Quantitative analysis: applications to biological systems

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Biological systems

Complex interacting systems
Self-regulating
Self-controlled
Autonomous (limited knowledge of the environment)
Massively parallel and dynamic
Scalable
Robust

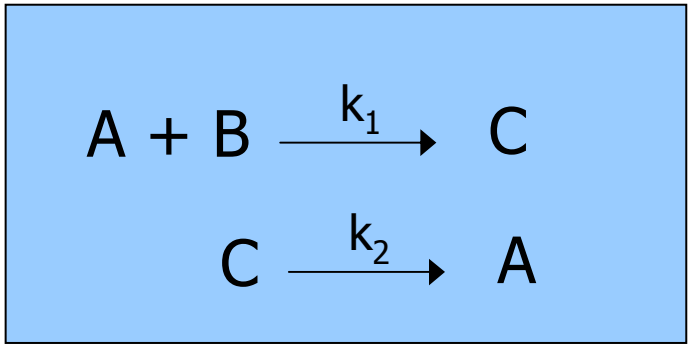
Deterministic modelling

Dynamics:

systems of differential equations

E.g.:

reactions



ODEs

$$dA/dt = -k_1AB + k_2C$$

$$dB/dt = -k_1AB$$

$$dC/dt = k_1AB - k_2C$$

Deterministic vs stochastic modelling

deterministic modelling of a biological system requires the precise knowledge of molecular dynamics

at higher level (less details known), dynamics are intrinsically stochastic

Example [Darren J. Wilkinson]
linear birth-death process:
X(t) individuals at time t; birth rate r; death rate s

$dX(t)/dt = (r-s)\, X(t)$  $X(t) = x_0 \exp((r-s)t)$

issues:
- individuals do not vary continuously
- depends on (r-s) only, same solution for different values of r, s

Deterministic modelling

compositionality?

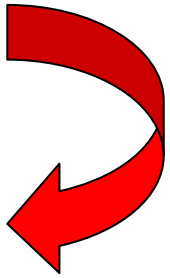
$$A + B \xrightarrow{k_1} C$$

$$C \xrightarrow{k_2} A$$

$$A + B \xrightarrow{k_1} C$$

$$C \xrightarrow{k_2} A$$

$$A \xrightarrow{k_3} B$$



$$dA/dt = -k_1AB + k_2C - k_3A$$

$$dB/dt = -k_1AB + k_3A$$

$$dC/dt = k_1AB - k_2C$$

Biology & process calculi

Desirable properties of a formalism potentially suitable to the description of bio-systems:

the formalism

should be scalable (to describe phenomena from biochemistry up to populations of cells);

should be amenable to computer execution (analysis and/or simulation);

should facilitate comparative studies of system dynamics and functions.

Biochemical stochastic pi-calculus, BioAmbients, Brane Calculi, Core Formal Biology, CCS-R, Beta-binders, Bio-PEPA, ...

Beta-binders

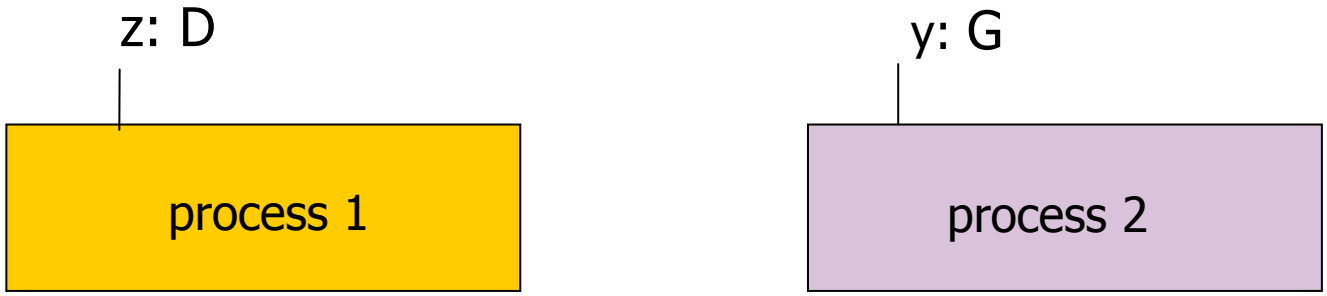
Enclosing surfaces (boxes) of entities

- Interaction at the level of virtual surfaces as well

Typed interfaces to allow promiscuity of interaction

- Biological interaction happens by affinity and not by exact complementarity

Beta-binders



- interaction between the two boxes is allowed if D "agrees" with G, and is based on a race condition
- complexation of the two boxes is driven by the affinity of the relevant sites

BetaWB: stochastic run-time environment for Beta-binders

Gillespie's Direct Method is implemented to answer:

N species can interact through one of M reactions in a fixed volume,

which will be the population levels of species after a period of time?

