

Simulation of biological processes with Multi-Agents System

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LaBRI - the research laboratory in computer science

- Research unit associated with CNRS, INRIA and Bordeaux Univ.
- More than 200 members: 100 teaching/research staff, 14 research staff and more than 95 doctoral students and post-docs.

Six teams

- Combinatorics and Algorithmics.
- Image and Sound.
- Languages, Systems and Networks.
- Formal Methods.
- Models and Algorithms for Bio-informatics and Data Visualisation.
- Supports and Algorithms for High Performance Numerical Applications.



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Our group:

- Biologists: Sophie Colombié and Martine Dieuaide
- Computer Scientists: Pascal Desbarats, Richard Moussa, Nicolas Parisey, Francois Vallée.
- The national group: SMABio

Multi-Agents System - History

Cellular automata - the ancestors

- From the von Neumann and Ulma idea of creating a machine able to reproduce itself (40's).
- Representing this machine by a set of cells on a grid.
- Cellular automata model:
 - uniform grid,
 - the laws follow by each cell are a set of rules which compute the cell state from its previous state and its nearby neighbours.

J. Conway's game of life

- A finite set of rules to proliferate, to stay in live and to dead.
- Simulations produce an infinite set of behaviours for the whole set of cells: grid motifs.

game of life

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J. Conway's game of life

- With a cellular automata the behaviors, the *"rules"* are attached to the cell.
- A more complex design can be obtained with the adding of the concept of **agent**.

Multi-Agents System - In Nutshell

What is an agent

- An autonomous entity interacting locally with its neighbors.
- Situated in a 2D or 3D environment.
- An agent can be defined as reactive or cognitive.

Cognitive vs reactive agent

- **Cognitive agent** has mental states, knowledge, belief, ... and cognitive processes like reasoning, learning, problem solving, planning, natural language processing
- Mainly they observe their neighborhood, choose a strategy, collaborate, decide and adapt their behavior in order to achieve a task.

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- Mainly they observe their neighborhood, choose a strategy, collaborate, decide and adapt their behavior in order to achieve a task.
- **Reactive agent** is an agent with perceptual and acting capabilities with a kind of **stimulus-response** behavior.

• **Reactive agents** interact only with / through their environment

Simulation of biological processes with Multi-Agents System

Multi-Agents System - In Nutshell

Cognitive Agent

- J. Ferber (Multi-Agent System - 1999) has formalized organization of social groups of agents.
- Extension: an agent can be a rule, a task, a social role,
- Using to model economy evolutions, market strategy, chain optimization and logistics, traffic analysis ...
- Training agents such as virtual tutors,

Reactive Agent/Social Agent

- Social agents are reactive agents but leave in their environment information to the others.
- They are organized in colonies.
- **Social spiders** can be used to segment image - the spider's web gives the result. Applications in medical imaging - MRI brain image.

Multi-Agents System - Applications

Classical use cases - Ecology

- **Individual based models** for ecology.
- Boids: C. Reynolds (1986) flocking behaviour of birds.
- School of fishes formations.
- Ants: search for the better way to find the food.
- Predator/Prey: wolf-cheep's competition, virus propagation. It must have some prey (or safe person) to keep in live the predator (the virus).

NetLogo simulator

Modelling in Biology

Biological objects

- **Intra-cellular level**: metabolites, proteins, enzymatic complexes, DNA chains ...
- Metabolism: biochemical reactions, energy transfers,
- Metabolic pathways: chains of reactions, successions of transformations from a set of inputs <substrates> to a set of outputs <produces>

Modelling in Biology

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- Examples: glycolisys, respiratory chain, Krebs cycle
...

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Biological processes

- A biological function performs by a protein, an enzyme, a transporter: catalysis, signal transductions, activation, inhibition ...
- Most often a function can be perform by different objects.
- One object can have several roles.

Simulation of Biological Processes

Cellular Level

- Biological objects interact at different levels: atoms, molecules, complexes.
- Physical and biochemical laws are known and describe by set of equations but they work at different scales of time.
- Whole system exhibits functions resulting to combinations of multiple interactions.

Classical Modelling

- Set of **differential equations** to simulate the evolution of molecule concentrations.
- Unable to take into account localization. Many *“had hoc”* parameters.
- Often only possible to solve numerically.

System Biology

Study at the system level

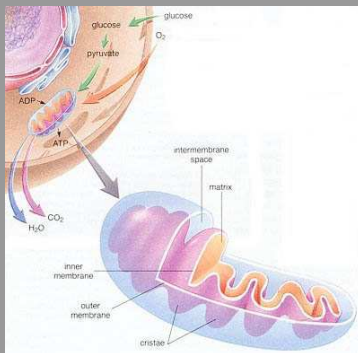
- New tools/technics to obtain data, large amount of data available.
- New biologist attempts: analyzing data in the system context.
- Large networks of local interactions.
- Living systems are complex system.

Secondary metabolism of tomato fruit

Mitochondria Metabolism

Mitochondria

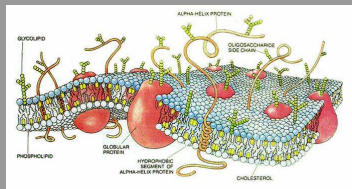
- Mitochondria is a small intra cellular organelle.



