



A&A for Modelling and Engineering Simulations in Systems Biology: a First Framework based on TuCSoN

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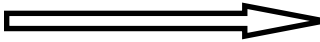
Our Contribution in a Nutshell

- A new model for modelling and simulating complex systems based on agent & *artifact* abstractions (A&A)
 - agent- & MAS-based modelling & simulation
 - artifacts to model and represent agent environment
- Here applied to Systems Biology
 - modelling, *simulating*, understanding biology at the *system* level

Biological Systems as Complex Systems (1/2)

- Hierarchy (different level of structural organization)
 - from sequences, molecules...
 - ... to pathways (such as metabolic or signaling) and networks (collection of cross-interacting pathways)...
 - ... to cells, organs
- Interaction
 - ... between molecules inside a compartment
 - ... between compartments in a cell
 - ... between cells of a system
 - e.g., immune system
 - ... between systems
 - e.g., immune, nervous, endocrine systems
- Interaction between system and environment

Biological Systems as Complex Systems (2/2)

- Interaction between component
 - Positive and negative feedback
 - Self-* and emergent behaviours / properties
 - stable states far from equilibrium
 - stochastic, non linear and chaotic behaviours
 - We need modelling and simulating tools to have a deep understanding of such complex systems
 - other than experimental tools
-  **Systems Biology**

Systems Biology

- Da una visione riduzionistica ad una d'insieme (integrazione)
- Understanding biology at the system level (Kitano)
 - focus on structure and dynamics of cellular and organismal function
 - ... rather than the characteristic parts of isolated parts of a cell or organism
- Two main aims (Cardelli)
 - obtain a massive amounts of data about whole biological systems via high-throughput experiments
 - with such data, build a science of the principles of operation of biological systems, based on the interactions between components
- “A new way of doing biology, starting with experimental knowledge, passing through *in silico* modelling” (Dhar)

Traditional approach

- Graphs
- Boolean Networks
- Bayesian Networks
- Mathematical modelling
 - Macroscopic view
 - Non linear differential equation (ODE), modeling substance-reaction relationship
 - Mathematical tools for *sensitivity analysis, equilibrium analysis and bifurcation analysis*
 - Mesoscopic view
 - Gillespie Algorithm, Stochsim Algorithm which calculate the probability that two molecules will react

Limit of traditional approach

- Not fully adequate to model & simulate & analyse biological system
 - Graphs and Boolean networks
 - Unable to model stochastic aspects
 - Mathematical models
 - Unable to model the interaction between components
 - Unable to model the interaction with the environment
 - Implement a top-down approach:
 - Describing global laws

Computational modelling

- Process algebra
 - modelling *actions* (as primitives) and *processes* (by algebraic composition)
 - algebraic composition, concurrency, communication
- Pi-calculus
 - minimal calculus where *names* play the twofold role of *communication channels* and *variables*
 - concurrency, communication, replication, new name creation
- Petri Nets
 - mathematical / graphical representation for discrete distributed systems
 - place nodes, transition nodes, and directed arcs connecting places and transitions
 - non-deterministic execution for concurrent system representation
- Multi-Agent Systems
 - agents and artifacts running as separate but coordinated distributed control flows
 - agents representing pro-active entities, encapsulating control & goal / task
 - artifacts representing reactive entities, encapsulating function / service

MAS 4 Systems Biology

- Promising choice for modelling and simulating biological complex systems
- Agent- & MAS-based models & simulation
 - autonomous heterogeneous entities situated in the same environment
 - interaction as a fundamental dimension
 - either direct or mediated by the environment
 - Global collective behaviours emerging from individual / local interactions

