Project proposal

Accelerating Biochemical reaction models: A neural Gillespie Algorithm

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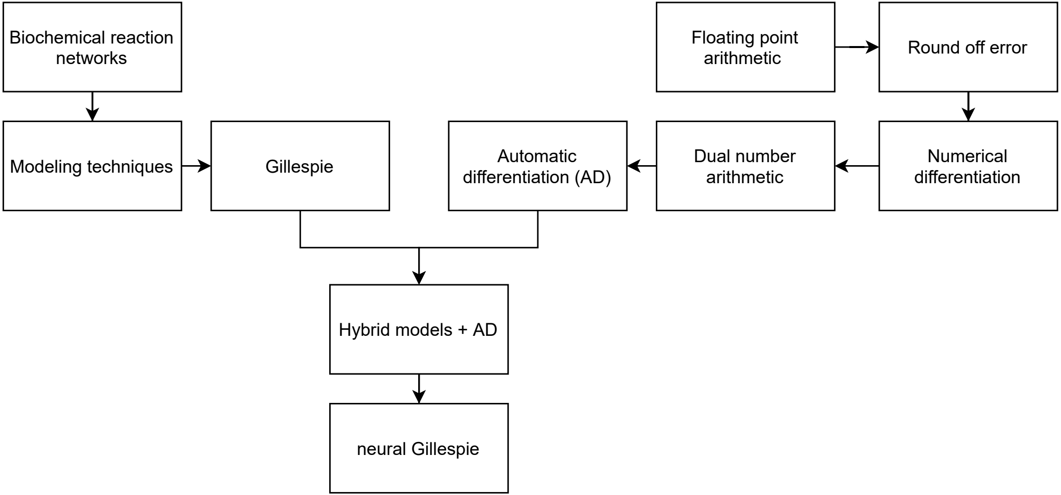
MELBOURNE

Talk overview



Biochemical reaction networks
Modeling techniques
Gillespie
Floating point arithmetic
Round off error
Numerical differentiation
Dual number arithmetic
Automatic differentiation (AD)
Hybrid models + AD
neural Gillespie

Disclaimer

- Presentation of a proposal → We haven't actually done anything yet.
- Subjective objective:
  - Collect thoughts.
  - Where do we see potential?
  - Come up with a plan.
- Present and discuss with group. → Feedback is very welcome.

Modeling biochemical reaction networks

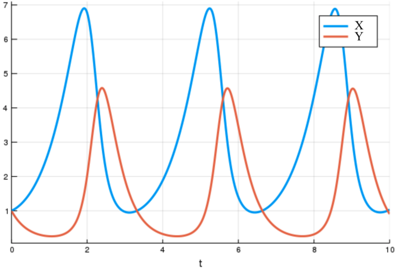
Example: Lotka -Volterra model

$$Y_1 \xrightarrow{k_1} 2Y_1,$$

$$Y_1 + Y_2 \xrightarrow{k_2} 2Y_2,$$

$$Y_2 \xrightarrow{k_3} \emptyset,$$

where Y_1, Y_2 are species and k_1, k_2, k_3 are rate constants.



Mass-action kinetics

→ Use them to formulate **rates** based on the reactions and rate constants.
→ These laws hold **only** under certain physical assumptions, such as "large molecule numbers for all species". [1]

Example: Second reaction of LV model:

- Reaction: $Y_1 + Y_2 \xrightarrow{k_2} 2Y_2$
- Rate based on mass action kinetics: $k_2[Y_1][Y_2]$

Deterministic, continuous case:

- We are not counting molecules but species are measured as e.g. moles/liter.
- Using mass-action kinetics, we can get ODE models.
- This *can* be good starting point as approximation even if we know the true process is discrete and stochastic.

[1] Details in e.g. D Schnoerr, G Sanguinetti, R Grima , "Approximation and inference methods for stochastic biochemical kinetics", Journal of Physics A: Mathematical and Theoretical, 2017.

