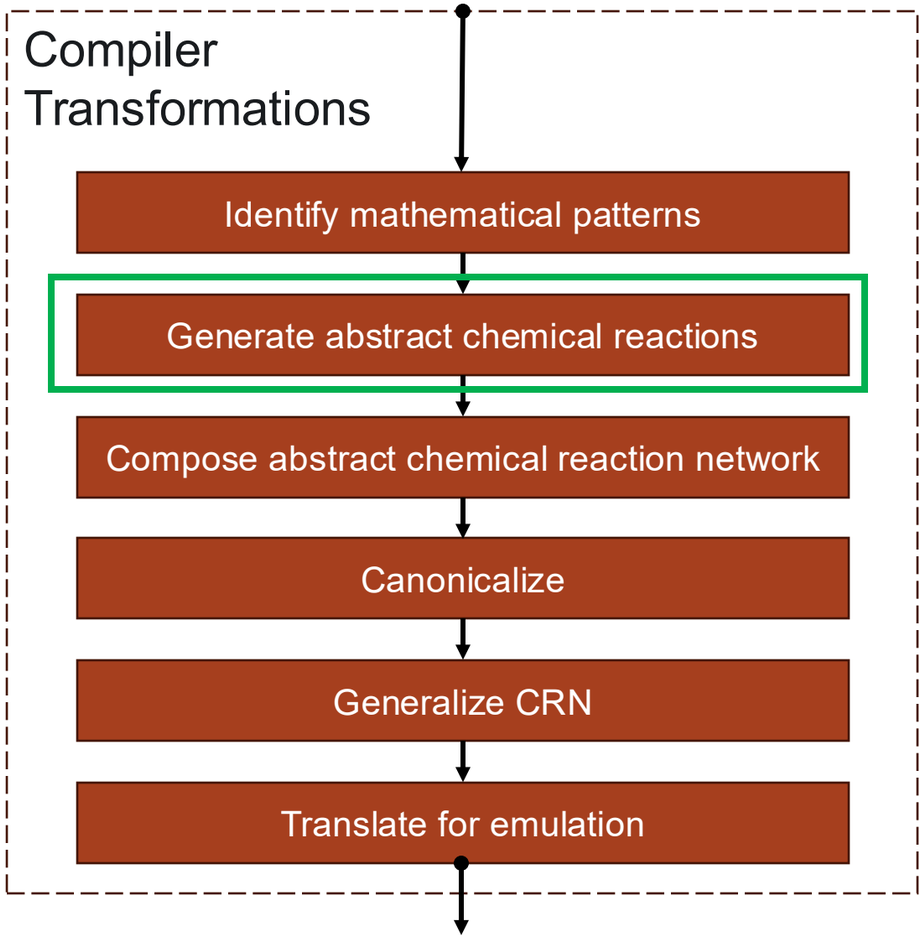


$\frac{dy}{dt} = f(t;\alpha)$ → Mathematical patterns → Abstract CRN → Concrete CRN → Device/Emulator → $y(t)$

Approach to compiler support

```
// Define reaction 1: 2H2 + O2 -> 2H2O
// Reaction 1 adjusts concentrations of H2, O2, and H2O
acr.reaction @reaction_1(%h2: !acr.species,
                         %o2: !acr.species,
                         %h2o :!acr.species,
                         %rate_constant: f32)
  -> (!acr.species, !acr.species, !acr.species) {
 // Define the stoichiometry: 2H2 + O2 -> 2H2O
 %h2_stoich = acr.stoich_coeff -2 : f32
 %o2_stoich = acr.stoich_coeff -1 : f32
 %h2o_stoich = acr.stoich_coeff 2 : f32

 %h2_o, %o2_o, %h2o_o = acr.react(%h2, %o2, %h2o,
  %h2_stoich, %o2_stoich, %h2o_stoich,
  %rate_constant) : (!acr.species, !acr.species, !acr.species,
                     f32, f32, f32,
                     f32) -> (!acr.species, !acr.species, !acr.species)
 return %h2_o, %o2_o, %h2o_o
}
```

