Kaemika app

Integrating protocols and chemical simulation

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CMSB 2020-09-25

Kaemika

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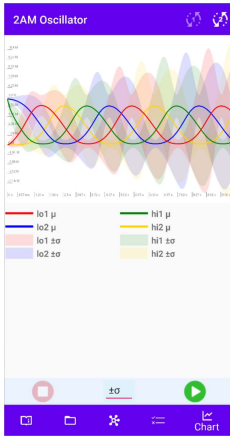
macOS

iOS

Android

Windows

GitHub



Search "Kaemika" in the app stores
http://lucacardelli.name/kaemika.html

An integrated language for chemical models & experimental protocols

- Deterministic (ODE) and stochastic (LNA) simulation
- Chemical reaction networks (CRNs) and liquid-handling protocols
- Reaction scores
- Functional scripting
- GUI

Chemical sublanguage and Simulation

CRN Models


//=====================================
// Lotka 1920, Volterra 1926
// (simplified with all rates = 1)
//=====================================
parameter x1₀ <- uniform(0,1)
parameter x2₀ <- uniform(0,1)
species x1 @ x1₀ M // prey
species x2 @ x2₀ M // predator
x1 -> x1 + x1 {1}// prey reproduces
x1 + x2 -> x2 + x2 {1}// predator eats prey
x2 -> ∅ {1}// predator dies
report x1, x2, ∅
equilibrate for 40
A+
A-
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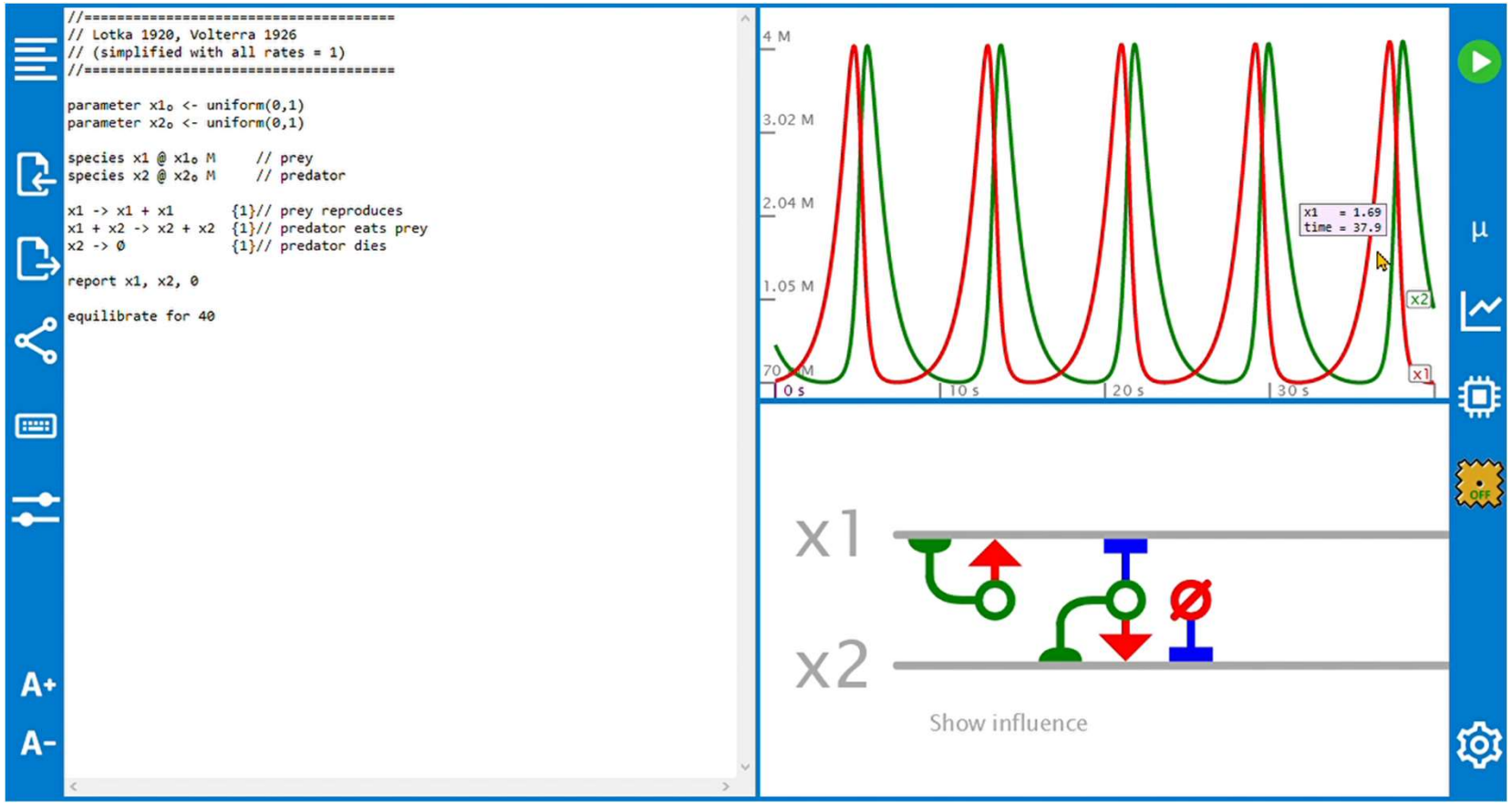
μ
OFF