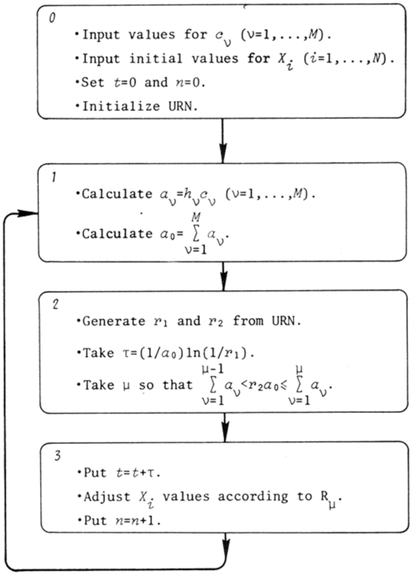
Stochasticity and discrete nature of true process

- Generally: Impact of stochasticity and discrete nature of the true process too significant to solely rely on "macroscopic" view via deterministic approximation.
- From molecular perspective: Time evolution of current state of the system is continuous time **Markov process with discrete state space**.
- Extension to stochastic mass-action kinetics:
  → Construct stochastic rates, based on reactions and rate constants.

Example: Second reaction of LV model:

- Reaction: $Y_1 + Y_2 \xrightarrow{k_2} 2Y_2$
- Rate based on stochastic mass action kinetics: $k_2 y_1 y_2$

Gillespie algorithm (Gillespie, 1977)



0

- Input values for c_ν $(\nu=1,\dots,M)$.
- Input initial values for X_i $(i=1,\dots,N)$.
- Set $t=0$ and $n=0$.
- Initialize URN.

1

- Calculate $a_\nu=h_\nu c_\nu$ $(\nu=1,\dots,M)$.
- Calculate $a_0=\sum_{\nu=1}^{M} a_\nu$.

2

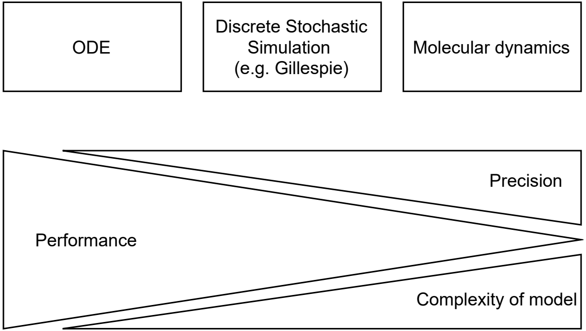
- Generate r_1 and r_2 from URN.
- Take $\tau=(1/a_0)\ln(1/r_1)$.
- Take μ so that $\sum_{\nu=1}^{\mu-1} a_\nu < r_2 a_0 \leqslant \sum_{\nu=1}^{\mu} a_\nu$.

3

- Put $t=t+\tau$.
- Adjust X_i values according to R_μ.
- Put $n=n+1$.

- Based on reactions and rates → Make exact simulation of true process.
- Most famous way to do this: → Gillespie algorithm.
- A single Gillespie simulation: → An **exact** sample from the probability mass function that is the solution of the master equation.

Context and limitations of Gillespie algorithm



ODE

Discrete Stochastic Simulation (e.g. Gillespie)

Molecular dynamics

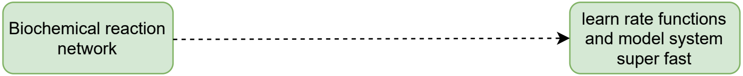
Precision

Performance

Complexity of model

- Models ever reaction event → Can be very slow.
- Biggest limitation: Speed.

Goal of project: Develop a new approach to make Gillespie faster.



Biochemical reaction network

learn rate functions and model system super fast

How? Using a neural approach.

Differentiating the Gillespie algorithm

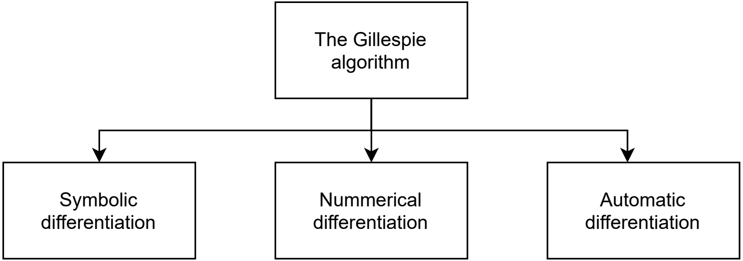
Question: What is the derivative with respect to p, where p is in the rate but not in the update function?