Define reaction $2H_2 + O_2 \rightarrow 2H_2O$



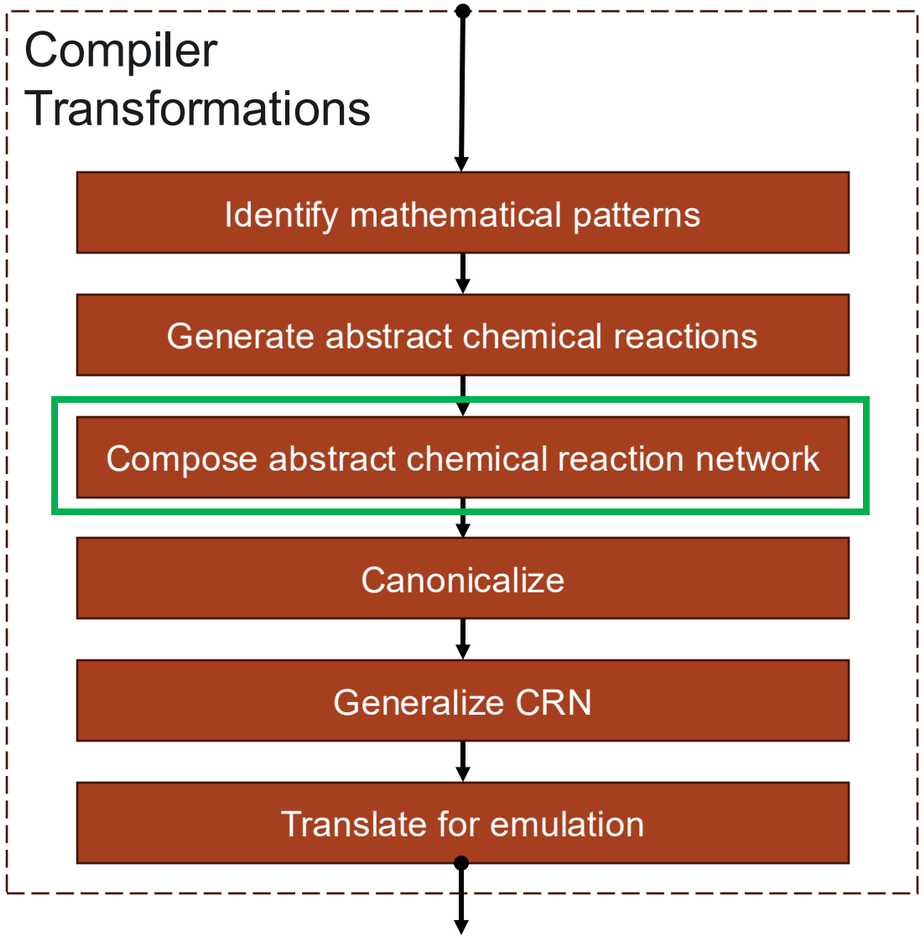
Approach to compiler support

```
// Declare reactions that were defined elsewhere
acr.reaction private @reaction_1( %h2: !acr.species, %o2: !acr.species,
   %h2o :!acr.species, %rate_constant: f32)
   -> (!acr.species, !acr.species, !acr.species)

acr.reaction private @reaction_2(%o2: !acr.species, %co: !acr.species,
                  %co2: !acr.species, %rate_2: f32)
   -> (!acr.species, !acr.species, !acr.species)

// Use reactions in a network
acr.crn @reaction_network(%h2: !acr.species, %o2: !acr.species,
                  %h2o : !acr.species, %co: !acr.species,
                  %co2: !acr.species,
                  %rate_1: f32, %rate_2: f32)
   -> (!acr.species, !acr.species, !acr.species, !acr.species, !acr.species) {
  // Instantiate reaction 1 within the network
  %h2_o, %o2_o, %h2o_o = acr.reaction_instance @reaction_1(%h2, %o2,
                                        %h2o, %rate_1)
   : (!acr.species, !acr.species, !acr.species, f32)
   -> (!acr.species, !acr.species, !acr.species)

  // Instantiate reaction 2 within the network
  %o2_o_final, %co_o, %co2_o = acr.reaction_instance @reaction_2(%o2_o, %co,
                                        %co2, %rate_2)
   : (!acr.species, !acr.species, !acr.species, f32)
   -> (!acr.species, !acr.species, !acr.species)

  // Return updated concentrations for all molecules: H2, O2, H2O, CO, and CO2
  return %h2_o, %o2_o_final, %h2o_o, %co_o, %co2_o
}
```

