From Gene Regulation to Stochastic Fusion Calculus

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Overview

- Many-to-Many Interaction in Biology
- Fusion Calculus - syntax and semantics
- Exponential Distribution
- Stochastic Fusion - syntax and semantics
- Distribution of Synchronization
- Stochastic Hyperbisimulation
- Axiomatization of Stochastic Hyperbisimulation
- Conclusion

Many-to-Many Interaction in Biology

- process algebras are working with one-to-one interactions, and so it is difficult to use them in describing (complex) biological systems
- for instance, gene regulatory network involves many-to-one or many-to-many interactions
- we overcome this limitation and present a stochastic fusion calculus where
  - we use equivalence classes of names when we have multiple interactions
  - the names from the same equivalence class are fusing under the same name used then in further interactions

Fusion Calculus

- developed by J.Parrow & B.Victor in 1997-98
- it derives from π-calculus, and inherits all its expressive power
- let $\mathcal{N}$ a countable set of names $u, v, \ldots z$
- for a sequence of names we use $\widetilde{x}$
- $\{\widetilde{x} = \widetilde{y}\}$ allows names to be interchanged
- if x and y are related by φ we write $x\varphi y$
- $\{\widetilde{x} = \widetilde{x}\} = \mathbf{1}$ identity relation

π-calculus vs Fusion Calculus (I)

In the π-calculus:

- effects of communication are local

$$\overline{a}x.P \mid a(y).Q \mid R \xrightarrow{\tau} P \mid Q\{x/y\} \mid R$$

- has two binding operators:
  - input $a(x).P$
  - restriction $(\nu x)P$
- input and output are asymmetric:
  - input always binds, output does not bind
- has several bisimulation relations: early, late,...

π-calculus vs Fusion calculus (II)

In the fusion calculus:

- effects of an interaction could be local and global
  Example:

$$\overline{u}vw.P \mid uxy.Q \mid R \mid S \overset{\{v=x,w=y\}}{\longrightarrow} P \mid Q \mid R \mid S$$

- there is only one binding operator called *scope* and is written $(x)P$, meaning that the x is local in P

$$(x)(y)(\overline{u}vw.P \mid uxy.Q \mid R) \mid S \xrightarrow{\mathbf{1}} (P \mid Q \mid R)\{v/x, w/y\} \mid S$$

- input and output are symmetric
- a new notion of bisimulation between processes

Exponential Distribution

Let $(\Omega, \mathcal{K}, P)$ be a probability space, $(X_t; t \geq 0)$ a stochastic process, and S a finite state space

- holding time for any state is exponentially distributed; an exponential distribution $P(X \leq t) = 1 - e^{-rt}$ is characterized by its rate r
- $(X_s, 0 \leq s \leq t)$ and $(X_u, t < u < \infty)$ are independent;
- exponential distribution guarantees *the memoryless property* which says that at each step in which an activity has started but not terminated yet, the remaining duration of the activity is still distributed as the entire duration of the activity: $P(X > u + t | X > t) = P(X > u)$, for all $u, t \geq 0$

Exponential Distribution Properties

- $P(\min(X_1, X_2) \leq t) = 1 - e^{-(r_1+r_2)t}$, where $X_i \sim Exp(r_i)$; it is assumed that it is a race among several transitions competing for a state change; the waiting time in i ends as soon as the first transition is ready to occur.
- $P(X_1 < X_2) = \dfrac{r_1}{r_1 + r_2}$, and $P(X_2 < X_1) = \dfrac{r_2}{r_1 + r_2}$ this property determines the probability of a specific transition to win such a race.

Stochastic Fusion Calculus

- Stochastic processes can be considered the basis of quantitative modelling performance and reliability
- SFC describes the dynamic behaviour of systems in terms of probability and waiting-time distributions

Prefixes: $\mu ::= (u\widetilde{x}, F_u) \mid (\overline{u}\widetilde{x}, F_{\overline{u}}) \mid (\varphi, F_\varphi)$

Processes:

$P ::= \mathbf{0} \mid \mu.P \mid P + Q \mid P \mid Q \mid (x)P \mid [x = y]P \mid [x \neq y]P \mid$