Example: Second reaction of LV model:

- Reaction: $Y_1 + Y_2 \xrightarrow{k_2} 2Y_2$
- Rate based on stochastic mass action kinetics: $k_2 y_1 y_2$
- p could be for example k_2.

→ So p influences distribution of dt.
Reminder: $\Delta t = rand(Exp(sum(\textbf{rates})))$

How do we differentiate something like this?



Numerical differentiation

Example:

- For function $f : \mathbb{R} \to \mathbb{R}$, the numerical differentiation via **finite differences** is given by,

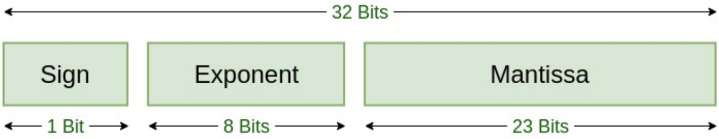
  $$f'(x) = \lim_{h \to 0} \frac{f(x+h) - f(x)}{h}$$

  where h represents a small change in x, $x \in \mathbb{R}$.
- Smaller step size h → better approximation.

The floating-point arithmetic

Floating-point arithmetic:
Representation of real numbers via floating-point arithmetic as an approximation (In Julia: e.g. Float32):

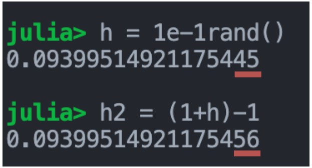
$$x = -32 * 10^{-5}$$



- Finite number of bits to save the real number x (trade off between range and precision).

Round off error

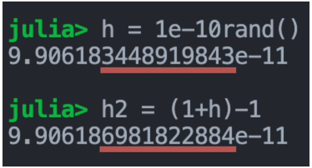
- One would assume: For $h \in \mathbb{R}$, it holds that (1+h)-1=h.
- Code example: Fix h and then do h2 = (1+h)-1. Question: Is h==h2?



```
julia> h = 1e-1rand()
0.09399514921175445

julia> h2 = (1+h)-1
0.09399514921175456
```

Make h smaller



```
julia> h = 1e-10rand()
9.906183448919843e-11

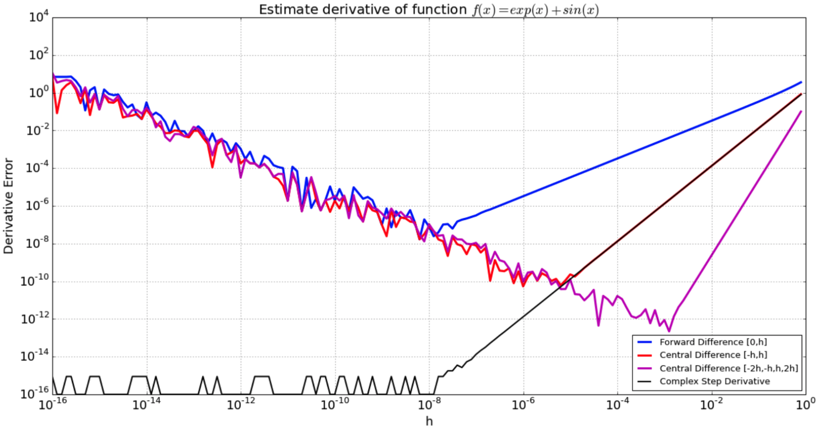
julia> h2 = (1+h)-1
9.906186981822884e-11
```

- Number of lost digits increases as the two numbers become more different.

$$\begin{array}{cccccccc} & 5 & 0 & 0 & 0 & & \\ + & & 0 & 0 & 1 & . & 1 \\ \hline & 5 & 0 & 0 & 1 & & \end{array} \qquad \begin{array}{cccccc} & 5 & 0 & 0 & . & 0 \\ + & 0 & 0 & 1 & . & 1 \\ \hline & 5 & 0 & 1 & . & 1 \end{array}$$

- Large number + small number (such as a very small h) → Large round off error.