Mitochondria Compartment

Inner Membrane Simulations

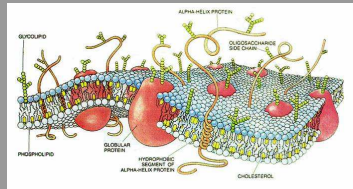
- A membrane is a set of phospholipids organized in bi-layer.



Mitochondria Compartment

Inner Membrane Simulations

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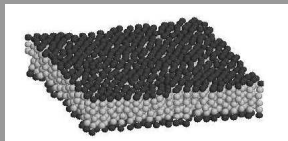
Set of problems

- Modelling a uniform membrane or from a geometric form is not satisfying.
- Designing interactions with membrane components is difficult.
- How insert enzymatic complexes in the membrane?

Mitochondria Compartment

Inner Membrane Simulations

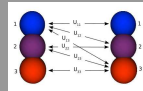
- A phospholipid has a head and a tail respect. hydrophilic and hydrophobic molecules.
- Coarse grain model to build an abstraction of phospholipids from the atom scale to the metabolism scale.
- Van der Waals forces code attraction/repulsion between phospholipids.



Farago model of membrane.

Coarse Graining Modelling

Existing tools



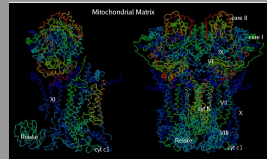
- We have used Farago 3 grains model .
- For each head, we have an attraction for the other head and a repulsion for all tails.
- A way to represent water - no possibility to represent explicitly water grains.

First agent model

- Each phospholipid is an agent.
- It has a body with 3 grains.
- Interactions between agent are computed at the grain level and summarized to compute a movement of the agent.

Enzymatic Complex Inside the Membrane

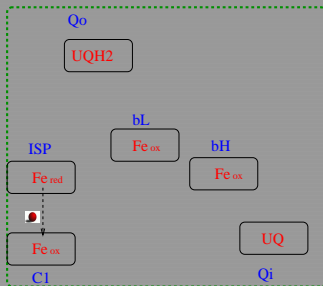
Complex III



- Crystallographic 3D structure is available.
- An enzymatic complex with 6 sites per monomer - 12 sites to take into account.
- Each site can be free or occupied.
- Reactions are constrained by red-ox potential rules.
- Metabolites can be in several states (2 or 3) from oxidized to reduced.

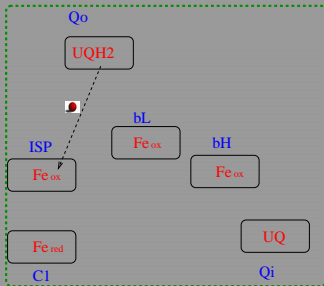
Ubiquinone Cycle

Etape 1



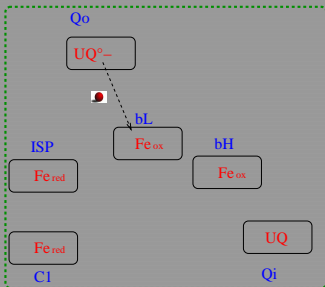
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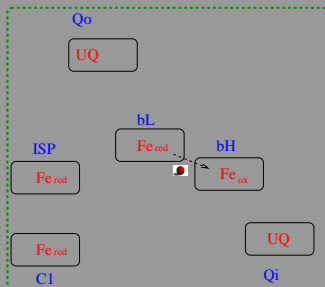
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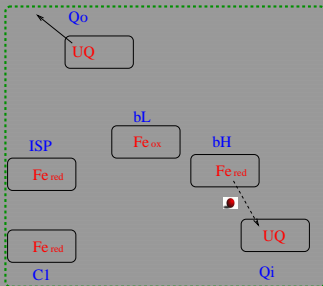
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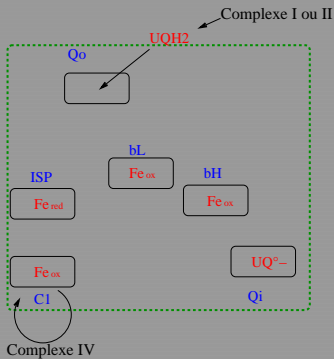
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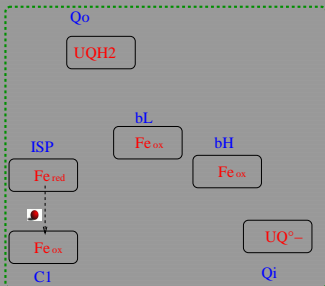
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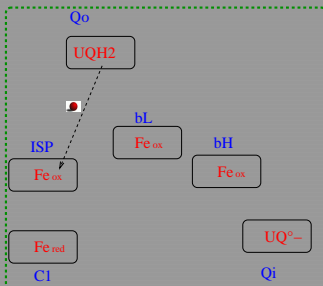
Ubiquinone Cycle