CRN Models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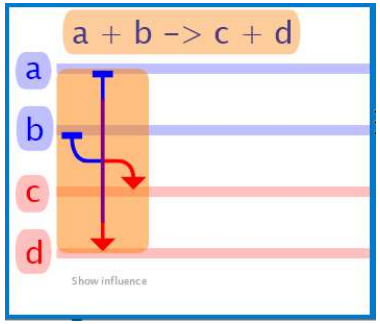
species x1 @ x1₀ M // prey
species x2 @ x2₀ M // predator
x1 -> x1 + x1 {1}// prey reproduces
x1 + x2 -> x2 + x2 {1}// predator eats prey
x2 -> ∅ {1}// predator dies
report x1, x2, ∅
equilibrate for 40
4 M
3.02 M
2.04 M
1.05 M
70 M
0 s
10 s
20 s
30 s
x1 = 1.69
time = 37.9
x2
x1
A+
A-
μ
OFF
x1
x2
Show influence

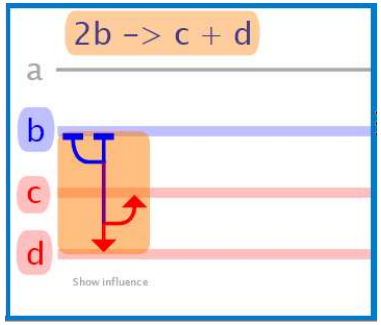
Reaction scores (graphical representation of reaction networks)

Horizonal lines: *species*. Vertical stripes: *reactions*. Blue: reagents. Red: products. Green: catalysts.

