

A Calculus of Looping Sequences for Modelling Microbiological Systems

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Ruciane-Nida – September 29, 2005

Introduction

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Terms

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Dynamics

An Application

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Introduction

Formal models for systems of interactive components can be easily used or adapted for the modelling of biological phenomena

- ▶ Examples: Petri Nets, π -calculus, Mobile Ambients

The modelling of biological systems allows:

1. the development of simulators
2. the verification of properties
3. (hopefully) the prediction of unknown behaviours

In this work:

1. we introduce a calculus for microbiological systems
2. we use the calculus for modeling an example of interaction among bacteria and bacteriophage viruses

The Calculus of Looping Sequences (CLS)

We assume a set \mathcal{E} of elementary constituents. A **Term** T of CLS is given by the following grammar:

$$T ::= a \mid T \cdot T \mid (T)^L \mid T \rfloor T \mid T \mid T$$

where a is a generic element of \mathcal{E}

The operators are:

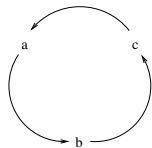
$T \cdot T$: Sequencing

$(T)^L$: Looping (if T is a sequence, it can rotate)

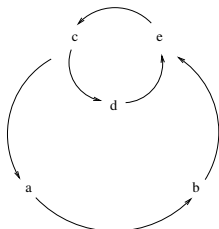
$T_1 \rfloor T_2$: Containment (if T_1 is a looping, it contains T_2)

$T_1 \mid T_2$: Parallel composition (groups separated terms)

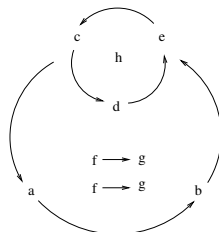
Example of Terms



(a)



(b)



(c)

$$(a) \quad (a \cdot b \cdot c)^L$$

$$(b) \quad ((c \cdot d \cdot e)^L \cdot a \cdot b)^L$$

$$(c) \quad (((c \cdot d \cdot e)^L \mid h) \cdot a \cdot b)^L \mid (f \cdot g \mid f \cdot g)$$

Structural Congruence

The **Structural Congruence** \equiv is the least congruence relation on terms satisfying associativity of $_ | _$ and $_ \cdot _$, right-associativity of $_ \rfloor _$ and the following axioms:

$$A1. \quad (T_1 | T) \cdot T_2 \equiv (T_1 \cdot T_2) | T \equiv T_1 \cdot (T_2 | T)$$

$$A2. \quad (T_1 | T_2) \rfloor T \equiv (T_1 \rfloor T) | T_2$$

$$A3. \quad (T | T_1)^L \equiv (T)^L | T_1$$

$$A4. \quad T | T_1 | T_2 \equiv T | T_2 | T_1$$

$$A5. \quad (T_1 \rfloor T_2) \rfloor T_3 \equiv T_1 \rfloor (T_2 | T_3)$$

$$A6. \quad (T_1 \cdot T_2)^L \equiv (T_2 \cdot T_1)^L$$

$$A7a. \quad a \rfloor T \equiv a | T$$

$$A7b. \quad (T_1 \cdot T_2) \rfloor T \equiv (T_1 \cdot T_2) | T$$

Dynamics of the Calculus (1)

Let V be a set of term variables (X, Y, Z, \dots) . Let \mathcal{T} be the set of ground terms and \mathcal{T}_V be the set of term which may contain variables.

- ▶ An *instantiation* is a function $\sigma : V \rightarrow \mathcal{T}$. Let Σ be the set of all the possible instantiations
- ▶ $T\sigma$ denotes the term obtained by replacing any variable X with $\sigma(X)$ in T

A **Rewrite Rule** is a triple (T, T', Σ') where:

- ▶ $T, T' \in \mathcal{T}_V$
- ▶ variables in T' are a subset of those in T
- ▶ Σ' are instantiations which can be applied to T and T'

Dynamics of the Calculus (2)

A rule (T, T', Σ') can be applied to all terms $T\sigma$ s.t. $\sigma \in \Sigma'$

Example: $(b \cdot X \cdot b, c \cdot X \cdot c, \Sigma')$

where $\Sigma' = \{\sigma \in \Sigma \mid \text{occ}(a, \sigma(X)) = 0\}$

- ▶ can be applied to $b \cdot c \cdot b$ (producing $c \cdot c \cdot c$)
- ▶ cannot be applied to $b \cdot a \cdot b$

Formally, given a set of rules \mathcal{R} , evolution of terms is described by the transition system given by the least relation \rightarrow satisfying

$$\frac{(T, T', \Sigma') \in \mathcal{R} \quad \sigma \in \Sigma'}{T\sigma \rightarrow T'\sigma}$$

and closed under structural congruence and all the operators

Application to a Microbiological System

A Calculus of
Looping Sequences
for Modelling
Microbiological
Systems

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We describe bacteria and bacteriophage viruses as terms of the calculus

Reproduction of bacteria (sporulation) and of the viruses (replication) are described as sets of rewrite rules

Alternative notation for rewrite rules: $T \longrightarrow T' [\mathcal{C}]$

- ▶ \mathcal{C} is condition on instantiations
- ▶ Σ' is the set of instantiations which satisfy \mathcal{C}
- ▶ Example: $b \cdot X \cdot b \longrightarrow c \cdot X \cdot c \quad [\text{occ}(a, \sigma(X)) = 0]$