$A(\widetilde{x}) \stackrel{def}{=} P$

SFC - semantics (I)

$$PREF : (\alpha, F).P \xrightarrow{(\alpha,F)}_1 P \qquad SUM : \frac{P_j \xrightarrow{\mu}_k P'}{\sum_{i \in I} P_i \xrightarrow{\mu}_{j.k} P'}$$

$$PAR_L : \frac{P \xrightarrow{\mu}_i P'}{P \mid Q \xrightarrow{\mu}_{(i,0)} P' \mid Q} \qquad PAR_R : \frac{Q \xrightarrow{\mu}_i Q'}{P \mid Q \xrightarrow{\mu}_{(0,i)} P \mid Q'}$$

$\mathsf{bn}(\mu) \cap \mathsf{fn}(Q) = \emptyset$ $\qquad$ $\mathsf{bn}(\mu) \cap \mathsf{fn}(P) = \emptyset$

$$PASS : \frac{P \xrightarrow{\mu}_i P',\ z \notin \mathsf{fn}(\mu)}{(z)P \xrightarrow{\mu}_i (z)P'} \qquad OPEN : \frac{P \xrightarrow{((\widetilde{y})u\widetilde{x},F)}_i P',}{(z)P \xrightarrow{((z\widetilde{y})u\widetilde{x},F)}_i P'}$$

$$z \in \widetilde{x} - \widetilde{y}, u \notin \{z, \overline{z}\}, F \in \{F_u, F_{\overline{u}}\}$$

SFC - semantics (II)

$$SCOPE : \frac{P \xrightarrow{(\varphi, F_\varphi)}_i P'}{(z)P \xrightarrow{(\varphi \backslash z, F_\varphi)}_i P'\{x/z\}} \quad COM : \frac{P \xrightarrow{(u\widetilde{x}, F_u)}_i P', Q \xrightarrow{(\overline{u}\widetilde{y}, F_{\overline{u}})}_j Q}{P \mid Q \xrightarrow{(\{\widetilde{x}=\widetilde{y}\}, F_\varphi)}_{(i,j)} P' \mid Q}$$

$$z\varphi x, z \neq x, \varphi \backslash z = \varphi \cap (\mathcal{N} - \{z\})^2 \cup \{(z, z)\}$$

$$MATCH : \frac{P \xrightarrow{\mu}_i P'}{[x = x]P \xrightarrow{\mu}_i P'} \quad MISMATCH : \frac{P \xrightarrow{\mu}_i P'}{[x \neq y]P \xrightarrow{\mu}_i P'}$$

$$SUBST : \frac{P\{\widetilde{y}/\widetilde{x}\} \xrightarrow{\mu}_i P'}{A(\widetilde{y}) \xrightarrow{\mu}_i P'}, \quad A(\widetilde{x}) \stackrel{def}{=} P$$

Example

Consider the process

$$P = (ux, F_u).\mathbf{0} \mid ((\overline{u}y, F_{\overline{u}}).\mathbf{0} + (\overline{u}y, F_{\overline{u}}).\mathbf{0})$$

$$(ux, F_u).\mathbf{0} \mid ((\overline{u}y, F_{\overline{u}}).\mathbf{0} + (\overline{u}y, F_{\overline{u}}).\mathbf{0}) \xrightarrow{(\{x=y\},F_\varphi)}_{(1,1.1)} \mathbf{0} \mid \mathbf{0}$$

$$(ux, F_u).\mathbf{0} \mid ((\overline{u}y, F_{\overline{u}}).\mathbf{0} + (\overline{u}y, F_{\overline{u}}).\mathbf{0}) \xrightarrow{(\{x=y\},F_\varphi)}_{(1,2.1)} \mathbf{0} \mid \mathbf{0}$$

Distribution of the Synchronization

How to define the distribution of the synchronization, F_φ?

- $F_i(t) = 1 - e^{\lambda_i t}, i = \overline{1,2}$, with *rate*$(F_i) = \lambda_i$
- the rate of the distribution of the synchronization is the product of the rates λ_i of the two synchronizing actions
- [Hill94] using the *apparent rate* $r_\alpha(P) = \sum_{P \stackrel{(\alpha,F_j)}{\longrightarrow} P_j} rate(F_j)$,

$$rate(F_\varphi) = \frac{rate(F_\alpha)}{r_\alpha(P)} \times \frac{rate(F_{\overline{\alpha}})}{r_{\overline{\alpha}}(Q)} \times \ \text{min}\{r_\alpha(P), r_{\overline{\alpha}}(Q)\}$$