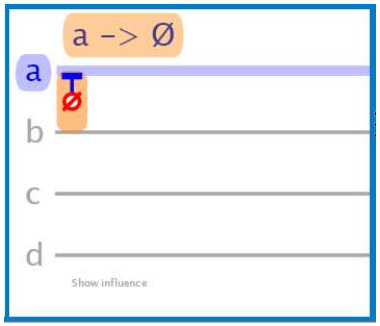
Reactants and products



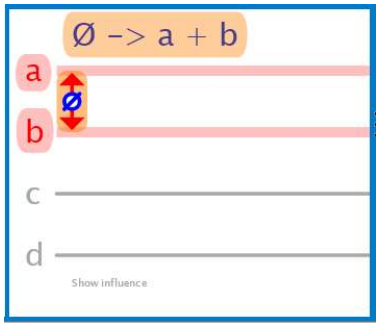
Repeated species



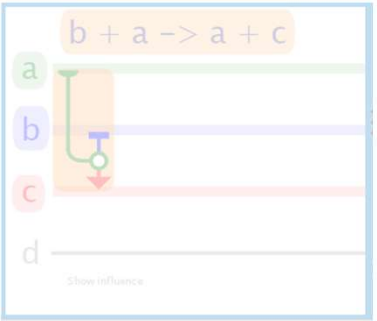
Reactants but no products



Products but no reactants

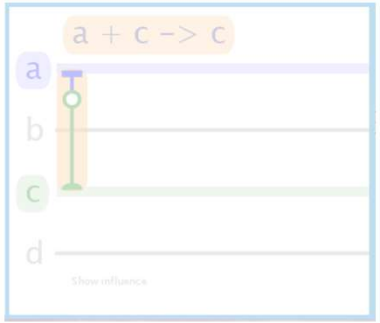


Catalyst

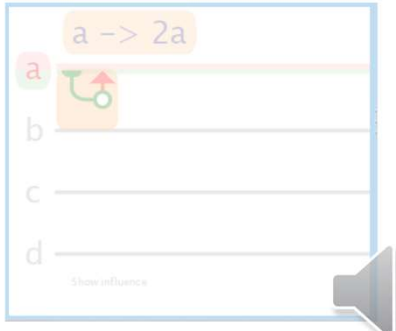


Catalyst but no reactants

Catalyst but no products



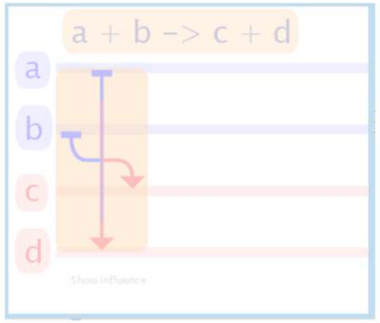
Autocatalyst



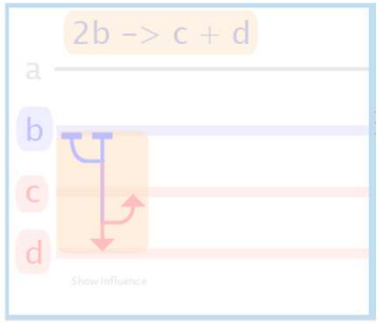
Reaction scores (graphical representation of reaction networks)

Horizonal lines: *species*. Vertical stripes: *reactions*. Blue: reagents. Red: products. Green: catalysts.