Round off error in numerical differentiation



- Floating point representation + numerical differentiation can be very dangerous.
- Focus on black line! → Here round off error not there. Why?

Complex step differentiation: Differencing in a different dimension

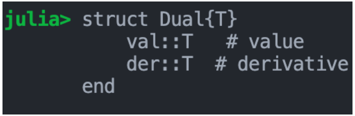
- Idea: Let $x \in \mathbb{R}$ and $f : \mathbb{R} \to \mathbb{R}$ analytic.
  $\to$ We want to calculate the *real* derivative wrt x.
- Taylor series expansion (in complex direction): → Add perturbation h to x, but in complex direction.

$$f(x+ih) = f(x) + f'(x)ih + \mathcal{O}(h^2) \iff if'(x) = \frac{f(x+ih) - f(x)}{h} + \mathcal{O}(h)$$

$$\iff f'(x) = \frac{Im(f(x+ih))}{h} + \mathcal{O}(h).$$

- Note h never directly interacts with x as in the **two dimensions of the complex numbers**. → Keeping small perturbation separate form large ones.
- In code: h and x – as the real and imaginary part of a complex number – are stored in two different floating point representations (e.g. **two** Float64).
- This method brings us to automatic differentiation: AD extends the idea of complex step differentiation beyond complex analytic functions.

New arithmetic: Dual numbers



```
julia> struct Dual{T}
           val::T   # value
           der::T  # derivative
       end
```

Idea: Derivative measures **sensitivity** of function: How much changes the function output when input changes by small ϵ

$$f(a+\epsilon) = f(a) + \epsilon f'(a) + o(\epsilon).$$

Formally set: $\epsilon^2 = 0$ and function f be will represented by value $f(a)$ and the derivative $f'(a)$, encoded as the coefficients of a degree-1 Taylor polynomial in ϵ:

$$\rightsquigarrow f(a+\epsilon) = f(a) + \epsilon f'(a).$$

→ Set rules for functions on dual numbers[2].

[2] John L. Bell, ''A Primer of Infinitesimal Analysis'', Cambridge University Press, 2008.

Functions of dual objects

Given

$$f(a+\epsilon) = f(a) + \epsilon f'(a)$$

and

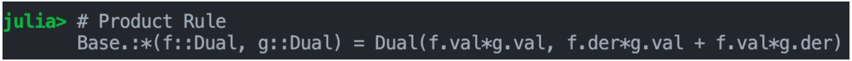
$$g(a+\epsilon) = g(a) + \epsilon g'(a)]$$

we manipulate the Taylor expansions to combine the functions.

Sum rule:

$$(f+g) = [f(a)+g(a)] + \epsilon[f'(a)+g'(a)]$$

Product rule:



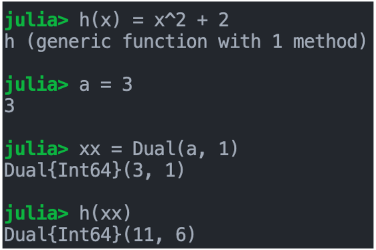
```
julia> # Product Rule
       Base.:*(f::Dual, g::Dual) = Dual(f.val*g.val, f.der*g.val + f.val*g.der)
```

→ Infer derivatives by taking the component of ϵ.

Example differentiation

→ Based on arithmetic of dual numbers, we can differentiate an arbitrary function h.

→ We present $a + \epsilon$ as Dual(a,1) which gives Dual(h(a),h'(a)) when applying h to it.



```
julia> h(x) = x^2 + 2
h (generic function with 1 method)

julia> a = 3
3

julia> xx = Dual(a, 1)
Dual{Int64}(3, 1)

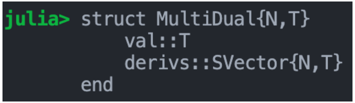
julia> h(xx)
Dual{Int64}(11, 6)
```

Test:$h(a) = 11,\ h'(a) = 2a = 6$ → Correct.