The A&A Approach

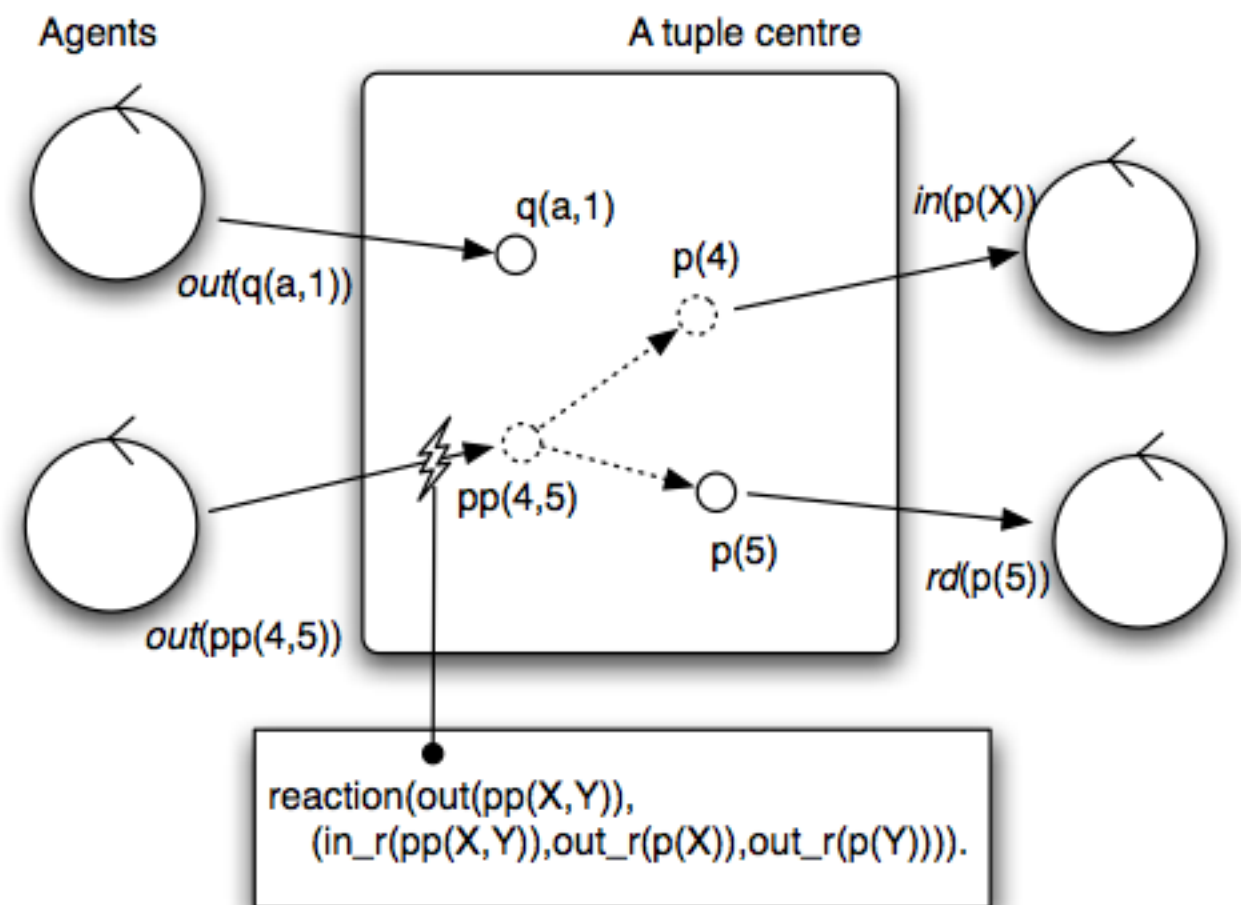
- Basic Meta-model: $MAS = Agents + Artifacts$
- *Agents*
 - used to model pro-active entities
 - encapsulating tasks & activities
 - decentralisation & encapsulation of control
 - acting & perceiving
- *Artifacts*
 - used to model passive / reactive entities
 - objects / entities co-constructed / co-used by agents
 - encapsulating functionalities, services
 - tools enabling, mediating and constraining agent interaction
 - basic building block to represent / engineer *agent environment*

The A&A Approach: Properties

- *Use-based interaction*
 - agents *use* artifacts through their usage interface
 - agents act on artifacts, executing operations
 - agents perceive artifact observable state and events
 - Fully uncoupled and asynchronous interaction
 - no global time
 - each agent/artifact has/can have a local notion of time
- Support for intelligent agents & autonomic properties
 - agents can inspect and reason about artifacts state and functionalities, and possibly change/adapt them accordingly

TuCSoN Model & Infrastructure

- *Tuple centre* artifacts
 - programmable logic-based tuple spaces
 - generative communication
 - coordination laws as reactions in ReSpecT language
- Infrastructure dimension
 - tuple centres are spread over TuCSoN nodes
 - multiple tuple centres, distributed across the Internet



Benefits

- **Modelling**
 - both individual & social modelling dimension
 - possibility to model explicitly the environment, its properties and rules
 - modelling non-linear and emergent behaviours
- **Engineering**
 - designing and building distributed simulations
 - reusable framework/infrastructure for engineering different simulation contexts
- **Online/offline analysis**
 - simulations as online experiments
 - manual/automated observation & control of system behaviour

Modelling/simulating biological systems: different levels of interactions

- Four levels

- Interaction between molecules inside a compartment
- Interaction between compartments in a cell
- Interaction between cells of a system
 - E.g. immune system
- Interaction between systems
 - Immune, nervous, endocrine

- Focus on Intra-cellular Interaction

- Metabolic Pathways
 - control the production, transformation & consumption of energy in cells
- Signalling Pathways
 - regulating the flow of information within and between cells

A&A Metamodel for BioSimulation

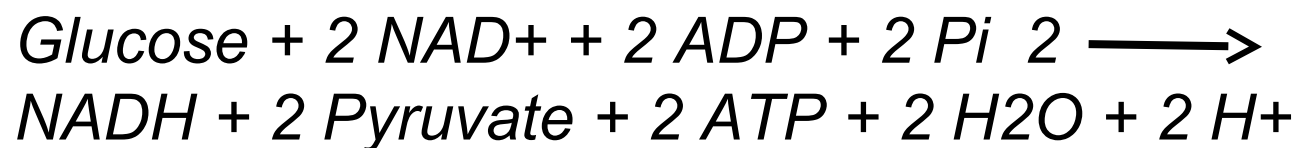
- Active bio-components as agents
 - encapsulating 'individual' chemical-reactions / behaviours
 - pro-active task/goal-driven activity
 - consuming, elaborating, producing molecules
 - examples: proteins like enzymes
- Biological compartments as artifacts
 - environment
 - encapsulating 'social'/ global chemical reactions / behaviours
 - collecting and managing molecules
 - governing bio-components interactions
 - choosing which reactions can take place
 - example: cytosol

