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Simulation of mitochondrial metabolism using multi-agents system

Charles Lales^{1&2}, Nicolas Parisey², Jean-Pierre Mazat², and Marie Beurton-Aimar^{1&2}

¹ Univ. Bordeaux 1, LaBRI CNRS UMR 5800, France

² Univ. Bordeaux 2, Mitochondrial Physiopathology Lab. INSERM U688, France

lales@labri.fr

nicolas.parisey@etud.u-bordeaux2.fr

jpm@u-bordeaux2.fr

aimar@labri.fr

Abstract. Metabolic pathways describe chains of enzymatic reactions. Their modelling is a key point to understand living systems. An enzymatic reaction is an interaction between one or several metabolites (substrates) and an enzyme (simple protein or enzymatic complex build of several subunits). In our Mitochondria in Silico Project, MitoScop, we study the metabolism of the mitochondria, an intra-cellular organelle. Many ordinary differential equation models are available in the literature. They well fit experimental results on flux values inside the metabolic pathways, but many parameters are difficult to transcribe with such models: localization of enzymes, rules about the reactions scheduler, etc. Moreover, a model of a significant part of mitochondrial metabolism could become very complex and contain more than 50 equations. In this context, the multi-agents systems appear as an alternative to model the metabolic pathways. Firstly, we have looked after membrane design. The mitochondria is a particular case because the inner mitochondrial space, ie matricial space, is delimited by two membranes: the inner and the outer one. In addition to matricial enzymes, other enzymes are located inside the membranes or in the inter-membrane space. Analysis of mitochondrial metabolism must take into account this kind of architecture.

1 Introduction

Metabolic pathways are a set of reactions catalyzed by enzymes which takes place inside cells. They constitute the cellular metabolism. In biology, numerical simulations allow interactions between molecules to test hypotheses about normal or pathologic behaviours. Metabolism can be viewed as a network. We have studied mitochondria, a specific intra-cellular organelle, which has its own enzymes and thus its own network, generally analyzed independently of the cell metabolism.

A classical way of modeling reaction chains is to use ordinary differential equations (ODE). With such models it is possible to describe the evolution of

the system. But many biological aspects are difficult to describe with ODE: particular situation where there are few molecules reacting (no average behaviour), influence of the mass or the conformation of the molecules, transient association of several molecules. However such examples correspond to biological cases like disturbance of the network caused by lack of some molecules during a small portion of time or genetic mutations which change enzyme conformation. All of this shows that new models for simulation like these using **multi-agents systems** may improve the understanding of biological processes.

One way to design a biological network is to see it as a world filled with more or less complex entities. One entity could be a simple molecule like a metabolite or an enzymatic complex. Each reaction is described by interactions between entities belonging to this world. In our model, each entity is represented by a reactive agent. This agent is situated in a 3D space and the reactions are scheduled by time steps.

In this paper, we show what is needed to model metabolism pathways with a multi-agents system (MAS) in the context of the mitochondrial metabolism. We present a first approach to a 3D molecular design and the application to the particular case of the two mitochondrial membranes: the inner and the outer one. Each of them is composed of a phospholipids bilayer containing enzymatic complexes. The attention is focused on a generic description of molecular interactions in order to use this behaviour both for simple case as lipids and for more complex one like respiratory chain enzymes.

2 Mitochondria: their membranes and their energetic metabolism

Mitochondria (see Fig.1) are intra-cellular organelles which are the power plant of the cell. They are delimited by a double membrane, composed of phospholipids, which are naturally arranged in a bilayer to minimize their interactions with water. The energy delivered by mitochondria comes from a complex mechanism, involving a series of oxido-reduction reactions called "*Respiratory chain*" using oxygen we breathe in and the nutriments we ingest. They are catalyzed by four highly structured protein complexes and electron transporters (CoenzymeQ and CytochromeC) embedded in the inner mitochondrial membrane. Electrons transfer is linked to an extrusion of protons outside the mitochondria, creating an electro-chemical gradient, which will be used for ATP synthesis and other works [6][7]. This process involves the respiratory chain and ATP synthesis, both of them called "*Oxidative phosphorylation*". Oxidative phosphorylation has been modelled for a long time in order to integrate all the kinetic and thermodynamic properties of chemiosmosis theory developed by Peter Mitchell [7].