Extension: Higher dimensional functions

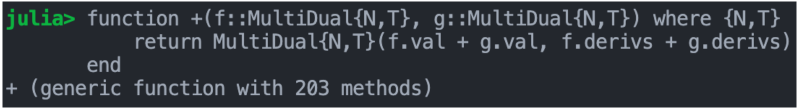
- Differentiating functions where $gg : \mathbb{R}^n \to \mathbb{R}$ such as $gg(x, y) = x^2 * y + x + y$
- In AD, we add n independent partial derivative components to dual numbers:

Multidimensional dual number in julia:



```
julia> struct MultiDual{N,T}
           val::T
           derivs::SVector{N,T}
       end
```

Defining primitive functions on them (via multiple dispatch):



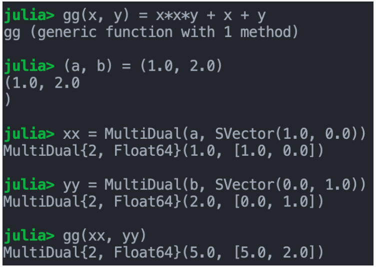
```
julia> function +(f::MultiDual{N,T}, g::MultiDual{N,T}) where {N,T}
           return MultiDual{N,T}(f.val + g.val, f.derivs + g.derivs)
       end
+ (generic function with 203 methods)
```

AD on higher dimensional functions

$$gg(x, y) = x^2 * y + x + y.$$

Example: $(x, y) = (a, b)$ where $a = 1, b = 2$.

- $gg(x, 2) = x^2 * 2 + x + 2 \iff gg(x, 2) = 2x^2 + x \xrightarrow{diff_x} gg'(x) = 4x + 1$
- $gg(1, y) = 1^2 * y + 1 + y \iff gg(1, y) = 2y + 1 \xrightarrow{diff_y} gg'(x) = 2$



```
julia> gg(x, y) = x*x*y + x + y
gg (generic function with 1 method)

julia> (a, b) = (1.0, 2.0)
(1.0, 2.0
)

julia> xx = MultiDual(a, SVector(1.0, 0.0))
MultiDual{2, Float64}(1.0, [1.0, 0.0])

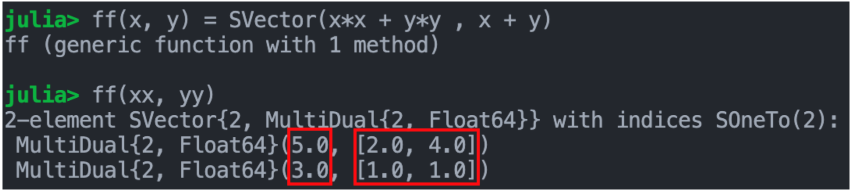
julia> yy = MultiDual(b, SVector(0.0, 1.0))
MultiDual{2, Float64}(2.0, [0.0, 1.0])

julia> gg(xx, yy)
MultiDual{2, Float64}(5.0, [5.0, 2.0])
```

Test:$gg(1, 2) = 2 + 1 + 2 = 5$, $gg'(1, 2) = (4x + 1, 2) = (5, 2) \rightarrow$ Correct.

Differentiating functions with multiple outputs

- Differentiating functions where $ff : \mathbb{R}^n \to \mathbb{R}^m$ such as $ff(x, y) = (x * x + y * y, x + y)$.
- In AD, we add calculate the mXn matrix of partial derivative components (e.i the Jacobian):