Exploiting the TuCSoN Model

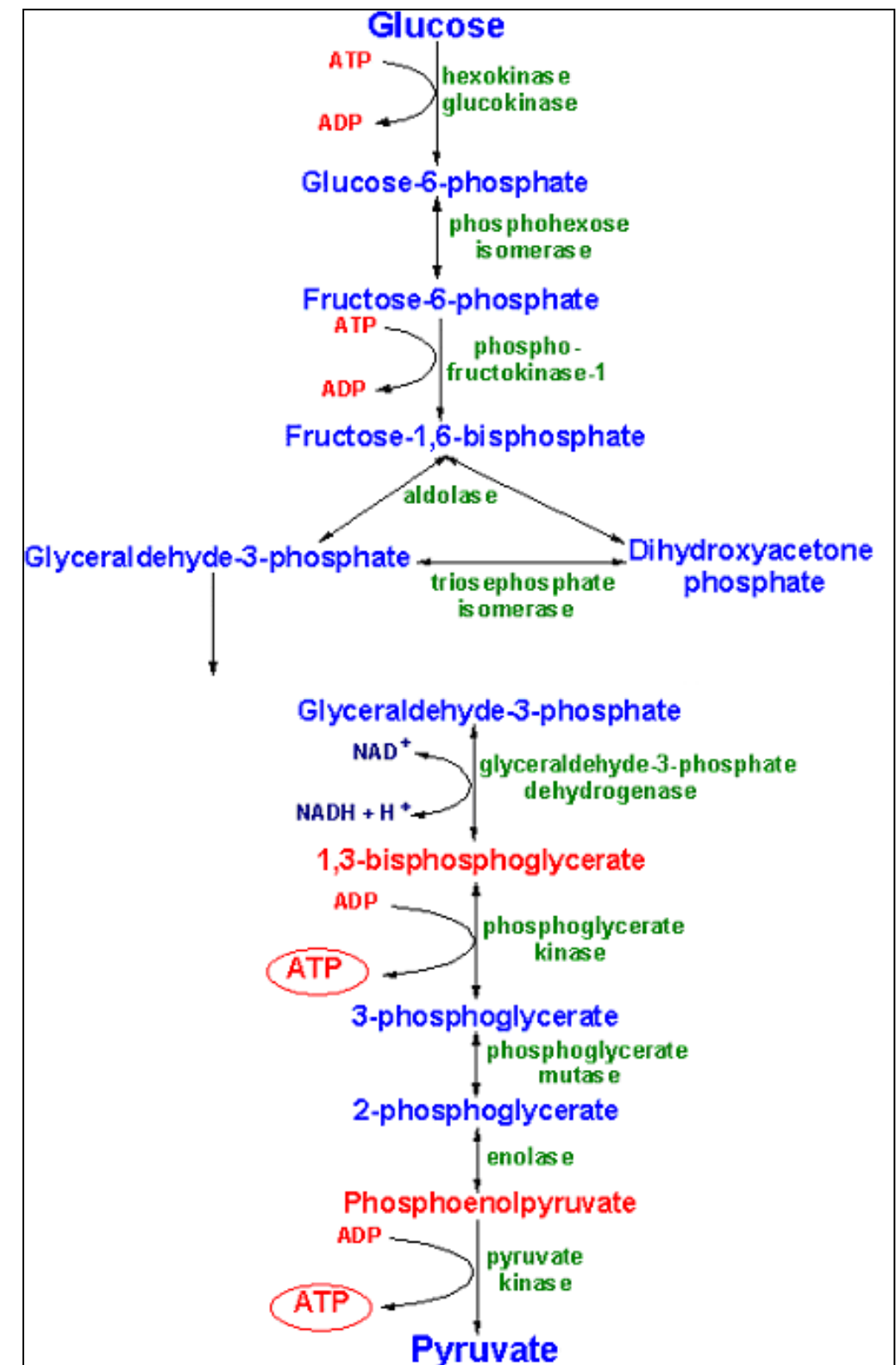
- Tuple centres to simulate bio-compartments
 - molecules represented by logic tuples
 - `molecule (Type, Number)`
 - operations available to agents for producing / consuming molecule
 - `bind(molecule_type(Qty, Affinity), ...)` → `in(...)`
 - `produce(molecule_type(Qty), ...)` → `out(...)`
 - `consume(molecule_type(Qty), ...)` → `in(...)`
- Programmed with reactions so as to
 - update & keep track of the molecules
 - select admissible interactions
 - with respect to affinity, stochastic effects, etc
 - execute 'global' chemical reactions

