An Agent-oriented Conceptual Framework for Biological Systems Simulation

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Systems biology

- From Bionformatics to Computational Biology [Claverie2000]
- … and to Systems Biology
- Part of modern biology regarding modelling and simulation of biological processes which aims at system level understanding of biological systems [Kitano2002]
- To describe in detail the system structure and behavior and comprehend its reaction in response to external stimuli or disruption

The challenge

- Incredible demanding scientific challenge involving computer scientists, mathematicians, biophysicists, biochemists, automatic control engineers……working in close partnership with life scientists
- Huge amount of knowledge at molecular level (at least data…) constitutes the solid ground for understanding living systems at the system level (cellular processes, cells , organs, organisms, community…)
- Immense prize to attain [Finkelstein2004]
  - In silico drug design and testing
  - Individualized medicine
  - ….

Molecular networks

- Gene regulatory networks
- Metabolic pathways
- Signal transduction cascades

Fundamental issues [Finkelstein2004]

- Information management framework
  - Model construction
  - Model analysis
  - Model validation
- Standardization and data exchange
  - Systems Biology Workbench project
  - SBML
  - CELLML
- User friendly interfaces

Biological Systems understanding

- Assembly of biological components
  - Description of the components
  - Description of the behavior
- 4 steps [Kitano2002]
  - System structure identification (network structure and parameters)
  - System behavior analysis (simulation)
  - System control (feedforward, feedback)
  - System design (software engineering)

Many different approaches

- ODE: GEPASI [Mendes 1993], COPASI, E-CELL[Tomita1999]
- LISP: QSIM [Kuipers1994]
- PI-calculus: Bio-calculus[Nagasaki1999], PiFPC[Regev2001], VICE[Chiarugi2004]
- Petri nets: [Nagasaki2004]
- MAS: Cellulat[Gonzalez2003], Stem-Cell[D'Inverno2004]

Motivations

- Need for an abstraction: not an in silico isomorphic image of the world itself [Finkelstein2004]
- Need for formal framework for modeling and simulation
- Apply existing methods and tools (property formal verification…) from computer science
- Intuitive graphical representation of systems

Molecule-as-computation

- Abstraction [Regev2002]. A metaphor?
- A system of interacting molecular entities can be described and modelled as a system of interacting computational entities
- Processes have internal state and interaction capabilities (sending and receiving messages)
- The process behavior is described by reaction rules: depending from internal state and input they produce changes in the state, in the interaction capabilities and/or sending message

Hierarchical description

- Structure and behavior can be described hierarchically
- Water, inorganic ions, sugars, aminoacids, nucleotides, fatty acids
- Macromolecules (polysaccharides, nucleic acids, proteins)
- Macromolecules aggregates (ribosome…)
- Cellular structures, compartments,…
- Cells
- Organs
- Organisms
- Community

An Agent-oriented framework

- We promote a conceptual framework for simulating biological systems heavily based on localization, distribution and interaction
- Engineering an agent society (MAS) which simulate the behavior of biological processes
- Agents are considered a promising approach for engineering simulation of complex systems
- They make it possible to simulate and analyze emergent properties which can be understood as properties of the ensemble in overall

Software agents

- Weak definition of agents
- Two basic foundational properties:
  - **Autonomy**: agents encapsulate the execution of independent activities/tasks within the overall system/environment; they encapsulate a state and a behavior (like software object) but they have the control of both
  - **Situatedness**: agents are persistent entity immerged within and interacting with an environment

Mediating artifacts

- Biological systems are typically characterized by complex and concurrent activities
- Agents can be suitably adopted for modelling the biological components responsible of such activities
- Mediating artifacts: the entities used by agents to engage different form of interaction (communication channel, shared data structure, scheduler, shared blackboard…)

Agent society

- Ensemble of agents and mediating artifacts involved in the social tasks characterizing the society
- Social task: coordinated execution and interaction of agent individual tasks to achieve an overall (society) objective
- Scaling with complexity: an individual agent at a more detailed level can be described as a society of agents and vice-versa (zoom-in, zoom-out)

Biological systems simulation

- MAS paradigm: a methodology for covering the whole simulation engineering spectrum (design, development, execution, runtime control)
- The control of mediating artifacts at runtime is the key for supporting the analytical and synthetical processes (system behavior and system control of [Kitano2002])
- TuCSoN [Omicini1999] is an example of MAS coordination infrastructure

System specification and verification

- To define the 3 different views suggested in [Peleg2002] we need languages and/or suitable notations (formal or semiformal)
- Static-structural: SBML
- Dynamic: UML-Activity Diagrams, SB-UML (suitable for translation to a formal notation – process algebra like)
- Functional: functions performed by the different actors

- Biological ontology to define biological concepts and arrange them in classification hierarchies