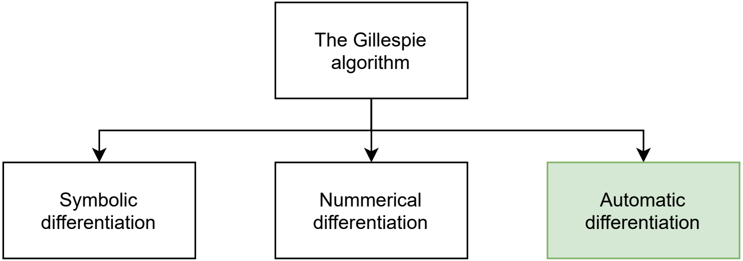
```
julia> ff(x, y) = SVector(x*x + y*y , x + y)
ff (generic function with 1 method)

julia> ff(xx, yy)
2-element SVector{2, MultiDual{2, Float64}} with indices SOneTo(2):
 MultiDual{2, Float64}(5.0, [2.0, 4.0])
 MultiDual{2, Float64}(3.0, [1.0, 1.0])
```

In red: Value and partial derivatives.

Summary: Dual numbers and AD + Back to Gillespie

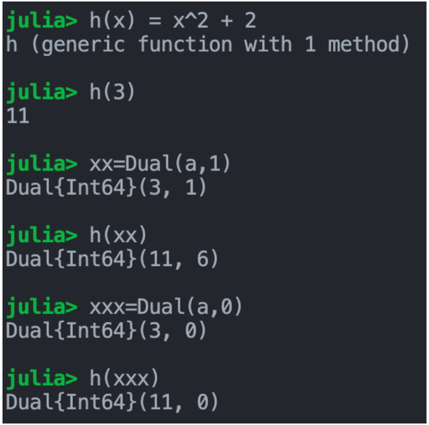
Question: What is the derivative of the Gillespie algorithm with respect to p, where p is in the rate but not in the update function?
Answer: AD takes a program → recompiles it in this different arithmetic of dual number → Accurate and fast calculation of directional derivatives.



Problematic with AD and Gillespie

- Δt is a constant.
- not dual → derivative part of dual is zero.

→ this breaks the whole differentiation chain.



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h (generic function with 1 method)

julia> h(3)
11

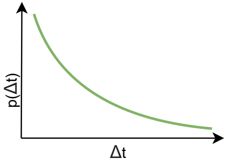
julia> xx=Dual(a,1)
Dual{Int64}(3, 1)

julia> h(xx)
Dual{Int64}(11, 6)

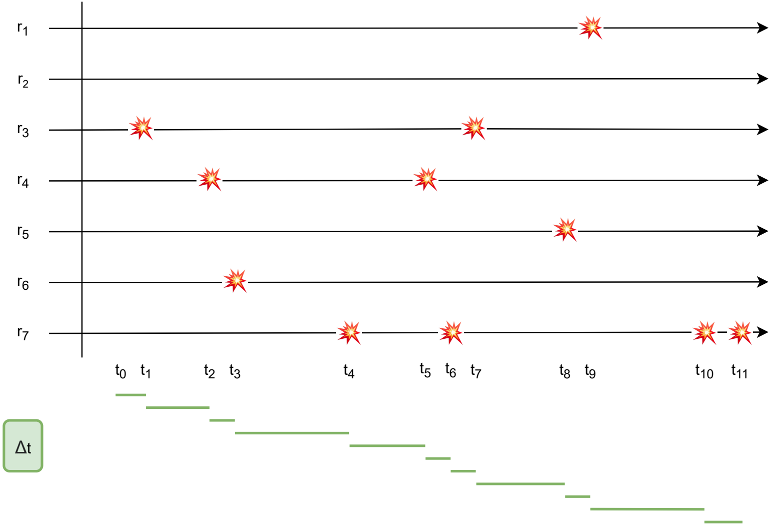
julia> xxx=Dual(a,0)
Dual{Int64}(3, 0)

