described in this paper, using both the differential (in Prolog) in
The practical work of this internship is to implement 
Our previous work on this subject is described in 
Main activities 
- combining both simulation algorithms with general criteria ensuring both correctness and maximum 
- small numbers of molecules. 
- by numerical integration (using implicit methods for stiff systems) but which is not correct for 
- first-order approximation of the mean stochastic behavior which is much more efficient to compute 
Equation (continuous-time Markov chain). The ordinary differential equation associated to a CRN is a 
The stochastic simulation algorithm (SSA) provides a numerical integration of the chemical master 
and can be interpreted at different levels of abstraction in a hierarchy of different dynamics: 
- CRN has an hypergraph structure (i.e. a bipartite graph species/reactions labelled with rate functions) 
- at a high-level of abstraction, without information on the kinetics of the reactions. 
The 450 researchers and engineers from Inria and its partners 
who work in the research centre's 31 teams, the 100 research 
support staff members, the high-level equipment at their disposal 
(image walls, high-performance computing clusters, sensor 
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research centre in the local landscape and one that is oriented 
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Its 200 agile project teams, generally with 
academic partners, involve more than 3,000 
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creation of over 160 startups. It strives to meet 
the challenges of the digital transformation of 
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About the research centre or Inria department 
Located at the heart of the main national research and higher 
education cluster, member of the Université Paris Saclay, a major 
actor in the French Investments for the Future Programme (Idex, 
LabEx, IRT, Equipex) and partner of the main establishments 
present on the plateau, the centre is particularly active in three 
major areas: data and knowledge; safety, security and reliability; 
modelling, simulation and optimisation (with priority given to 
energy).

The formalism of chemical reaction networks (CRNs) is used to model biological processes at the 
cellular level. They explain complex phenotypes as the result of elementary molecular interactions. A 
CRN has an hypergraph structure (i.e. a bipartite graph species/reactions labelled with rate functions) 
and can be interpreted at different levels of abstraction in a hierarchy of different dynamic 
differential, stochastic, Petri net or Boolean. The differential and stochastic simulations can make 
quantitative predictions, while the Petri net and Boolean interpretation can serve analysis purposes 
and can be interpreted at different levels of abstraction in terms of the kinetics of the reactions. 
The stochastic simulation algorithm (SSA) provides a numerical integration of the chemical master 
equation (continuous-time Markov chain). The ordinary differential equation associated to a CRN is a 
first-order approximation of the mean stochastic behavior which is much more efficient to compute 
by numerical integration (using implicit methods for stiff systems) but which is not correct for 
small numbers of molecules.

Hybrid stochastic-differential simulations aim at providing automatic dynamic strategies for 
combining both simulation algorithms with general criteria ensuring both correctness and maximum 
efficiency.

Main activities 
Our previous work on this subject is described in 

Hui-Ju Chiang, François Fages, Jie-Hong Jiang, 
Sylvain Soliman. Hybrid Simulations of 
Heterogeneous Biochemical Models in SBML. ACM 
[ preprint ]

The practical work of this internship is to implement 
in Prolog in BIOCHAM-4 the dynamic strategy 
described in this paper, using both the differential
integrator and the event mechanism as a mean to implement the SSA.

The research will consist in experimenting further the dynamic partitionning strategies described in the paper and evaluate them on the repository of models BioModels.

Theoretical work on this subject is possible concerning the correctnes criteria, as well as for instance the search of correctness criteria weaker than approximation in all time points.

The expected results aim to lead to both an international publication and an integration in the next release of BIOCHAM-4 to be routinely used for stochastic simulation of CRNs in BIOCHAM commands for sensitivity and robustness analysis, parameter search in high-dimension, artificial evolution of CRNs, and machine learning CRNs from data.

Skills
This subject requires common and basic knowledge in algorithmics, programming, and in numerical integration methods for ordinary differential equations.

Specific knowledge of the the Prolog programming language or of Computational Systems Biology will be a plus.

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