An Example: Modelling Glycolysis

- Well-known & studied metabolic pathway
- Global reaction

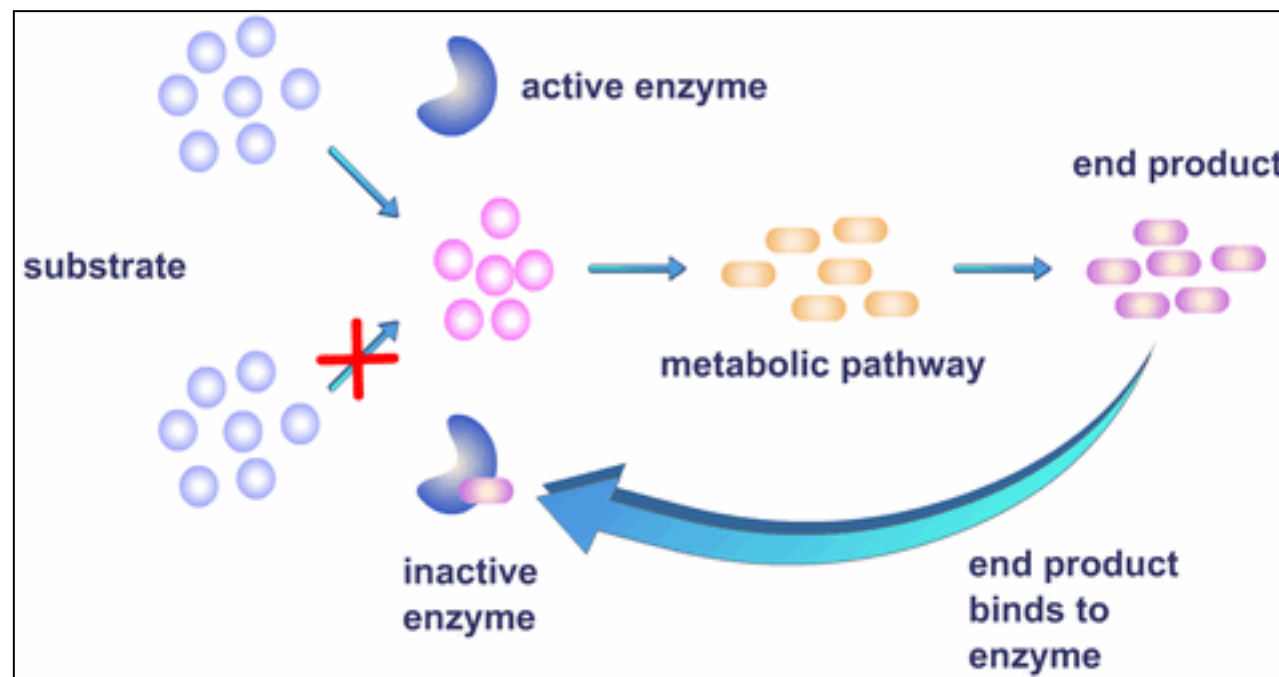


- 10 steps carried on by enzymes
 - catalysers
 - controllers of the overall process through allosteric regulating mechanism to guarantee:
 - enough ATP for cellular metabolism
 - not too much products (ATP & Pyruvate)



The Allosteric Regulating Mechanisms

- Controller enzymes modelled as agents
 - hexokinase (HK) as EnzHk Agent
 - phosphofructokinase-I (PFK-I) as EnzPfk Agent
 - pyruvate kinase (PK) as EnzPk Agent
- Compartments modelled as artifacts (tuple centres)
 - cytosol compartment as cytosol Tuple Centre

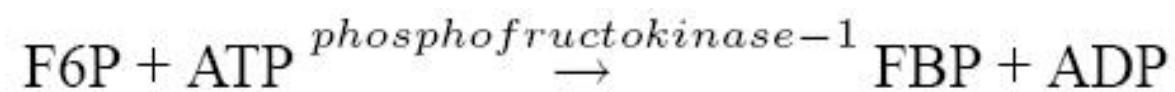


Modelling Phosphofructokinase-I (PFK-I)

- EnzPfk agent

- Goal

- controller of the glycolytic flow
 - converts fructose-6-phosphate & ATP to fructose-1,6-bisphosphate & ADP