julia> h(xxx)
Dual{Int64}(11, 0)
```

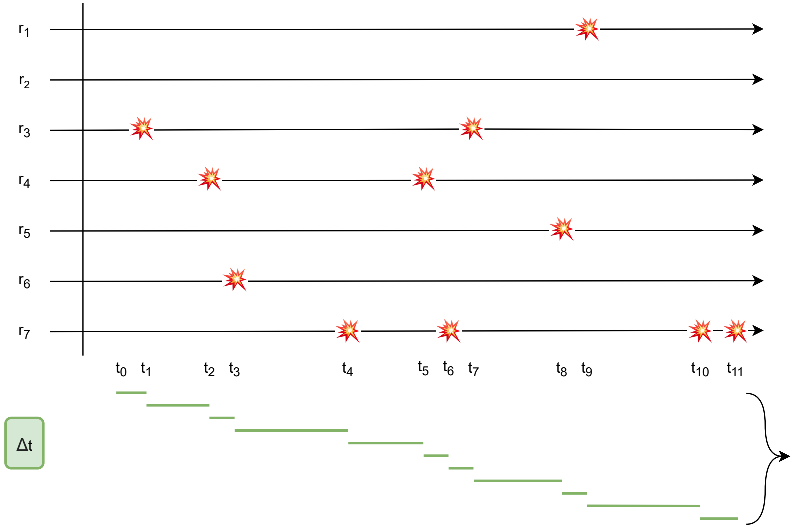
1. Gillespie: SSA



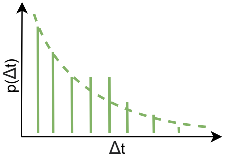
p(Δt) =exp(sum(rates))



1. Gillespie: SSA

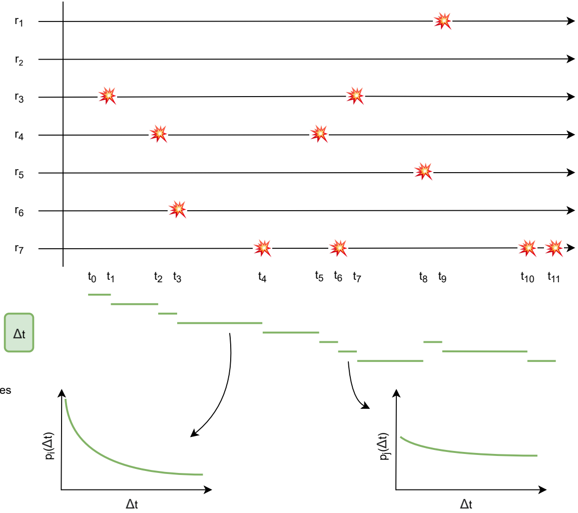


1.a. Constant rates



p(Δt) =exp(sum(rates))

1. Gillespie: SSA

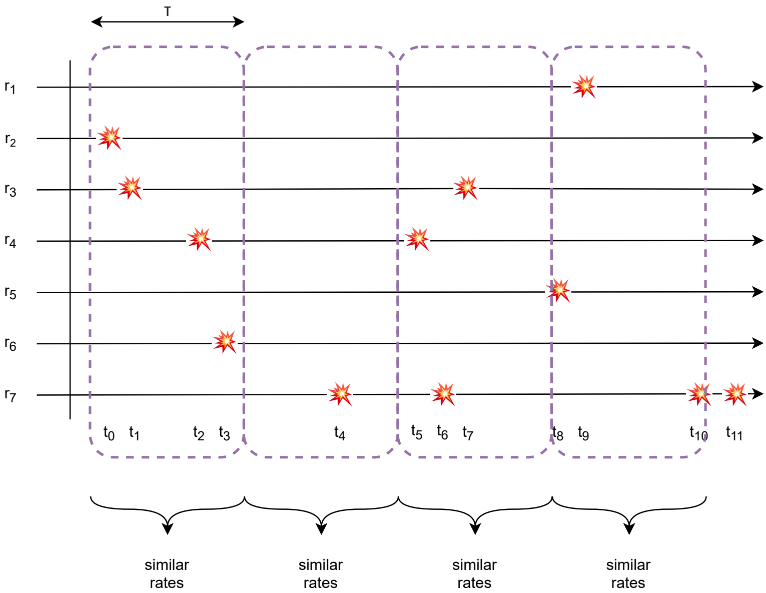


1.b. Non-constant rates

$p_i(\Delta t)$ =exp(sum(rates$_i$))

$p_j(\Delta t)$ =exp(sum(rates$_j$))

2. τ- leaping


τ
r_1
r_2
r_3
r_4
r_5
r_6
r_7
t_0
t_1
t_2
t_3
t_4
t_5
t_6
t_7
t_8
t_9
t_{10}
t_{11}
similar rates
similar rates
similar rates
similar rates

τ-leaping method: Approximating the SSA to be faster.

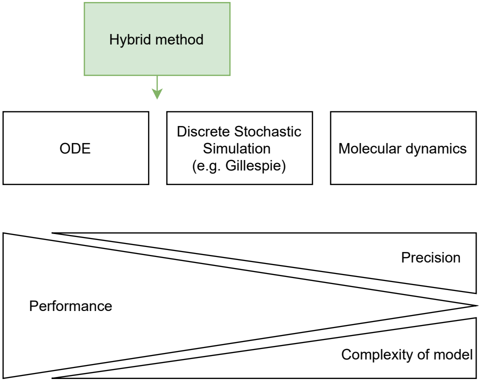
Leap Condition: Require τ to be small enough that the change in the state during $[t, t+\tau]$ will be so slight that no propensity function will suffer an appreciable(i.e., macroscopically noninfinitesimal) change in its value.

τ-leaping method: Select largest τ that fulfils the Leap Condition.

τ-leaping method

- Helpful for speeding up the SSA.
- Popular option for speeding up the SSA.
- But: I don't see how it is helpful for the differentiation problem we want to solve.
- We want to use a neural approach to speed up Gillespie, we are looking at other methods to find something that helps us with the differentiation problem, not speed up directly.

Hybrid methods



- Also method to speed up SSA.
- Slow reactions with species that occur in small numbers → SSA.