Instantiate CRN

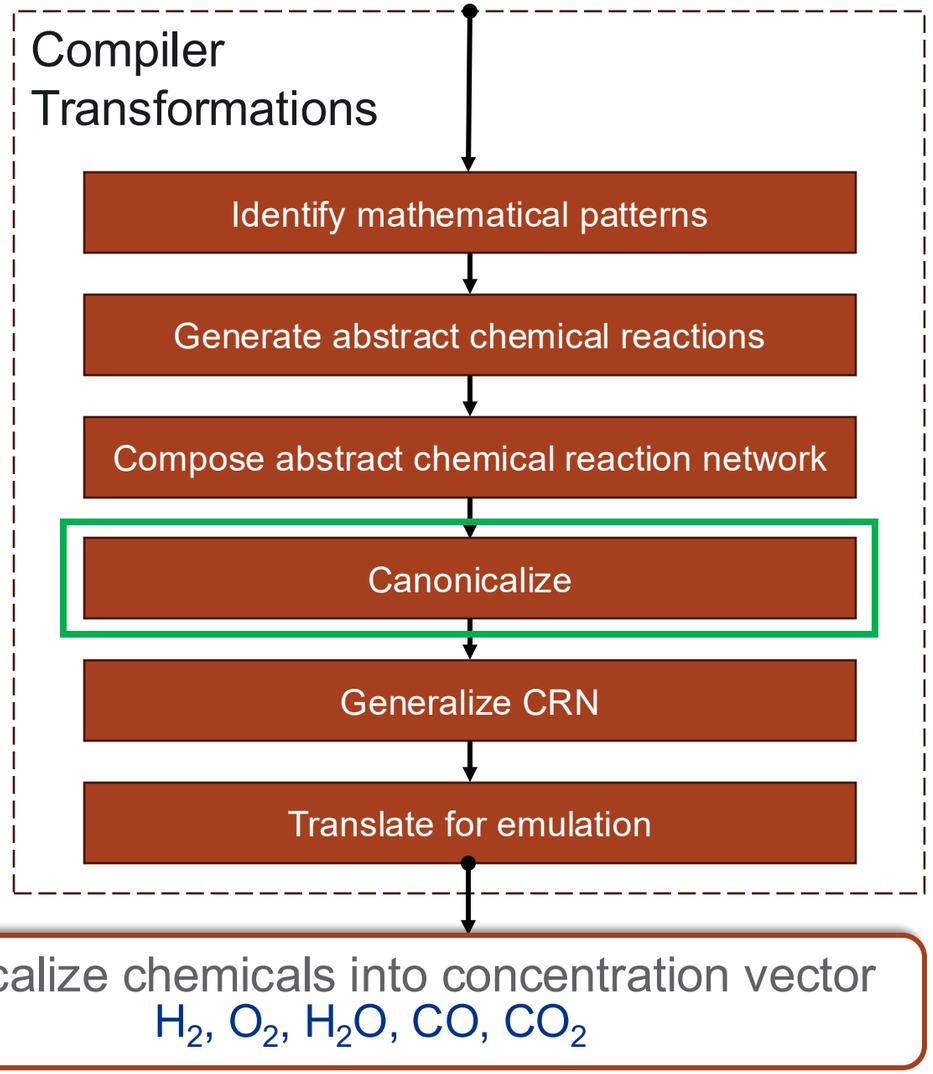
$2H_2 + O_2 \rightarrow 2H_2O$

$2CO + O_2 \rightarrow 2CO_2$



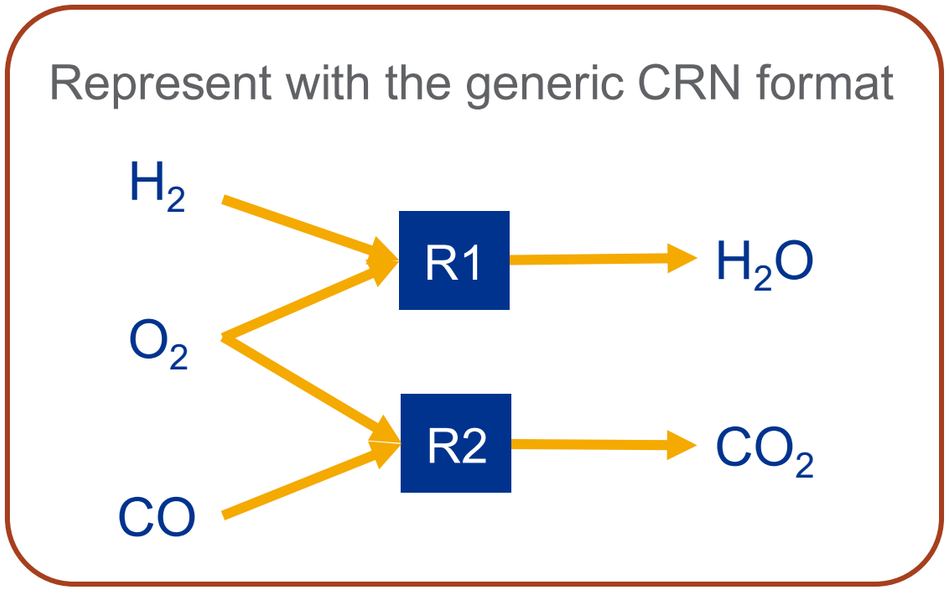
Approach to compiler support

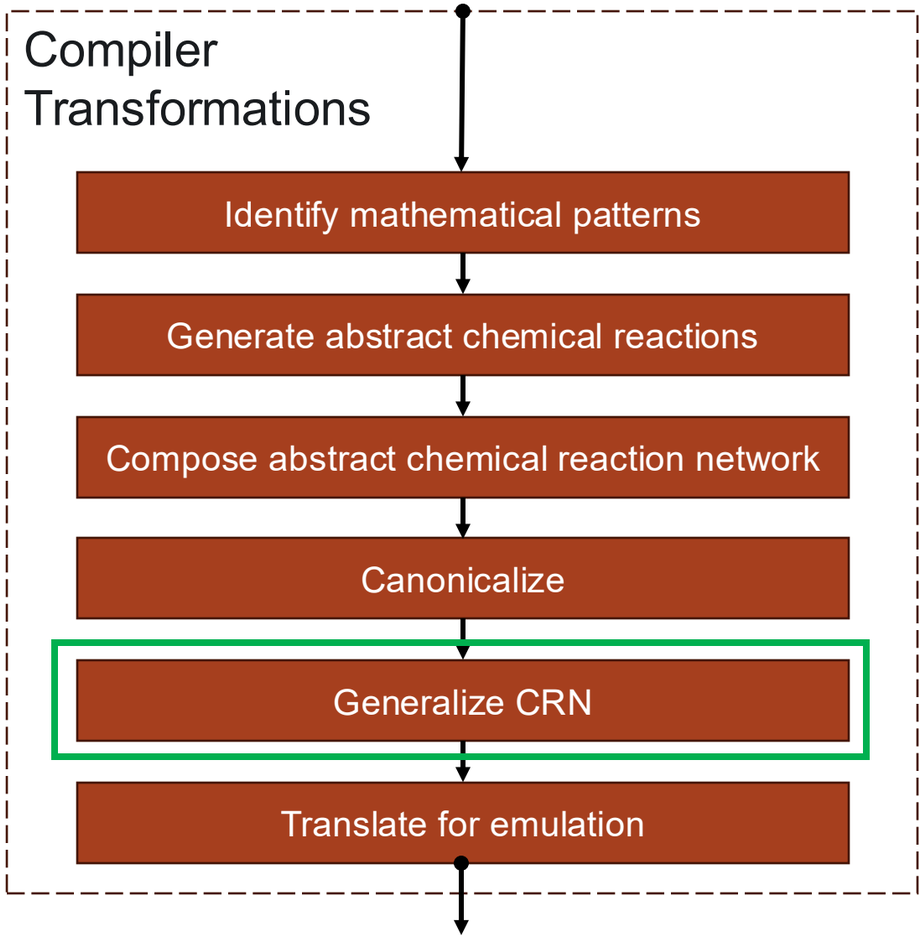
```
// Also declare @reaction_1 and @reaction_2 in canonical form
// Omitted here for conciseness...

// Define the CRN operation
acr.crn @reaction_network(%species_vec: vector<5x!acr.species>,
                          %rate_vec: vector<2xf32>)
  -> (vector<5x!acr.species>) {
 // For these 5 species: H2, O2, H2O, CO, CO2
 // Define the stoichiometry: 2H2 + O2 -> 2H2O
 //    and the stoichiometry: O2 + 2CO -> 2CO2

 // Select the subvector for reaction 1
 %subvector_r1 = vector.gather %species_vec, [0, 1, 2]
  : vector<5x!acr.species>, vector<3xindex>
 // Instantiate reaction 1 with the rate constant as an input
 %subvector_r1_out = acr.reaction_instance @reaction_1(%subvector_r1,
                                        %rate_vec[0])
  : (vector<3x!acr.species>, f32)
  -> vector<3x!acr.species>
 // Update the original species vector with the output subvector
 %species_vec_out1 = vector.scatter %species_vec, %subvector_r1_out, [0, 1, 2]
  : vector<5x!acr.species>, vector<3x!acr.species>, vector<3xindex>

 // Select the subvector for reaction 2
 %subvector_r2 = vector.gather %species_vec_out1, [1, 3, 4]
  : vector<5x!acr.species>, vector<3xindex>
 // Instantiate reaction 2 with the rate constant as an input
 %subvector_r2_out = acr.reaction_instance @reaction_2(%subvector_r2,
                                        %rate_vec[1])
  : (vector<3x!acr.species>, f32)
  -> vector<3x!acr.species>
 // Update the original species vector with the output subvector
 %species_vec_out = vector.scatter %species_vec_out1, %subvector_r2_out,
                          [1, 3, 4]
  : vector<5x!acr.species>, vector<3x!acr.species>, vector<3xindex>

 return %species_vec_out }
```



