Process algebra and systems biology

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(Thanks to Jane Hillston and Federica Ciocchetta)

Motivation

- process algebra
  - different model of computation, reactive system
  - more explicit model than differential equations
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  - for systems biology
  - for computer science
  - for this seminar
- survey of existing research
  - what is a process algebra?
  - what has been done?
  - what can be done?

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- three main approaches
  - Communicating Sequential Processes (Hoare, Brooke, Roscoe)
  - Algebra of Communicating Processes (Baeten, Klop)
  - Calculus of Communicating Systems (Milner)

Process algebra (continued)

- CSP, denotational semantics
  - processes mapped to mathematical objects, $[\![P]\!]$
  - traces, failures, ready sets
  - equivalence of processes from equality over these objects $P \equiv Q$ if $[\![P]\!] = [\![Q]\!]$

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- ACP, algebraic/axiomatic semantics
  - equations that describe processes with same behaviour $P \mid Q \equiv Q \mid P$
  - infer other equivalent processes from equations

Process algebra (continued)

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  - process can perform actions, transitions to other processes
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- stochastic process algebra
  - passing of time associated with transitions, random variable
  - describes dynamic behaviour and properties
  - PEPA, Performance Evaluation Process Algebra (Hillston)

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- structured operational semantics, two example rules

$$\frac{}{(\alpha, r).E \xrightarrow{(\alpha,r)} E} \qquad \frac{E \xrightarrow{(\alpha,r)} E' \quad F \xrightarrow{(\alpha,r)} F'}{E \underset{L}{\bowtie} F \xrightarrow{(\alpha,r)} E' \underset{L}{\bowtie} F'}(\alpha \in L)$$

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- can infer transitions using rules, labelled transition system
  - $\big((\alpha, r).P_1 + (\beta, s).P_2\big) \underset{\{\alpha\}}{\bowtie} (\alpha, r).Q \xrightarrow{(\alpha,r)} P_1 \underset{\{\alpha\}}{\bowtie} Q$
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Systems biology modelling

- general approach (Regev, Silverman, Shapiro)

Concurrency	**Molecular biology**	**Metabolism**	**Signal transduction**
Concurrent computational processes	molecules	enzymes and metabolites	interacting proteins
Synchronous communication	molecular interaction	binding and catalysis	binding and catalysis

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- aims of modelling
  - sufficiently faithful
  - type and tractability of analysis

Systems biology modelling in PEPA

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  - pathway-centric: each subpathway is a process
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  - translate to ordinary differential equations (ODEs)
  - generate a stochastic simulation with Gillespie's algorithm
  - model checking of properties using PRISM
  - find equivalent processes using a behavioural equivalence – need to find suitable equivalence

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- modularity, composition, reasoning
- refinement, abstraction, causality

Example

- example, single substrate enzyme catalyzed reaction

$$E + S \underset{unbind}{\overset{bind}{\rightleftharpoons}} ES \xrightarrow{produce} E + P$$

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- reagent-centric PEPA model
- high and low concentrations, discretized

$$\begin{array}{rcl@{\qquad}rcl}
S_h & \overset{def}{=} & (b, r_b).S_\ell & S_\ell & \overset{def}{=} & (u, r_u).S_h \\
E_h & \overset{def}{=} & (b, r_b).E_\ell & E_\ell & \overset{def}{=} & (u, r_u).E_h + (p, r_p).E_h \\
ES_\ell & \overset{def}{=} & (b, r_b).ES_h & ES_h & \overset{def}{=} & (u, r_u).ES_\ell + (p, r_p).ES_\ell \\
P_\ell & \overset{def}{=} & (p, r_p).P_h & & &
\end{array}$$

$$\Big((S_h \underset{\{b,u\}}{\bowtie} E_h) \underset{\{b,u,p\}}{\bowtie} ES_\ell \Big) \underset{\{p\}}{\bowtie} P_\ell$$

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- model of MAP Kinase cascade (Calder, Duguid, Gilmore, Hillston)
  - original Schoeberl model based on ODEs, Matlab analysis
  - PEPA model created, extracted ODEs, matched results
  - stochastic simulation results differed from ODE results
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- new process algebra, Bio-PEPA (Ciocchetta, Hillston)
  - reagent-centric, includes stoichiometry
  - better modelling of reaction rates, general kinetic laws
  - new syntax, parameterised

Other process algebra approaches

- stochastic π-calculus (Regev, Shapiro, Silverman, Priami, Cardelli)
  - binary communication only, individual-based, mobility
  - analysis by stochastic simulation
  - models of metabolic pathways, gene transcription, signal transduction
  - cell cycle control in eukaryotes (Lecca, Priami)
  - lymphocyte-endothelial interactions in inflamed brain venules (Lecca, Priami, Laudanna, Constantin)
  - VIrtual CEll (VICE) (Chiarugi, Curti, Degano, Marangoni)

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- Brane Calculus (Cardelli, Danos, Pradalier)
  - deals with spatial aspects
  - models membranes explicitly
  - description of virus infection

Other process algebra approaches (continued)

- beta binders (Priami, Quaglia)
  - beta boxes contain π-calculus terms
  - beta boxes have external sites for interaction with others
  - very detailed
  - affinity between sites can be defined
  - potential use in drug discovery

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- Bio-Ambients (Regev, Panina, Silverman, Cardelli, Shapiro)
  - based on ambient calculus, extension of π-calculus
  - movement, location, compartments
  - hypothalamic weight regulation system, multiple levels
  - simulation results give support for model

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- κ-calculus (Danos, Laneve)

The future

- process algebra as modelling technique for systems biology
  - build formal models with explicit interaction and compositionality using simple but descriptive language
  - many types of analysis from one syntactic description
  - provide insights, generate hypotheses
  - allow experimentation *in silico*
  - multi-scale (concentrations vary), stiff (reaction rates vary)
  - compositionality to model different levels
  - techniques for insufficient data, abstraction
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- gold standard: biological insights achieved through use of process algebra that are not possible through existing approaches

The future (continued)

- process algebra as model/metaphor for systems biology

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- process algebra as model/metaphor for systems biology
- Noble's ten principles of systems biology
  1. Biological functionality is multi-level
  2. Transmission of information is not one way
  3. DNA is not the sole transmitter of inheritance
  4. There is no privileged level of causality
  5. Gene ontology will fail without higher-level insight
  6. There is no genetic program
  7. There are no programs at any other level
  8. There are no programs in the brain
  9. The self is not an object
  10. There are many more to be discovered

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- reactive system computing is a more general model than program-as-a-function computing