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

\[ A + B \xrightarrow{k_1} C \]
\[ C \xrightarrow{k_2} A \]

ODEs

\[
\frac{dA}{dt} = -k_1AB + k_2C \\
\frac{dB}{dt} = -k_1AB \\
\frac{dC}{dt} = k_1AB - k_2C
\]
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) \quad \Rightarrow \quad 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?

\[
\begin{align*}
A + B & \xrightarrow{k_1} C \\
C & \xrightarrow{k_2} A
\end{align*}
\]

\[
\begin{align*}
dA/dt &= -k_1AB + k_2C - k_3A \\
dB/dt &= -k_1AB + k_3A \\
dC/dt &= k_1AB - k_2C
\end{align*}
\]
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-binding, Bio-PEPA, ...
Beta-bindners

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
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:

\[ P(\tau, \mu) \, d\tau = \text{probability at time } t \text{ that the next reaction is } R_\mu \]

and occurs in the infinitesimal interval \((t+\tau, t+\tau+d\tau)\)
Gillespie’s Direct Method

Given

\[ c_\mu \, dt = \text{average probability that a particular combination of } R_\mu \text{ reactant molecules will react in the next infinitesimal interval } dt \]

\[ h_\mu = \text{number of distinct } R_\mu \text{ molecular reactant combinations} \]

\[ P(\tau,\mu) \, d\tau = a_\mu \exp(-a_0 \, \tau) \quad (t \geq 0) \]

where

\[ a_\mu \, dt = h_\mu \, c_\mu \, dt = \text{probability that an } R_\mu \text{ reaction will occur in } (t, t+dt) \]

\[ a_0 = \sum_{j=1..M} a_j \]
Simulation algorithm

1. Initialization (set the values $c_\mu$ and the population levels)

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

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

4. Adjust population levels according to $R_\mu$ and set $t=t+\tau$
   then iterate from step 2.
Happy with simulations?

\[ E + S \xrightarrow{k_1} ES \xrightarrow{k_2} E + P \]
Happy with simulations?

cell cycle
Thanks!