Approach to compiler support

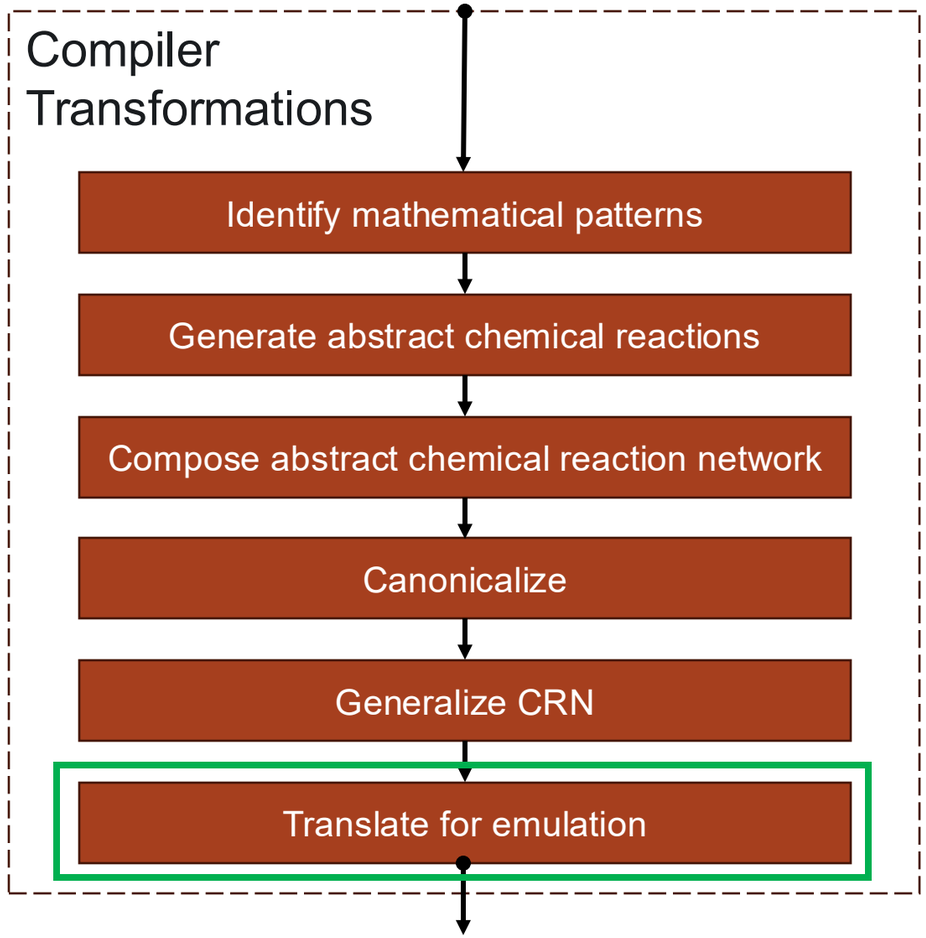
```
// A generic operation that can represent any CRN
acr.crn_generic {stoich_matrix =
[
   // With the following order of species:
   // H2, O2, H2O, CO, CO2
   [-2,-1, 2, 0, 0], //2H2 + O2 -> 2H2O
   [ 0,-1, 0,-2, 2]  //2CO + O2 -> 2CO2
] : tensor<5x2x>
 } (%species_vec: vector<5x!acr.species>, %rate_vec: vector<2xf32>)
   -> (vector<5x!acr.species>)
```