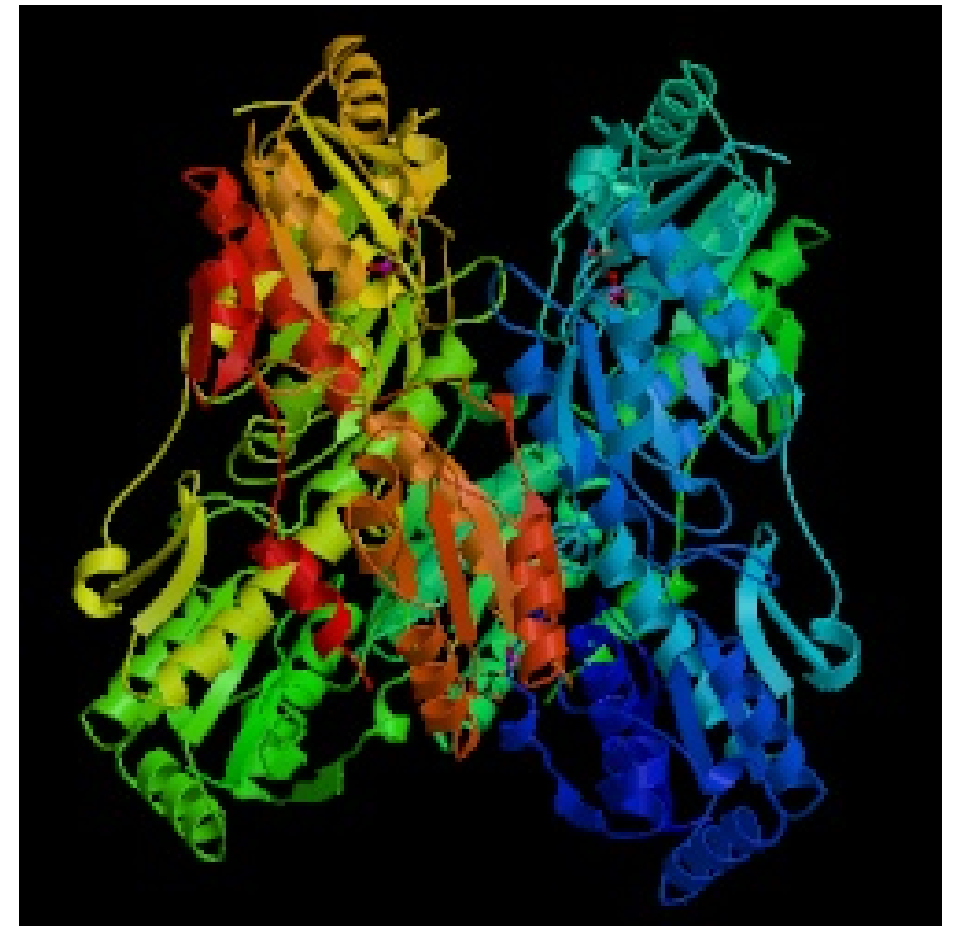


- Interaction

- consuming fructose-6-phosphate & ATP
 - producing fructose-1,6-bisphosphate & ADP