Reactants and products

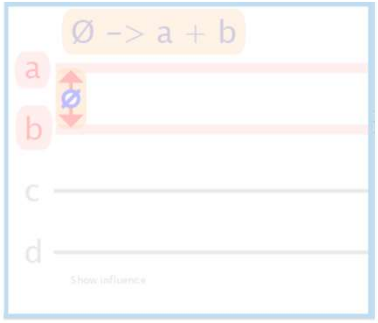


Repeated species

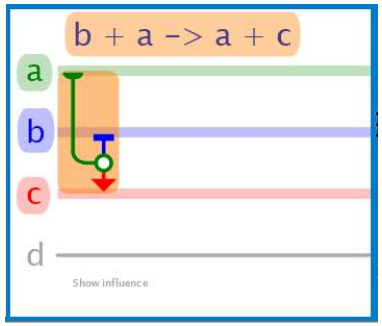


Reactants but no products

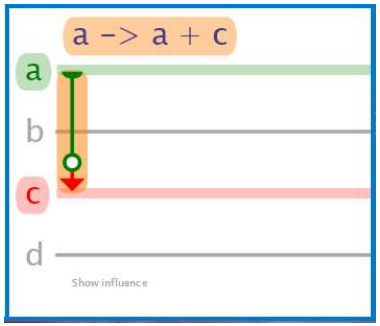
Products but no reactants



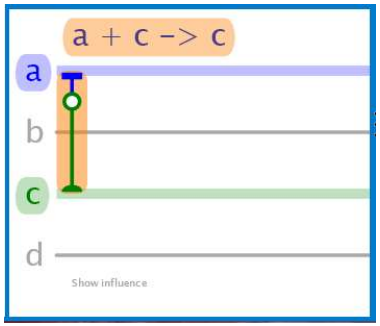
Catalyst



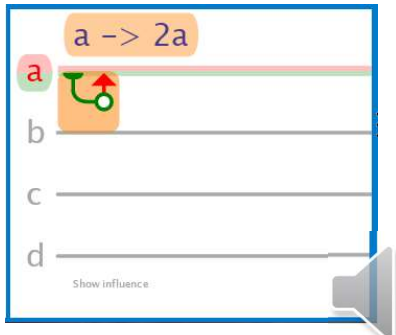
Catalyst but no reactants



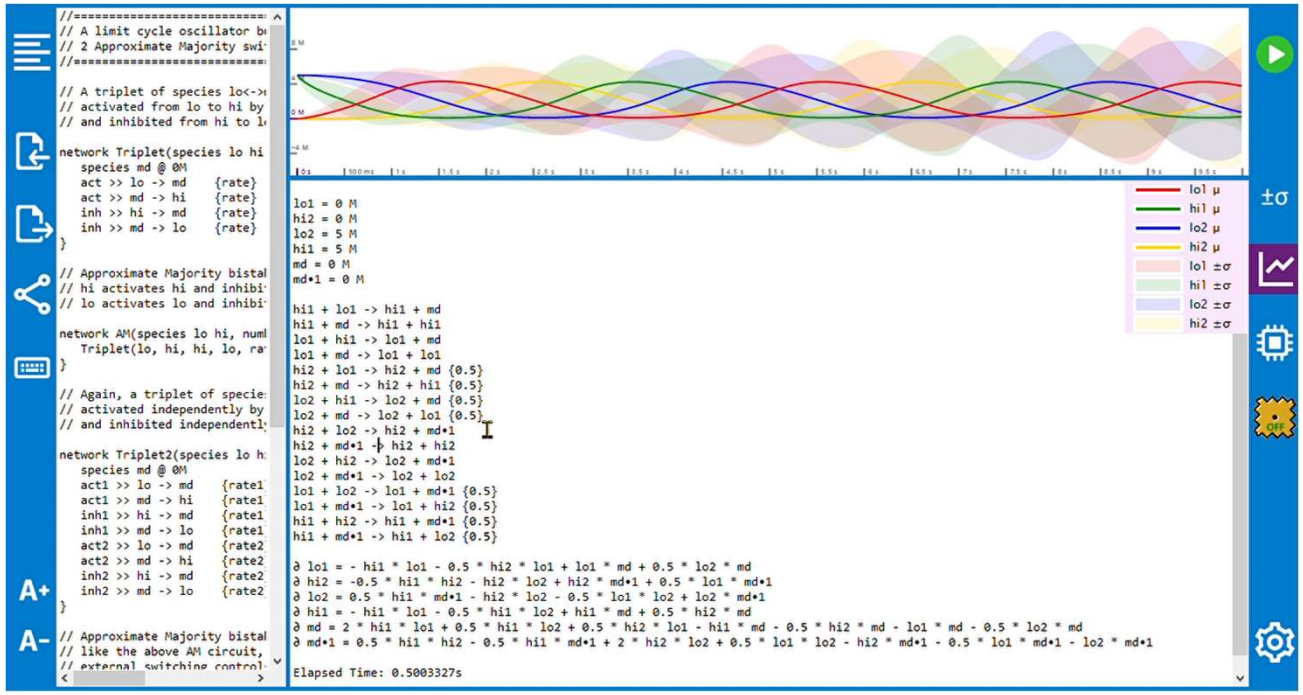
Catalyst but no products

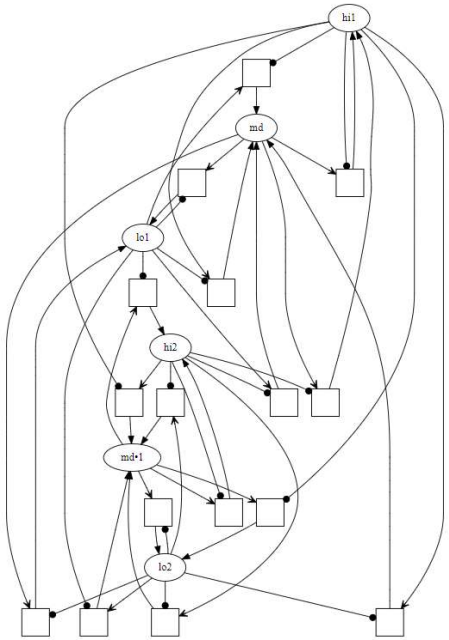


Autocatalyst



A larger reaction score





GraphViz

The Modeling Language

- Models are generated by programs

  Freely containing both chemical reactions and control flow
  Can generate unbounded-size reaction networks