Approach to compiler support

```
{
  // Reactions are written in a list.
  // Species follow the order: H2, O2, H2O, CO, CO2
  "reactions": [
    {
      // 2H2 + O2 -> 2H2O
      // 2A + B -> 2C
      "species"   : ["A", "B", "C", "D", "E"],
      "reactants" : [2, 1, 0, 0, 0],
      "products"  : [0, 0, 2, 0, 0],
      "rate": 0.1,
      "name": "R1"
    },
    {
      // O2 + 2CO -> CO2
      // B + 2D -> 2E
      "species"   : ["A", "B", "C", "D", "E"],
      "reactants" : [0, 1, 0, 2, 0],
      "products"  : [0, 0, 0, 0, 2],
      "rate": 0.05,
      "name": "R2"
    }
  ],
  // Initial concentrations
  ”concentrations": {
     "A": 1, "B": 1, "C": 0, "D": 1, "E": 0
  },
  // List of species to track on the simulator,
  // this is the concentration that should implement our ODE
  "tracked_species": ["O2"]
}
```



Abstract reactions can be instantiated to concrete biochemical reactions

Problem → **Abstraction**

Mathematical pattern: x + y → Reaction(s)

Scientific problem: f(x) → Reaction network

Instantiated ← **Transformed**

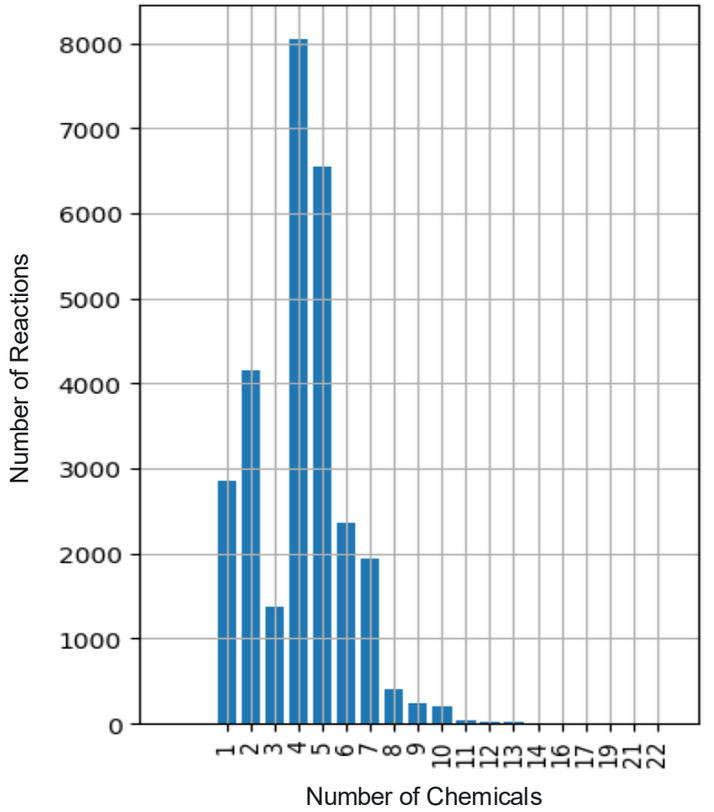
Generic form

$2H_2O \leftarrow 2H_2 + O_2$; $2C \leftarrow 2A + B$

$2CO_2 \leftarrow 2CO + O_2$; $2E \leftarrow 2D + B$

Species/Chemical concentrations

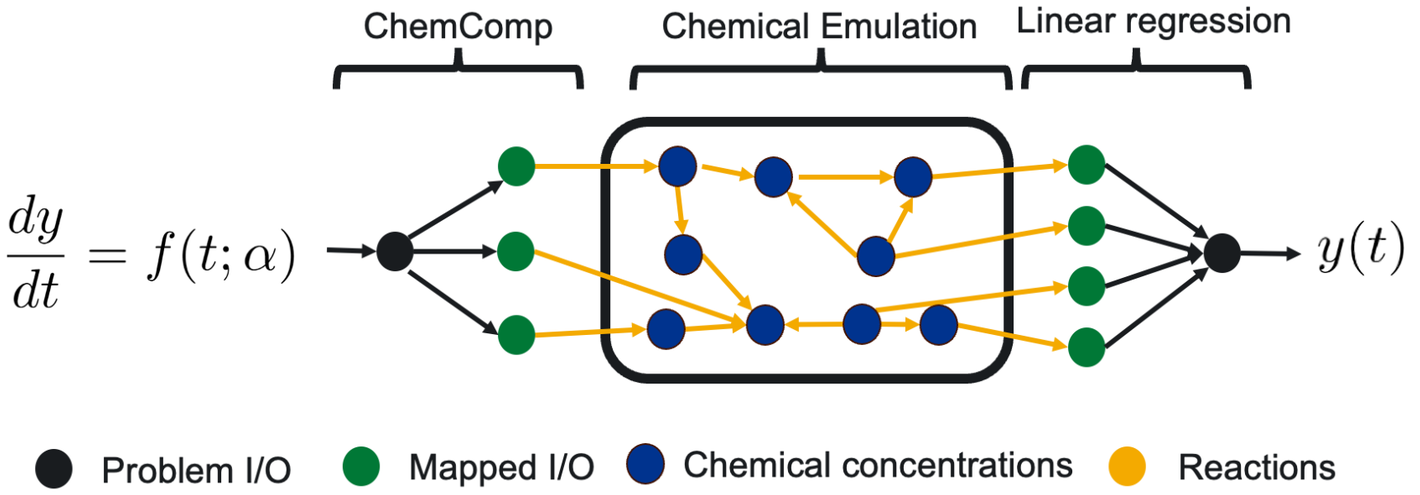
Reactions



Possible Abstract Reaction	Concrete Reaction (Motifs)
$A_2B + 2C_2 \rightleftharpoons 2A + BC_4$	$H_2S + 2O_2 \rightleftharpoons 2H + SO_4$
$2A_2B \rightarrow 2A_2 + B_2$	$2H_2O \rightarrow 2H_2\ O_2$
$AB_3 + B2C \rightarrow AB_4CB$	$NH_3 + H2O \rightarrow NH_4OH$

Emulator approach

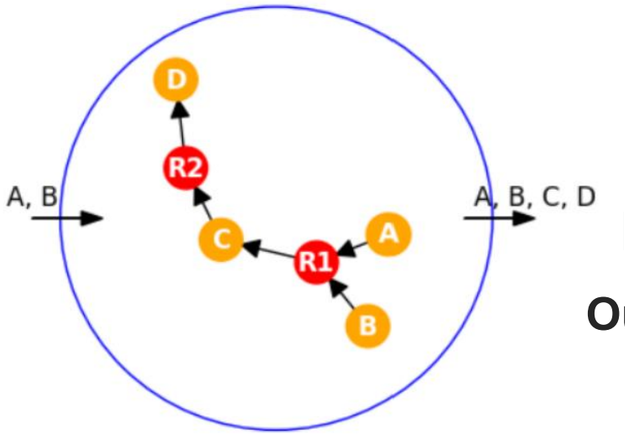
- Model device using Reservoir Computing
- Model reactions using continuum well-stirred system
- We can emulate both abstract and continuous reaction forms but are currently not considering noise