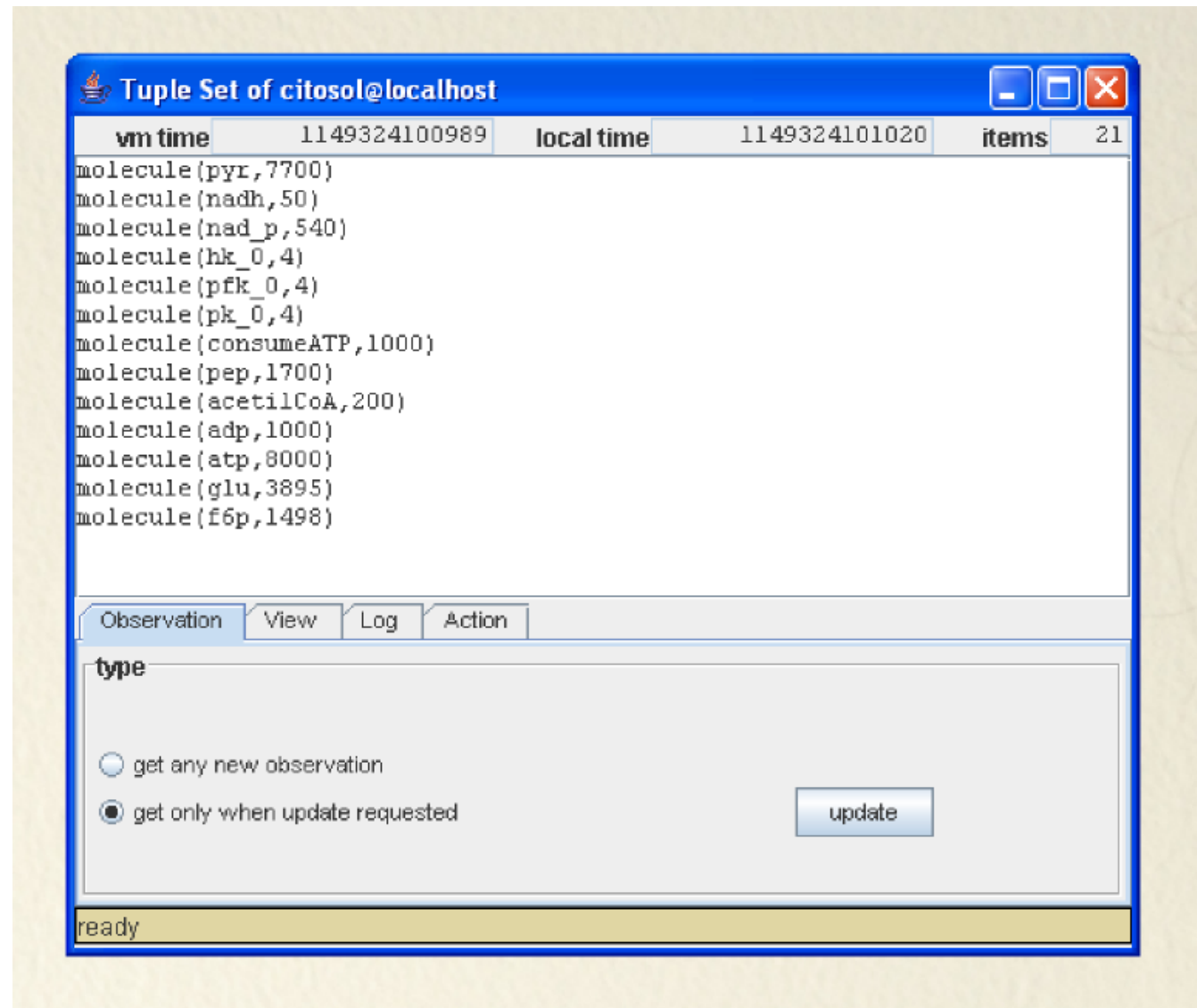
- Internal states

- ready, active, inhibited, reactive



Modelling Cytosol

- **cytosol tuple centre**
 - keeping track of & managing molecules involved in glycolysis
 - governing enzymes interactions
 - production / consumption of glycolysis molecules
 - stochastic behaviour in selecting the interactions that take place



First Tests

- Choosing / deducing starting values of system parameters

- From literature / empirical data

- number of molecules
 - number of enzymes (agents)
 - kinetic rate constants
 - affinity coefficients