- Reactions where all species in large numbers → Reaction rate equations (ODEs).

Hybrid methods

- Linda Petzold: "We thought it's great, then we tried on our real problem and it failed." [3]
- Postulated reason: Cannot efficiently handle fast reactions involving species present in small numbers.
- Their published solution: Slow scale SSA (ssSSA) [4]
  → Stochastic partial equilibrium approximation for the not addressed ones.
- But: Hybrid models are differentiable!

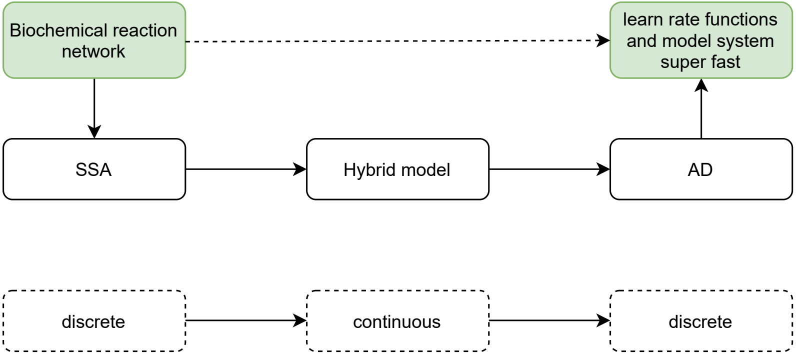
[3] Talk by Petzold: "Discrete stochastic simulation of spatially inhomogeneous biochemical systems", published 10 Nov 2012: `https://www.youtube.com/watch?v=vvE4U7o51cU&ab_channel=MathsStatsUNSW`

[4] Cao, Petzold, Gillespie, "The slow-scale stochastic simulation algorithm", THE JOURNAL OF CHEMICAL PHYSICS, 2004.

Hybrid models

- In Julia, implemented as VariableRateJumps combinable with normal ODEs and **differentiable**.
- Use ODE formulation to derive sensitivity for strong solution u(t) wrt. p for set of random numbers.
- Sequential algorithm → we propagate through the sequence of events → we get sensitivity for each event → brings us back to discrete space.
- Average sensitivities to get the gradient.
- TO DO: Show that exchange of derivatives i.e. expected value of derivative is equal to the derivative of the expected value.

Project overview and proposal


Biochemical reaction network
learn rate functions and model system super fast
SSA
Hybrid model
AD
discrete
continuous
discrete