$A + B \rightarrow C$

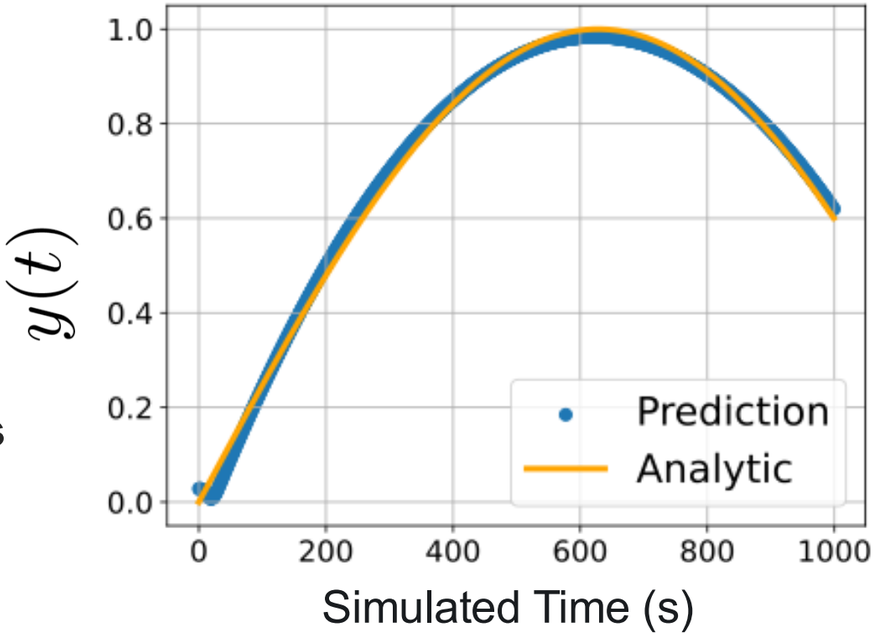
$C \rightarrow D$

Generic form



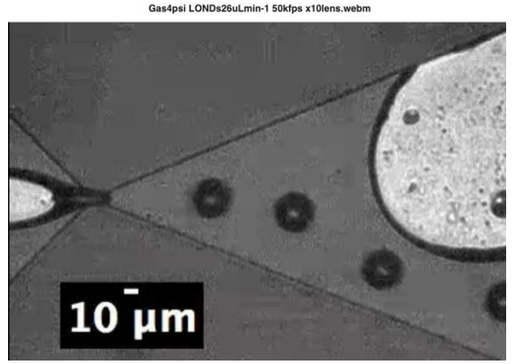
Modeled CRN

Outputs

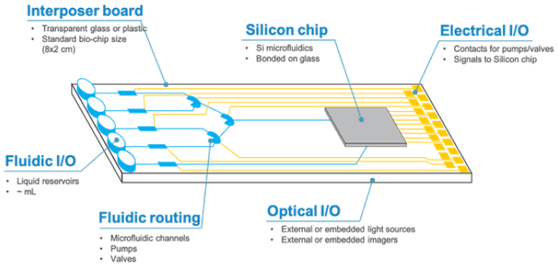


The future of bio-chemical computing devices: Scalability vs Feasibility

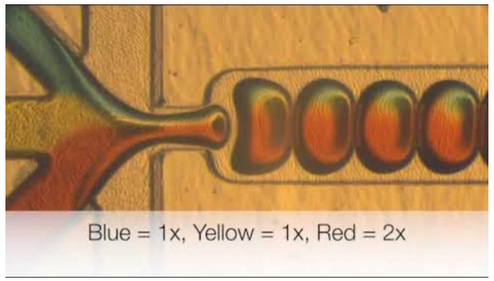
www.gaudi.ch/OpenDrop



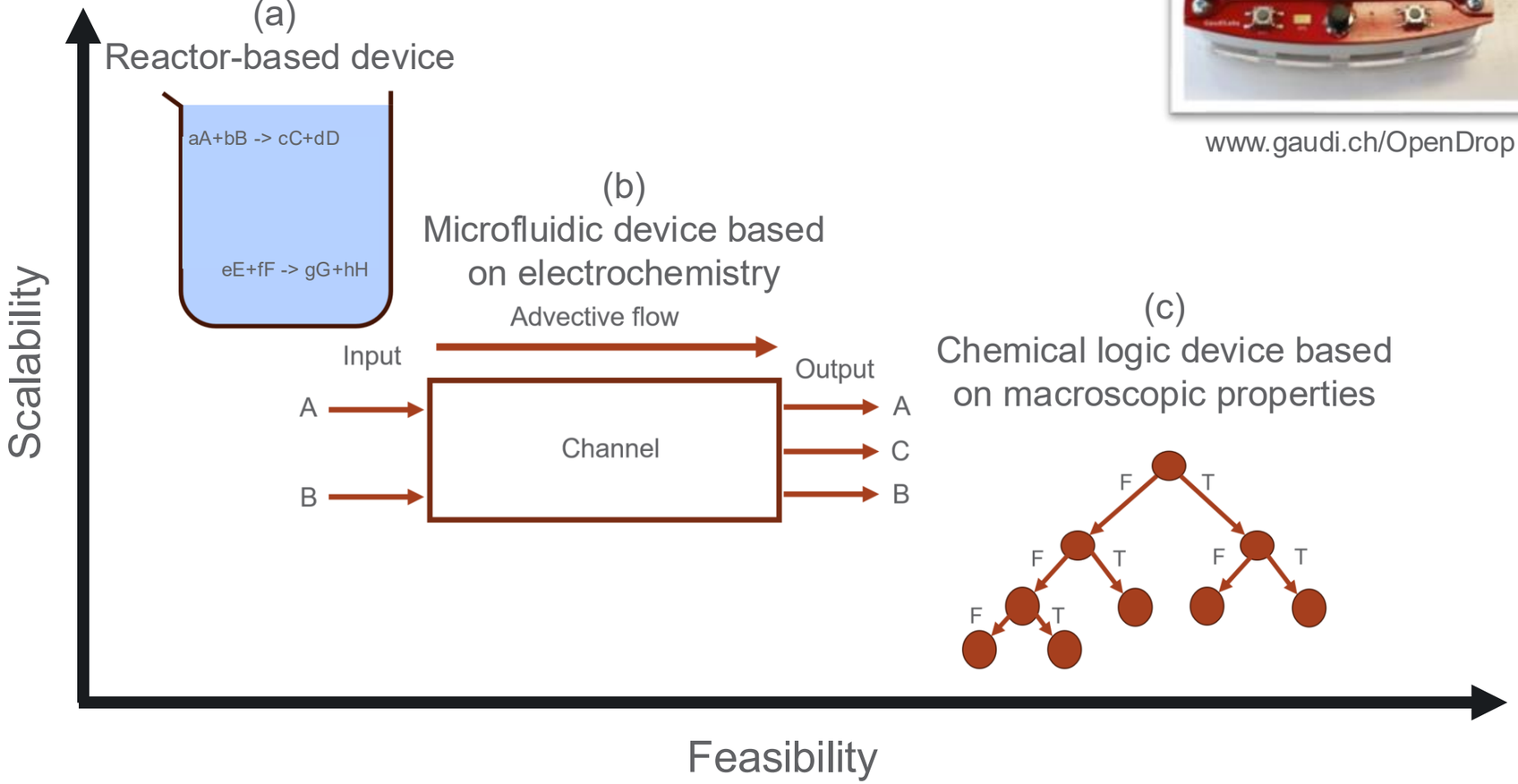
50kfps recording of droplets avoiding a bubble



Imec's lab on a chip



Content-, Size-, and rate- controlled microfluidic flow-focusing droplet generation



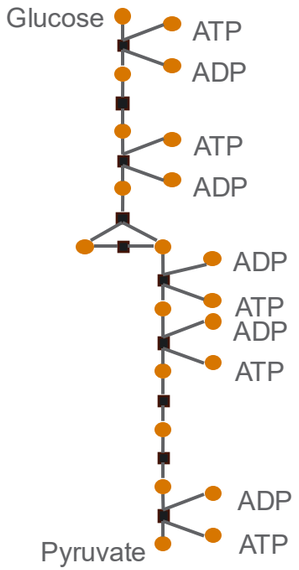
Closing the loop: Using compilers to study biochemical systems

Concrete CRN | CRN Dynamics | Abstract CRN | ODE-representation

Ordinary Differential Equations

Compiler

Chemical Reactions



d(Glucose)dt =

.
.
.
.
.