- Calculating the rate of each reaction

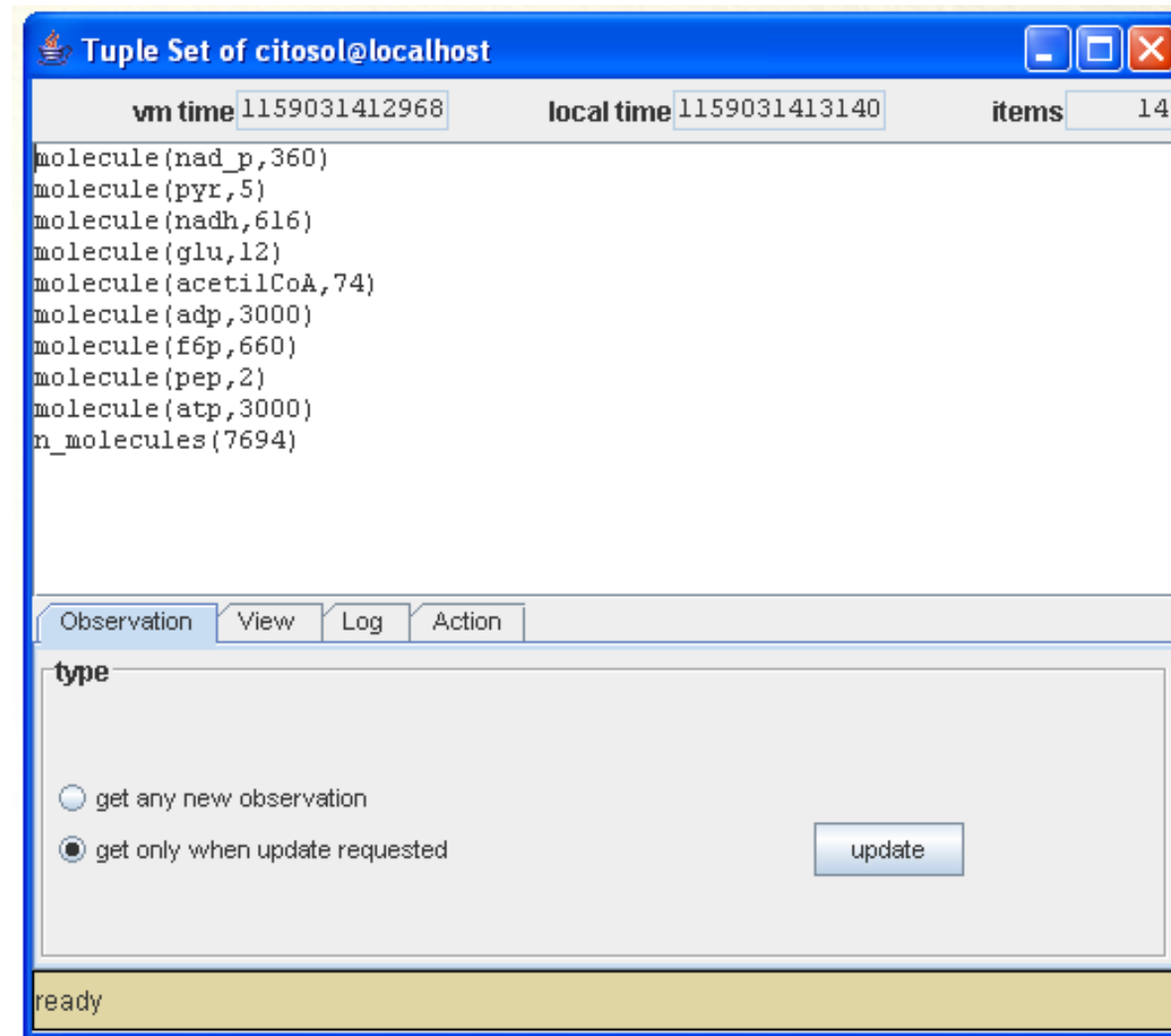
- From literature kinetic law formula

- as function of the overall number of molecules

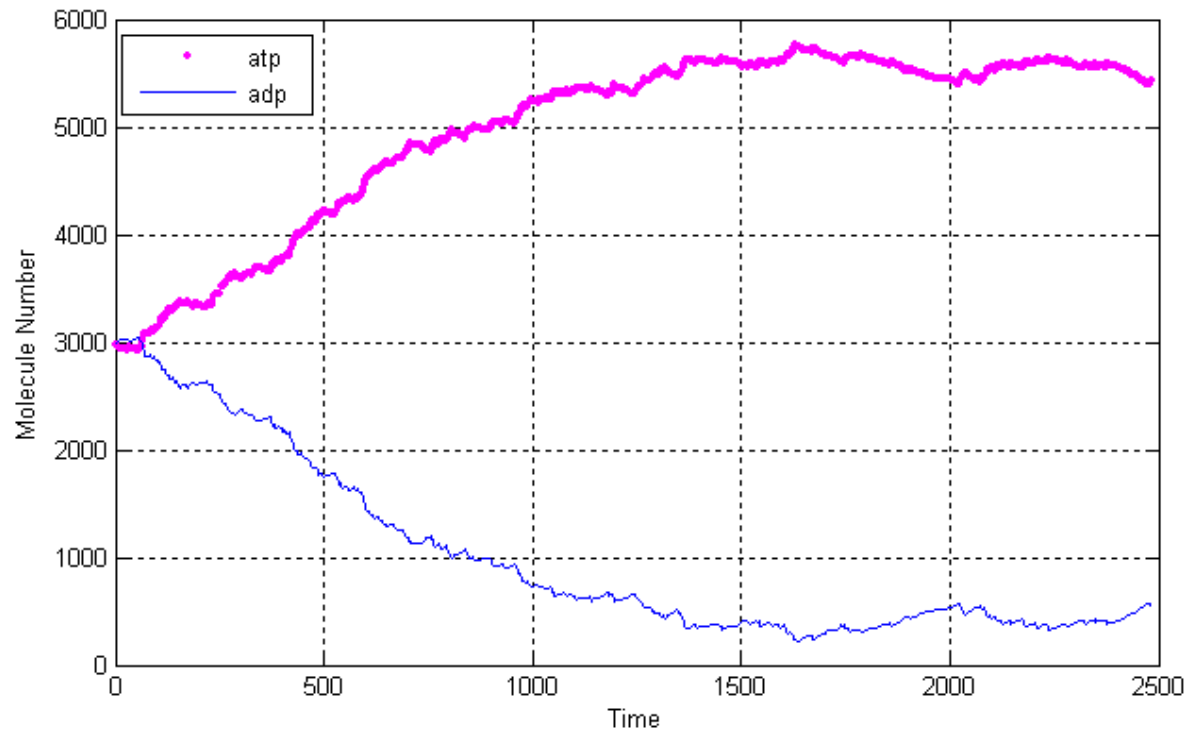
Biophysical Chemistry, Volume 72, Issues 1-2 ,
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Sustained oscillations in glycolysis: an experimental
and theoretical study of chaotic and complex periodic
behavior and of quenching of simple oscillations