- Rich data types

  numbers, *species*, *functions*, *networks*, *lists*, *flows* *(time-courses)*
  flows are composable functions of time used in ***rates***, ***plotting***, and ***observation***

- Modern abstractions

  Functional: programs take *data* as parameters and produce *data* as results
  Monadic: programs also produce *effects* (*species*, *reactions*, *liquid handling*)
  Nominal: *lexically scoped* chemical species (species are not "strings")

Ex.: Predatorial

```
//=====================================
// Creates a stack of predator-prey
// relationships in Lotka-Volterra style,
// and returns the apex predator.
//=====================================

function Predatorial(number n) {
  if n = 0 then
    define species prey @ 1 M
    prey -> 2 prey // prey reproduces
    report prey
    yield prey
  else
    define species predator @ 1/n M
    species prey = Predatorial(n-1)
    prey + predator ->{n} 2 predator
    predator -> ∅
    report predator
    yield predator
  end
}

species apexPredator = Predatorial(5)
equilibrate for 50
```

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Protocol sublanguage and Microfluidics

Describing a Protocol

- *Samples* (e.g. test tubes)
  - Are characterized by a volume and a temperature
  - Contain a specified set of species
  - Evolve according to reactions that operates on those species
  - Isolate species and reactions

- *Protocol Operations* (e.g. liquid handling)
  - Accept and produce samples
  - Accepted samples are *used up* (they can only be operated-on once)

Mix and Split

```
//=====================================
// Example of Sample Manipulation
//=====================================

species {c}

sample A {1µL, 20C}
species a @ 10mM in A
amount c @ 1mM in A
a + c -> a + a
equilibrate A1 = A for 100

sample B {1µL, 20C}
species b @ 10mM in B
amount c @ 1mM in B
b + c -> c + c
equilibrate B1 = B for 100

split C,D = A1
dispose C

mix E = D, B1
a + b -> b + b

equilibrate F = E for 1000
dispose F
```

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Ex: Phosphate-buffered saline (PBS)

```
species {NaCl#58.44, KCl#74.5513, NA2HPO4#141.96, KH2PO4#136.086}
report NaCl, KCl, NA2HPO4, KH2PO4

function Autoclave(sample PBS, number t) {
   define
      // increase temperature, preserve volume:
      regulate hot = PBS to 121C
      // bake
      equilibrate hot for t
      // decrease temperature, preserve volume:
      regulate PBS = hot to 20C
   yield PBS
}

function MakePBS() {
   define
      sample PBS {800mL, 20C}
      amount NaCl @ 8g in PBS
      amount KCl @ 0.2g in PBS
      amount NA2HPO4 @ 1.44g in PBS
      amount KH2PO4 @ 0.24g in PBS

      sample topup {200mL, 20C}
      mix PBS = PBS,topup
   yield Autoclave(PBS, 20*60)
}

sample PBS = MakePBS()
```

Cold Spring Harbor Protocols

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Recipe

Phosphate-buffered saline (PBS)

Reagent	Amount to add (for 1× solution)	Final concentration (1×)	Amount to add (for 10× stock)	Final concentration (10×)
NaCl	8 g	137 mM	80 g	1.37 M
KCl	0.2 g	2.7 mM	2 g	27 mM
Na_2HPO_4	1.44 g	10 mM	14.4 g	100 mM
KH_2PO_4	0.24 g	1.8 mM	2.4 g	18 mM
If necessary, PBS may be supplemented with the following:				
$CaCl_2 \cdot 2H_2O$	0.133 g	1 mM	1.33 g	10 mM
$MgCl_2 \cdot 6H_2O$	0.10 g	0.5 mM	1.0 g	5 mM

