Kaemika app
Integrating protocols and chemical simulation

Luca Cardelli, University of Oxford
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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

Search "Kaemika" in the app stores

http://lucacardelli.name/kaemika.html
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 @ x1o M  // prey
species x2 @ x2o M  // predator

x1 -> x1 + x1  [1]// prey reproduces
x1 + x2 -> x2 + x2  [1]// predator eats prey
x2 -> 0  [1]// predator dies

report x1, x2, 0

equilibrate for 40

/kimika/
CRN Models

```r
// ------------------------------
// 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 -> 0 [1] // predator dies
report x1, x2, 0
equilibrate for 40
```

Show influence

x1
x2
Reaction scores (graphical representation of reaction networks)


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)

Horizontal lines: *species*. Vertical stripes: *reactions.*  

**Reactants and products**

- \(a + b \rightarrow c + d\)
- \(2b \rightarrow c + d\)

**Repeated species**

- \(a \rightarrow c + d\)
- \(\emptyset \rightarrow a + b\)

**Reactants but no products**

- \(a \rightarrow \emptyset\)
- \(a \rightarrow a + c\)
- \(a + c \rightarrow \emptyset\)
- \(a \rightarrow 2a\)

**Products but no reactants**

- Catalyst
- Catalyst but no reactants
- Catalyst but no products
- Autocatalyst
A larger reaction score
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

```javascript
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 -> Ø
        report predator
        yield predator
    end
}

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

c
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
Ex: Phosphate-buffered saline (PBS)

```plaintext
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()
```

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

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

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

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

split C,D = A1
dispose C

mix E = D, B1
a + b -> b + b
equilibration F = E for 1000
dispose F
Digital Microfluidics Compiler

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

```plaintext
sample A {3µL, 20°C}
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

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

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

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

split C,D = A1
dispose C
mix E = D, B1
a + b -> b + b
equilirate F = E for 1000
dispose F
```

Show influence

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The protocol
Conclusions

**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

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**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.

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

**No thanks to:**
- XAML (bug generator)