K. Nielsen, P. G. Sørensen, F. Hynne and H. -G. Busse

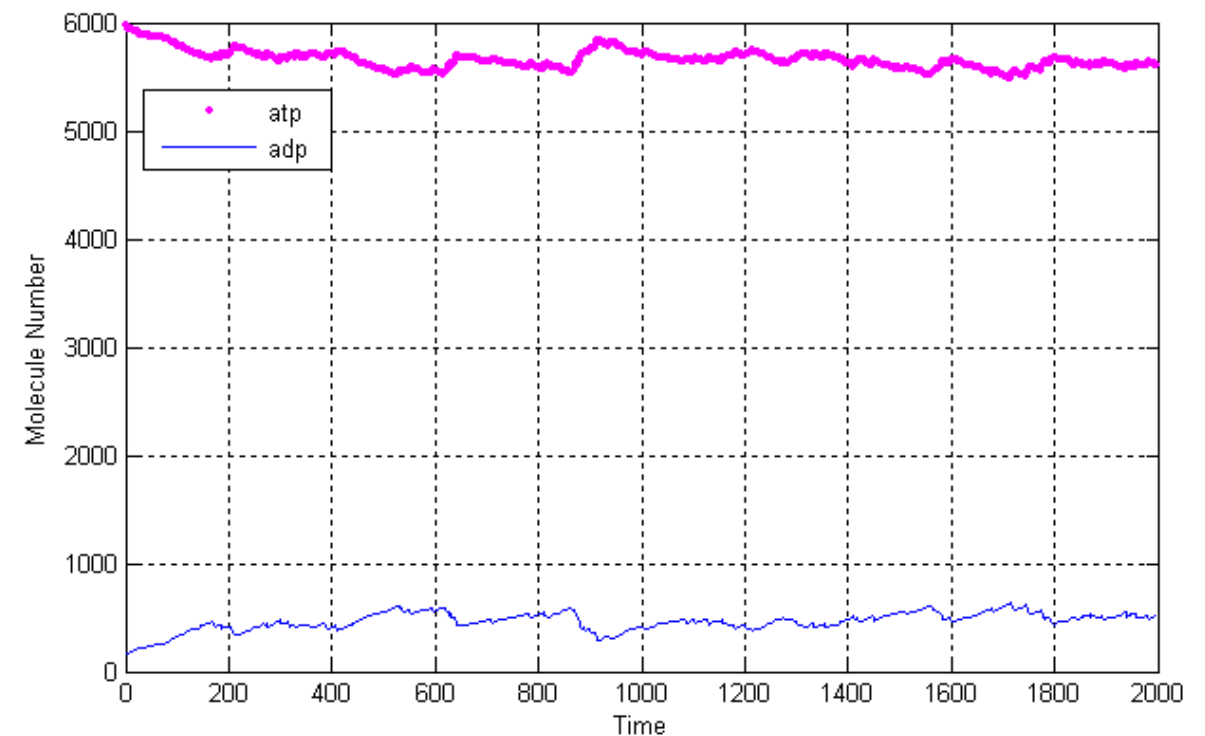
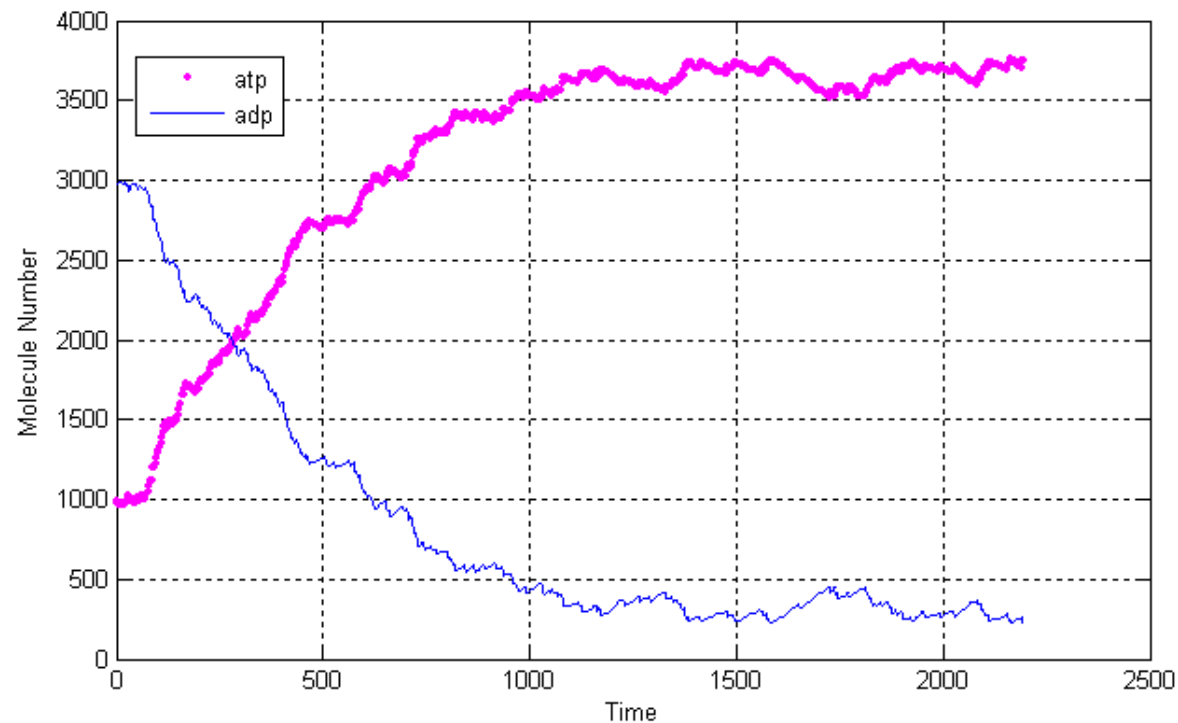


First results



Some interesting results from first tests:

- during the simulation, with different initial conditions, the ATP / ADP ratio tends to the same values observed / known from real experiments (about 10:1)



Conclusions

- A&A meta-model for engineering simulations
 - both agents and agent environment used as modelling and designing abstraction
 - promoting *online simulation / experiments*
- TuCSoN as concrete MAS model / infrastructure
 - tuple centres as artifacts
 - supporting distributed simulations
- First investigation in the Systems Biology context
 - Modelling and simulating intra-cellular dynamics
 - metabolic & signaling pathways
 - First tests of glycolysis metabolic pathway

Future Works

- Scientific
 - Improving the basic model
 - affinities & stochastic behaviour
 - reaction time
 - exploring in deep the *online experiment* metaphor & view
 - detailed comparison with existing approaches
 - Modelling MAPK (Mithogen-Activated Protein Kinase) transduction pathway
 - a key role in cell growth & cell cycle
- Engineering
 - Creating specialised API & tools on top of the basic infrastructure for rapid prototyping / execution / visualisation / control of (distributed) simulations



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