d(Pyruvate)dt =

$$0 \rightleftharpoons U$$

$$0 \longrightarrow V$$

$$2U + V \longrightarrow 3U$$

$$\frac{dy}{dt} = a - yx^2$$

$$\frac{dx}{dt} = yx^2 - x + b$$

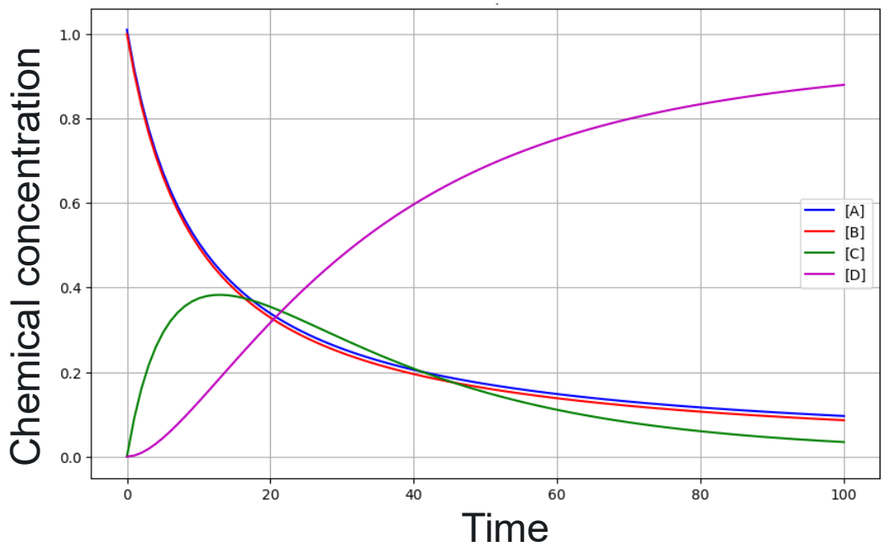
Glycolysis pathway | Complex ODE | Sel'kov-Schnakenberg reaction system | Lower-dimension model

Take-home messages

- Chemistry can be utilized for ‘unconventional’ computation with a ‘chemical advantage’

- ChemComp developed necessary compilation and emulation frameworks

- Feasibility of a CRNCM needs to consider the physics, chemistry, and math: enter Chemical Information Science (CIS)



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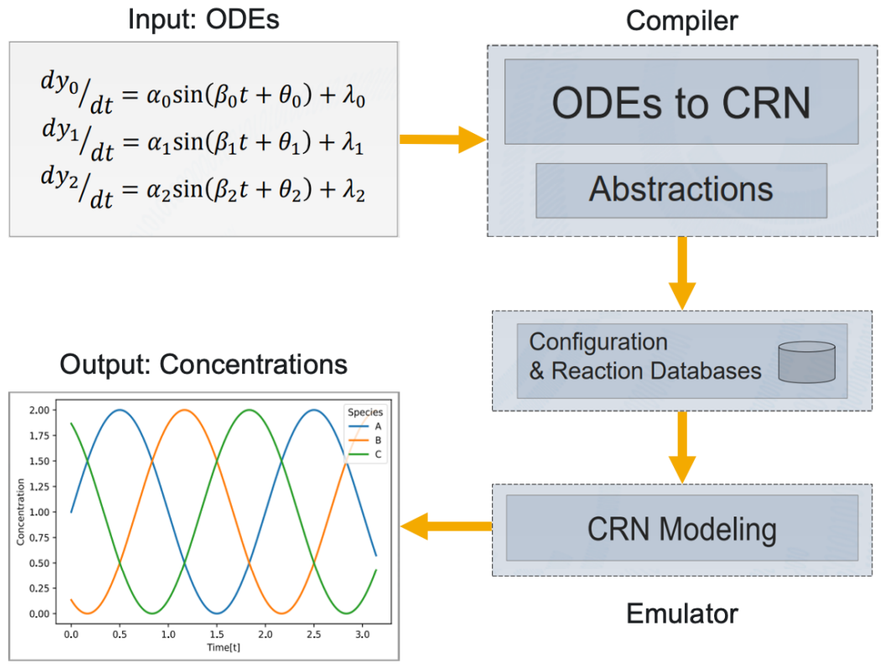

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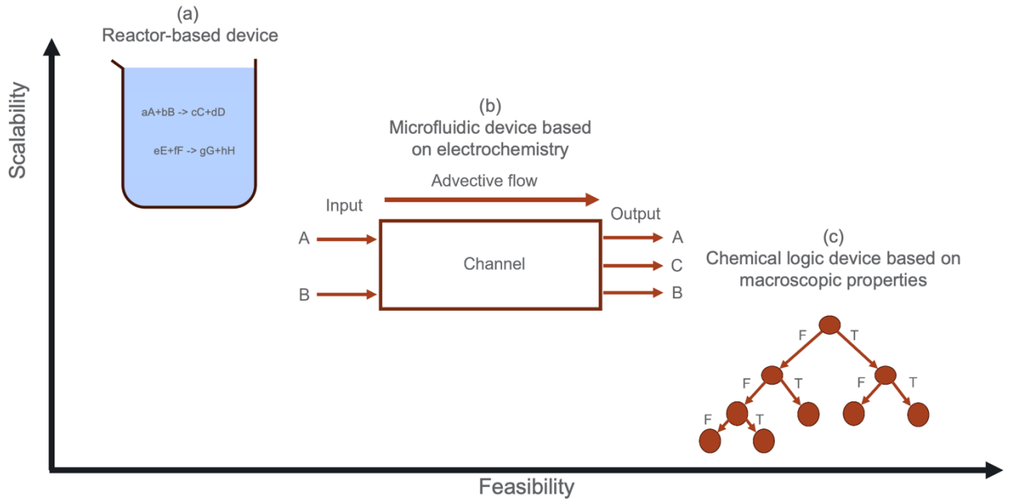

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Thank you

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