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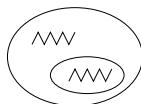
Sporulation (Reproduction of Bacteria) (1)



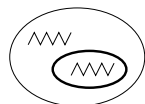
The bacterium



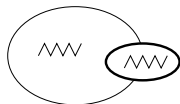
Step 1: Duplication



Step 2: Prespore



Step 3: Coat



Step 4: Release

Sporulation (2)

$$BACTERIUM ::= (\underbrace{m \cdot \dots \cdot m}_n)^L \rfloor DNA_b$$

$$PRESPORE ::= (\underbrace{m \cdot \dots \cdot m}_{\frac{n}{2}})^L \rfloor DNA_b$$

$$SPORE_1 ::= (\underbrace{c \cdot \dots \cdot c}_{\frac{n}{2}})^L \rfloor PRESPORE$$

$$SPORE_2 ::= (\underbrace{d \cdot \dots \cdot d}_{\frac{n}{2}})^L \rfloor PRESPORE$$

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Rules for Sporulation (1)

$$S1. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (DNA_b \mid X) \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (DNA_b \mid DNA_b \mid X) \quad [occ(DNA_b, X) = 0]$$

$$S2. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (DNA_b \mid DNA_b \mid X) \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (DNA_b \mid PRESPORE \mid X)$$

$$S3. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid PRESPORE \mid Y) \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid SPORE_1 \mid Y)$$

Rules for Sporulation (2)

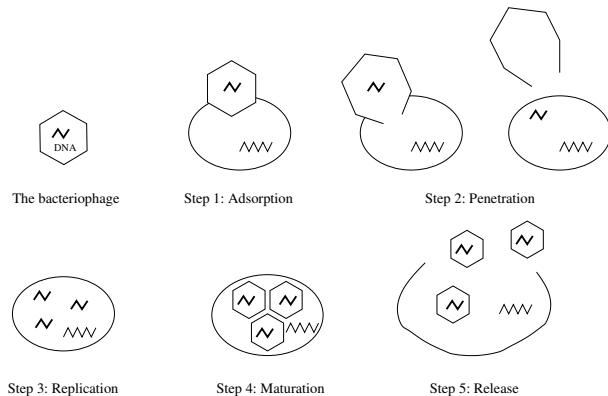
$$S4. \quad (\underbrace{m \cdot \dots \cdot m}_n)^L \mid (X \mid SPORE_1 \mid Y) \longrightarrow$$

$$(\underbrace{SPORE_1 \cdot m \cdot \dots \cdot m}_n)^L \mid (X \mid Y)$$

$$S5. \quad (\underbrace{SPORE_1 \cdot m \cdot \dots \cdot m}_n)^L \mid X \longrightarrow ((\underbrace{m \cdot \dots \cdot m}_n)^L \mid X) \mid SPORE_2$$

$$S6. \quad SPORE_2 \longrightarrow \underbrace{d \cdot \dots \cdot d}_{\frac{n}{2}} \mid (\underbrace{m \cdot \dots \cdot m}_n)^L \mid DNA_b$$

Virus Replication (1)



$$VIRUS ::= \underbrace{(v \cdot \dots \cdot v)}_k^L \mid DNA_v$$

Rules for Virus Replication (1)

$$V1. \text{ VIRUS } | \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor X \longrightarrow (\text{VIRUS} \cdot \underbrace{m \cdot \dots \cdot m}_n)^L \rfloor X$$

$$V2. (\text{VIRUS} \cdot \underbrace{m \cdot \dots \cdot m}_n)^L \rfloor X \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X | \text{DNA}_v) | \underbrace{v \cdot \dots \cdot v}_k$$

Rules for Virus Replication (2)

$$V3. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid DNA_v) \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid DNA_v \mid DNA_v) \quad [occ(DNA_v, X) < max]$$

$$V4. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid DNA_v) \longrightarrow \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor (X \mid VIRUS) \quad [occ(DNA_v, X) > max - s]$$

$$V5. \underbrace{(m \cdot \dots \cdot m)}_n^L \rfloor X \longrightarrow \underbrace{m \cdot \dots \cdot m}_n \mid X \quad [occ(VIRUS, X) > max - s]$$

The membrane of the bacterium may break when the number of viruses in it is in the interval $[max - s, max]$

Verification of Properties

The rules for sporulation and virus replication are **monotonic** (they do not decrease the number of elementary particles)

- ▶ reachability of states is decidable
- ▶ Example: it is possible to prove that

$$BACTERIUM|VIRUS|VIRUS|VIRUS$$

can reach a state where the bacterium contains more than max of DNA_V .

More general properties can be proved by using model checking

- ▶ Example: if replication of DNA of bacteria is inhibited and if at least one virus is present, eventually all bacteria will be destroyed

Conclusions

We have introduced a calculus which can be used for modelling microbiological systems

- ▶ it models membranes as looping sequences

We have shown an example of application to a microbiological system. We have modelled

- ▶ sporulation of bacteria
- ▶ replication of bacteriophage viruses

We have discussed the verification of properties of the modelled system by means of

- ▶ monotonicity of the rewrite rules
- ▶ model checking