Etape 2



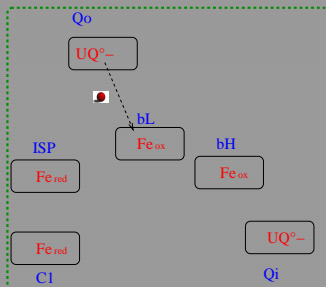
Ubiquinone Cycle

Etape 2



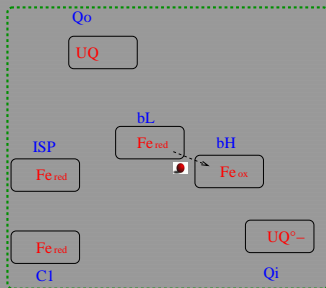
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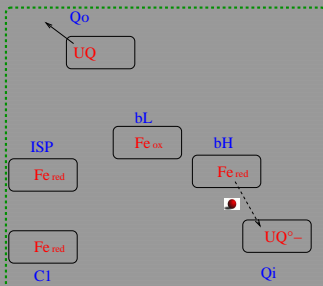
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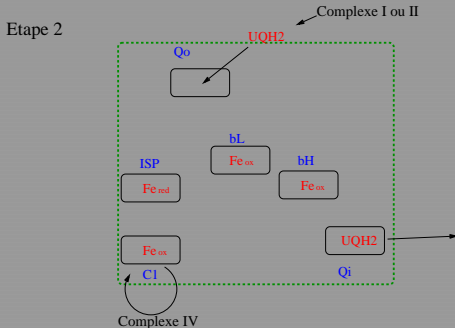


Ubiquinone Cycle

Etape 2



Ubiquinone Cycle



Combinatorial Explosion

Too many cases to take into account

- Existing ODE model represents only 12 situations for non-pathologic cases.
- More than 500 possibles states for the whole system.
- A few number of object types.
- A very few number of states for each biological object.
- A multi-agents system does not require to describe the whole sets of states but all situations can occur by simulation.
- Each interaction between molecules is not really complex. Allows local computations.

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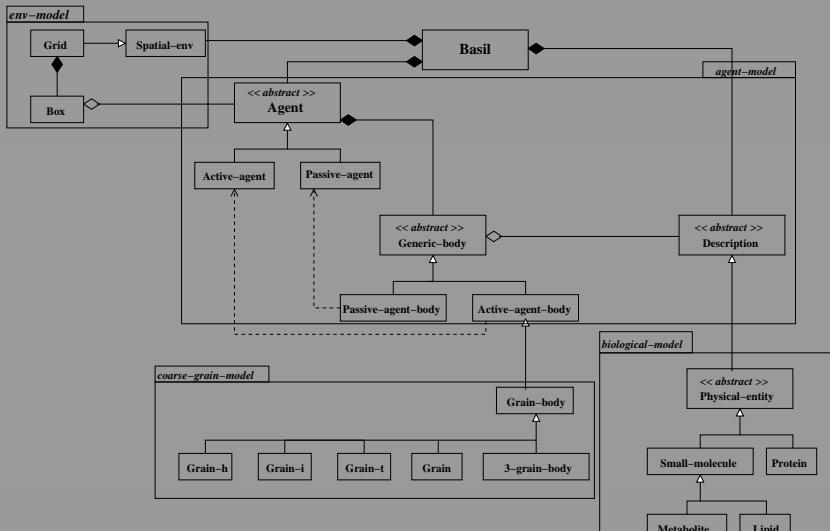
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- Each interaction between molecules is not really complex. Allows local computations.
- **Goal:**
 - Building a model which links protein movement and redox reactions.
 - Finding a way to extend coarse graining model to proteins.
 - Designing a specific agent model to represent agent with physical behaviors.

A new model for molecules

Biological agent

- Agent for molecules cannot be cognitive nor social.
- We keep **reactive** agent as basis but defined two subclasses: **active agent** and **passive agent**.
- **Active agent** observes its neighborhood, is able to capture small molecules (metabolites), and reacts.
- **Passive agent** has a random move. It is smaller and has no capability to have function.
- Each agent has a body. This body can follow a coarse graining model to move.

Multi-Agents Systems for Biology



Simulations - the “in silico” lab

- **Complex system**: with laboratory experiments, it is possible to observe per to per interactions between molecules but not to observe their links at the system level.
- Observing **emergence** of complex behaviors: membrane formation, consequences of coupling interactions.
- Providing a set of modules, independent but compatible.

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Limitations of the approach

- Memory consuming: number of agents/molecules.
- Time consuming: how many steps for a simulation?
- How to analyze the results? how to interpret them? simulations artefacts.
- How to compare simulations to lab experiments?
- ...

Parallelisation with GPU

- GPU is a very cheap solution
- Several solutions: CUDA and OpenCL
- Complexity is mainly only based on number of steps
- Parallel simulations allows to simulate real life: several active process at the same time, competition between entities can be reproduced.
- Probably the most popular technology in many domains for the next ten years
- Re-using Multi-agent system for image processing: segmentation of MRI Brain or cellular images.

Thanks for your attention !

QUESTIONS ?