PBS can be made as a 1× solution or as a 10× stock. To prepare 1 L of either 1× or 10× PBS, dissolve the reagents listed above in 800 mL of H_2O. Adjust the pH to 7.4 (or 7.2, if required) with HCl, and then add H_2O to 1 L. Dispense the solution into aliquots and sterilize them by autoclaving for 20 min at 15 psi (1.05 kg/cm^2) on liquid cycle or by filter sterilization. Store PBS at room temperature.

http://cshprotocols.cshlp.org/content/2006/1/pdb.rec8247

Digital Microfluidics

- A general, *programmable*, platform to execute the main liquid-handling operations

- To close the cycle, it can support many automated observation techniques on-board or off-board via peripheral pumps (sequencing, mass spec, …) although these are all very hardware-dependent.

Digital Microfluidics

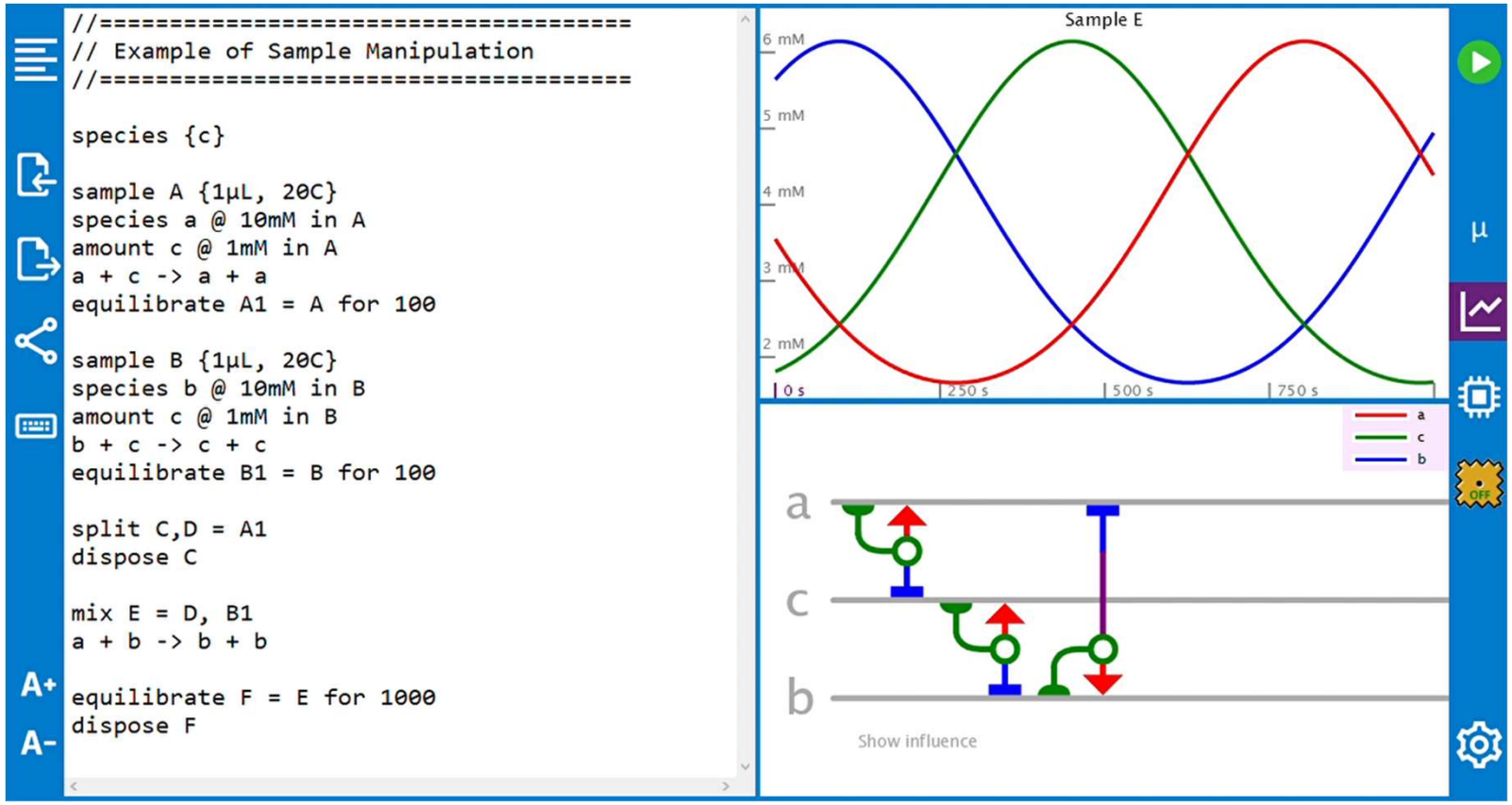
OpenDrop

https://www.youtube.com/watch?v=ncfZWqPm7-4

Speed test

https://www.youtube.com/watch?v=pSls9L_h3Q0

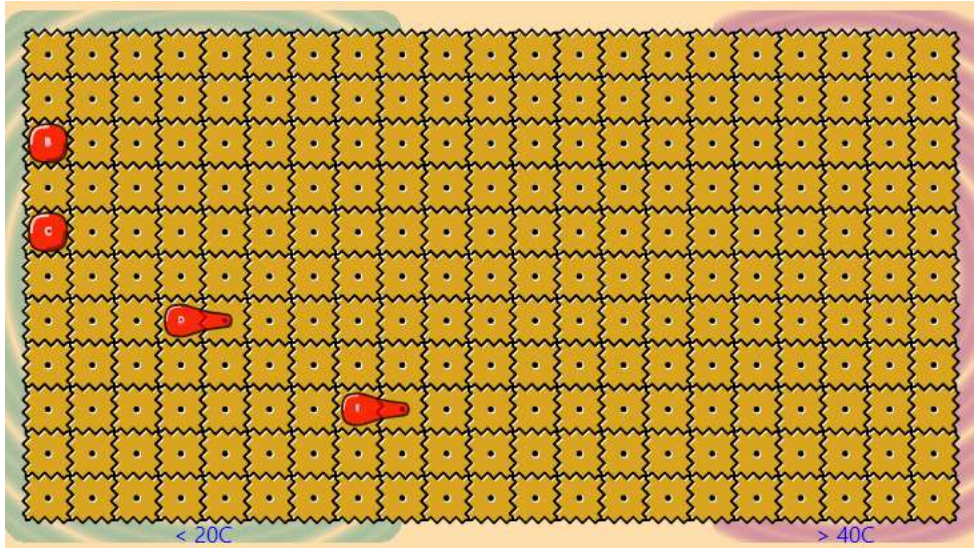
Digital Microfluidics Compiler



Digital Microfluidics Compiler

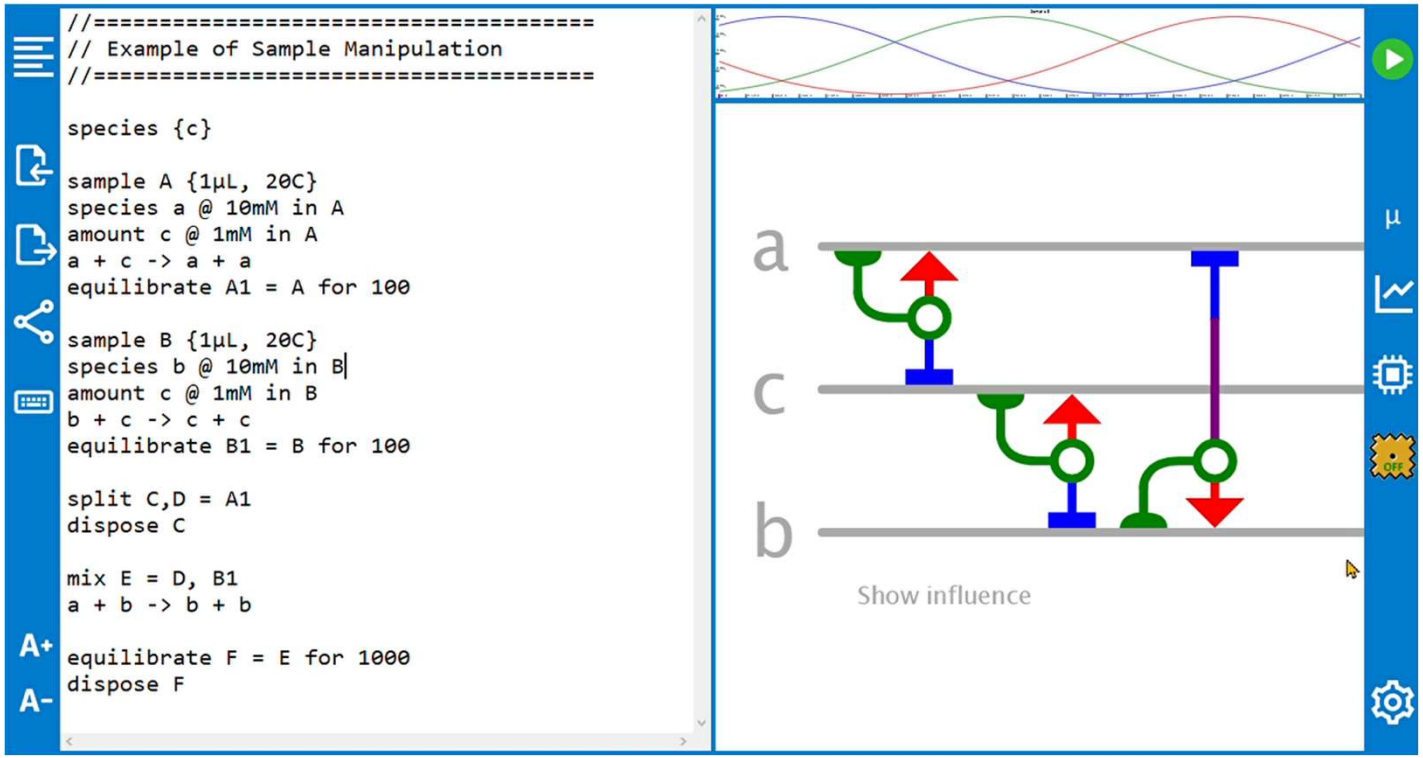
- Mix, split, equilibrate, dispose
- Automatic routing – no geometrical information
- Hot/cold zones

```
sample A {3µL, 20C}

split B,C,D,E = A

mix F = E,C,B,D

dispose F
```

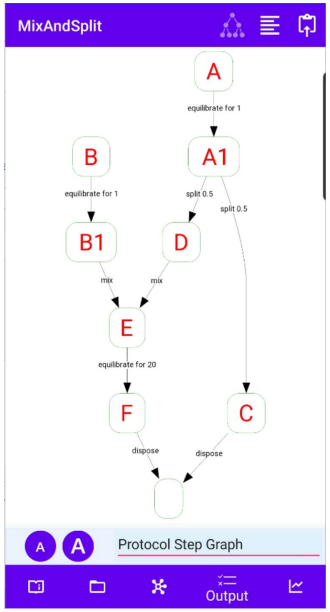


The model AND the protocol

Extracting the Model and the Protocol



The protocol



Conclusions

Experimental biological protocols with formal semantics
Alessandro Abate, Luca Cardelli, Marta Kwiatkowska,
Luca Laurenti, Boyan Yordanov. CMSB 2018.

Kaemika app - Integrating protocols and chemical simulation
Luca Cardelli. CMSB 2020.

Integrated modeling
- Of chemical reaction networks and protocols
- How the Kaemika app supports it

Closed-loop modeling, experimentation and analysis
- For complete lab automation
- To “scale up” the scientific method

Thanks to:
- Gold (parser)
- OSLO (simulator)
- C#/Xamarin (IDE)
- App reviewers

No thanks to:
- XAML (bug generator)