SFC - Structural Congruence

The structural congruence between processes, denoted by $\equiv$, is the least congruence satisfying the following axioms:

(fus) $(\varphi, F_\varphi).P \equiv (\varphi, F_\varphi).P\sigma$, for σ a substitutive effect of φ

(par) $P \mid \mathbf{0} \equiv P \quad P \mid Q \equiv Q \mid P \quad P \mid (Q \mid R) \equiv (P \mid Q) \mid R$

(scope) $(x)\mathbf{0} \equiv \mathbf{0} \quad (x)(y)P \equiv (y)(x)Q \quad (x)(P + Q) = (x)P + (x)Q$

(scope extension) $(z)P \mid Q \equiv (z)(P \mid Q),$ where $z \notin \text{fn}(Q)$

Fusion Calculus - Hyperbisimulation

- *Bisimulation* is a binary symmetric relation $\mathcal{S}$ over processes such that $P \, \mathcal{S} \, Q$ implies if $P \xrightarrow{\gamma} P'$ with bn(γ)$\cap$fn$(Q) = \emptyset$, then $Q \xrightarrow{\gamma} Q'$ and $P'\sigma \, \mathcal{S} \, Q'\sigma$ for some substitutive effect σ of γ. Notation $P \,\dot{\sim}\, Q$.
- Bisimilarity is not preserved under fusion prefixes:

$$x.0 \mid \overline{y}.0 \;\dot{\sim}\; x.\overline{y}.0 + \overline{y}.x.0$$

$$\{x = y\}x.0 \mid \overline{y}.0 \;\dot{\nsim}\; \{x = y\}(x.\overline{y}.0 + \overline{y}.x.0)$$

- A $hyperbisimulation$ is a substitution closed bisimulation

Stochastic Hyperbisimulation

- A *stochastic hyperbisimulation* is an equivalence relation $\mathcal{R}$ over the processes space $\mathcal{P}$ satisfying the following properties:
  - $\mathcal{R}$ is closed under arbitrary substitution σ;
  - for each pair $(P,Q) \in \mathcal{R}$, for all actions α, and for all equivalence classes $C \in \mathcal{P}/\mathcal{R}$:

$$\gamma_\alpha(P,C) = \gamma_\alpha(Q,C),$$

where $\gamma_\alpha(R,C) = \sum\{rate(F_\alpha) \mid R \xrightarrow{(\alpha,F_\alpha)}_i R',\ R' \in C\}.$

- Notation: $P \sim_{SH} Q$

SFC - Axiomatization (I)

We follow essentially [MPW92].

- **Summation**
  - S1 $P + \mathbf{0} = P$
    S2 $P + Q = Q + P$
    S3 $P + (Q + R) = (P + Q) + R$
  - S4 $(\alpha, F_{1\alpha}).P + (\alpha, F_{2\alpha}).P = (\alpha, F).P$, where F is the distribution function given by

$$P(\min(X_1, X_2) \leq t) = 1 - e^{-(\lambda_1+\lambda_2)t},$$

where $X_i \sim Exp(\lambda_i)$

SFC - Axiomatization (II)

- **Scope**

  R1 $(x)\mathbf{0} = \mathbf{0}$

  R2 $(x)(y)P = (y)(x)P$

  R3 $(x)(P + Q) = (x)P + (x)Q$

  R4 $(x)(\alpha, F_\alpha).P = (\alpha, F_\alpha).(x)P$, if $x \notin$ n(α)

  R5 $(x)(\alpha, F_\alpha).P = \mathbf{0}$, if x is the subject of α

- **Match and Mismatch**

  M1 $\widetilde{M}P = \widetilde{N}P$ if $\widetilde{M} \Leftrightarrow \widetilde{N}$

  M2 $[x = y]P = [x = y](P\{x/y\})$

  M3 $MP + MQ = M(P + Q)$

  M4 $[x \neq x]P = 0$

  M5 $P = [x = y]P + [x \neq y]P$

SFC - Axiomatization (III)

- **Match and Scope**

  RM1 $(x)[y=z]P = [y=z](x)P$ if $x \neq y,\ x \neq z$

  RM2 $(x)[x=y]P = 0$, if $x \neq y$

- **Fusion**

  F1 $(\varphi, F_\varphi).P = (\varphi, F_\varphi).[x=y]P$, if $x\varphi y$

  F2 $(z)(\varphi, F_\varphi).P = (\varphi \setminus z, F_\varphi).P$, if $z \notin$ fn(P)