Gillespie's Direct Method

The algorithm (D. Gillespie, The Jour. of Physical Chemistry, 1977)

calculates explicitly **which** reaction occurs next and **when** it occurs

(i.e. generates a trajectory: a sequence of state transitions and the times at which they occur)

This is done probabilistically, by computing:

$\mathbf{P}(\tau,\mu)\, d\tau =$ probability at time t that the next reaction is R_μ and occurs in the infinitesimal interval $(t+\tau, t+\tau+d\tau)$

Gillespie's Direct Method

Given

c_μ dt = average probability that a particular combination of R_μ reactant molecules will react in the next infinitesimal interval dt

h_μ = number of distinct R_μ molecular reactant combinations

$$\mathbf{P}(\tau,\mu)\, d\tau = a_\mu \exp(-a_0\, \tau) \qquad (t \geq 0)$$

where

a_μ dt = h_μ c_μ dt = probability that an R_μ reaction will occur in (t,t+dt)

$a_0 = \Sigma_{j=1..M}\, a_j$

Simulation algorithm

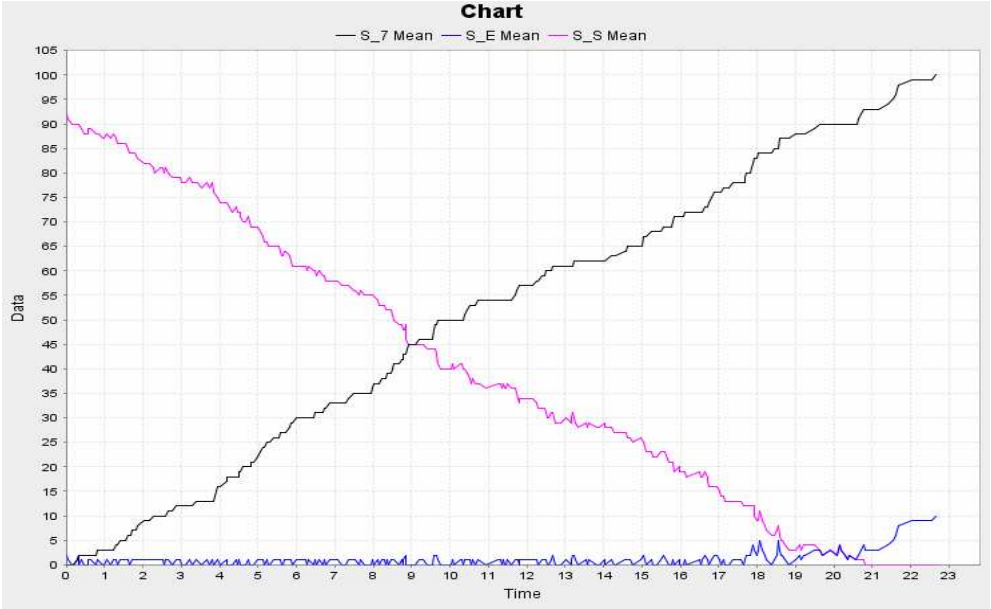
1. Initialization (set the values c_μ and the population levels)

2. Compute $a_0 = \Sigma_{j=1..M} a_j$

3. Generate two random numbers n_1, n_2 in [0,1] and compute $\tau = (1/a_0) \ln (1/n_1)$ $\quad \mu : \Sigma_{j=1..\mu-1} a_j < n_2 a_0 \leq \Sigma_{j=1..\mu} a_j$

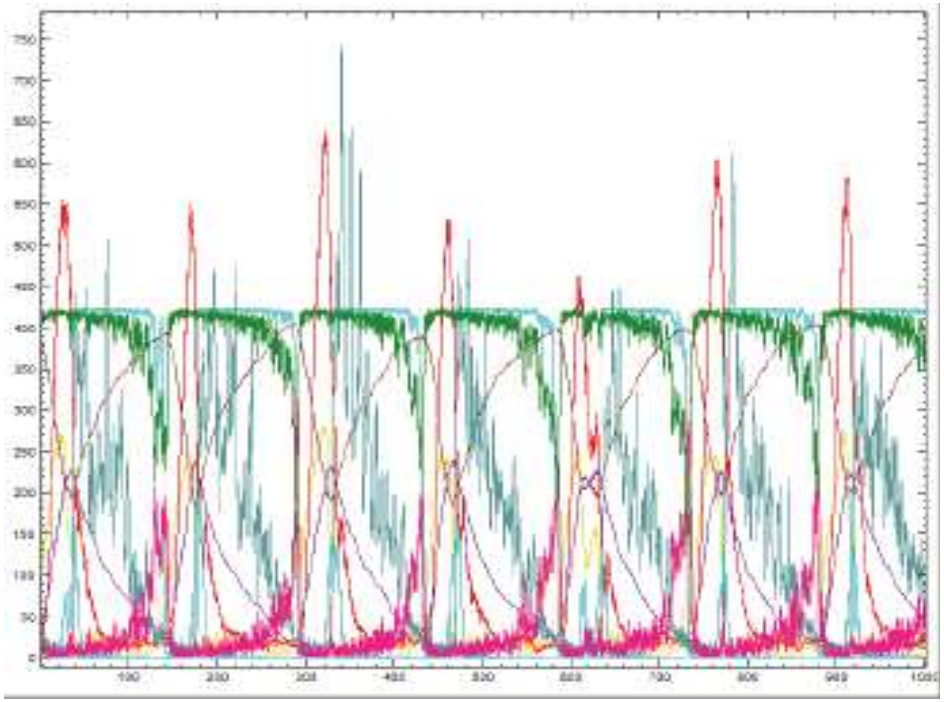
4. Adjust population levels according to R_μ and set $t=t+\tau$ then iterate from step 2.

Happy with simulations?



$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

Happy with simulations?



cell cycle

Thanks!