SFC - Axiomatization (IV)

- **Expansion**

$P \equiv \sum_i M_i(\widetilde{x_i})(\alpha_i, F_{\alpha_i}).P_i$ and $Q \equiv \sum_j N_j(\widetilde{y_j})(\beta_j, F_{\beta_j}).Q_j$

$$P \mid Q = \sum_i M_i(\widetilde{x_i})(\alpha_i, F_{\alpha_i}).(P_i \mid Q) +$$

$$+ \sum_j N_j(\widetilde{y_j})(\beta_j, F_{\beta_j}).(P \mid Q_j) +$$

$$+ \sum_{\alpha_i \equiv \overline{u}\widetilde{z_i} \wedge \beta_j \equiv u\widetilde{w_j}} M_i N_j(\widetilde{x_i})(\widetilde{y_j})(\{\widetilde{z_i} = \widetilde{w_j}\}, F_\varphi).(P_i \mid Q_j),$$

where F_φ is the distribution function for fusion.

SFC - Soundness

Theorem 0.1. $ASHE \vdash P \equiv Q \Rightarrow P \sim_{SH} Q$

Sketch of proof. We prove only for Expansion axiom, the third term.

$P \mid Q \sim_{SH} R$. $E = \{(P \mid Q, R), \mid P, Q, R$ processes$\} \cup$ **Id**.

For $P|Q$ applying PASS, MATCH, SUM and in the end COM we have:

$$P \mid Q \xrightarrow[(i.m,j.n)]{(\{\widetilde{z}_i = \widetilde{w}_j\}, F_\varphi)} (\widetilde{x}_i)P_i \mid (\widetilde{y}_j)Q_j$$

For the third term of R we apply PASS , MATCH , and SUM :

$$R \xrightarrow[m]{(\{\widetilde{z}_i = \widetilde{w}_j\}, F_\varphi)} (\widetilde{x}_i)(\widetilde{y}_j)(P_i \mid Q_j)$$

By scope extension applied twice,

$$(\widetilde{x}_i)P_i \mid (\widetilde{y}_j)Q_j = (\widetilde{x}_i)(\widetilde{y}_j)(P_i \mid Q_j)$$

□

SFC - Completeness

Theorem 0.2. $P \sim_{SH} Q \Rightarrow ASHE \vdash P \equiv Q$

Sketch of proof. Completeness can be proved by direct application of the proof idea given in [MPW92]. Here we define a head normal formal (HNF) with the above extended syntax using the HNF defined in [MPW92], replacing the actions with the new extended action syntax with delay parameters. Then we use induction on the depth of the processes in HNF (see proof of Theorem 5.4 in [PaVic98]). This is because the rates of transitions remain unchanged in all the steps required in the proof. □

Conclusions

- Stochastic approach of the fusion calculus allowing to describe multiple (not only one-to-one) interactions
- The stochastic nature: the labels are pairs (α, F)
- We defined the rate corresponding to the distribution of the synchronization using the apparent rate as in [Hill94]
- We define a stochastic hyperbisimulation and a (sound and complete) axiom system ASHE for it
- Further work
  - Considering more general probabilistic distributions
  - Modelling complex (many-to-many) biological systems

References

[CioMis05] G. Ciobanu and J. Mishra. Performance analysis and name passing errors in probabilistic fusion. *Scientific Annals of "A.I.Cuza" University*, Tome XV, 57-76, 2005.

[deAlf98] L. de Alfaro. Stochastic transition systems. In *CONCUR '98: Proceedings of the 9th International Conference on Concurrency Theory*, pages 423–438. Springer-Verlag, 1998.

References

References

[HHK02] H. Hermanns, U. Herzog, and J.P. Katoen. Process algebra for performance evaluation. *Theor. Comput. Sci.*, 274(1-2):43–87, 2002.

[PaVic98] J. Parrow and B. Victor. The fusion calculus: Expressiveness and symmetry in mobile processes. In *LICS '98: Proceedings of the 13th Annual IEEE Symposium on Logic in Computer Science*, page 176. IEEE Computer Society, 1998.