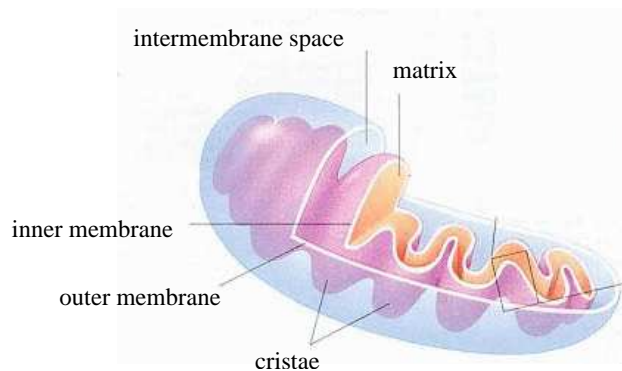


Fig. 1. Mitochondria from <http://universe-review.ca/>

However some aspects, particularly the electron transports between complexes I or II and complex III of the respiratory chain by a molecule called CoQ presenting different redox states, is rather complex [8]. CoQ is certainly a central point in electron transport in respiratory chain. This transport appears rather difficult to model with ODE [1] due to the great variety of interactions, of the reactions involved at different reacting sites and of the amount of the various redox CoQ species. In addition, these reactions take place inside the inner mitochondrial membrane which is a highly heterogeneous medium (see Fig.1).

All these questions could be addressed with a multi-agents model. In fact these problems illustrate how an MAS approach is highly suited to take care of spatial disposition of the various enzymatic complexes, competition between different complexes to access to some finite resources, complex interactions between several types of molecules (membranes and enzymes) sometimes in low quantity, environment effects (locally or not).

In the next section, we firstly describe the generic characteristics of the retained MAS. Finally, we describe the specific molecular modeling (section 4).

3 A multi-agents model for metabolic pathways

Our MAS uses a 3D continuous space where the agents are situated. *Situated* Agents use space as modality of their interactions. The distances between agents are used to describe neighbouring rules. All the agents have a local perception of their neighbourhood. A grid divides space into neighbouring units which simplify interactions complexity giving directly neighbour positions.

The MAS is called *open* because of the variable number of the agent during simulation. The continuous degradation and synthesis of molecules is a common biological process.

The time is discretized and a scheduler is defined for each type of agents. Actually, the inner-mitochondrial membrane is composed of enzymes and phospholipids. An enzymatic reaction should not be simulated on the same time-scale as two phospholipids interaction. One can also notice that it is possible to simulate time continuity with a discretization based on events and not on time steps.

In general, the level used for representing the biological objects, i.e. the model granularity, varies from atom to molecular groups (see [4] for a short review). One can notice that an abstraction by a single point is not sufficient to take into account a dynamic 3D structure and its spacial orientation (see Fig.2). On the contrary, molecular modeling simulation (atom by atom) is not possible for a whole organelle due to the large number of entities to compute.

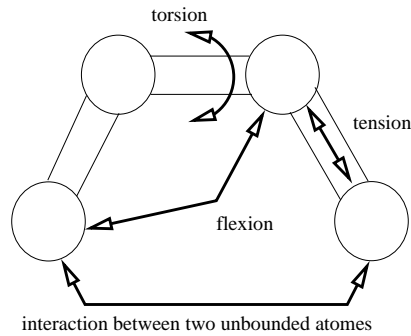


Fig. 2. Potentials deformations applied to a simple molecule.

A phospholipids model published by Edwards [2] uses two interacting points per molecule. In order to design a more generic model, we have extended this previous model. Our model is suitable for modeling metabolites and enzymes alike. Thus we have chosen to reduce each agent (molecule) to its gravity center and its interacting points. An interacting point is a portion of molecule that could be affected by external forces: hydrophobia, electrostatic charges, etc Fig.3 shows the generic 3D structure (part A) and its application to a phospholipid design (part B). Forces and torques are applied at the gravity center. Forces induce linear acceleration whereas torques induce angular acceleration as in classical mechanics.

Spatial localization of each interacting point is defined by a vector in the local frame associated with the agent (molecule) using its gravity center as origin. This design gives information about the 3D structure of the molecule and its space orientation but also its internal dynamics.

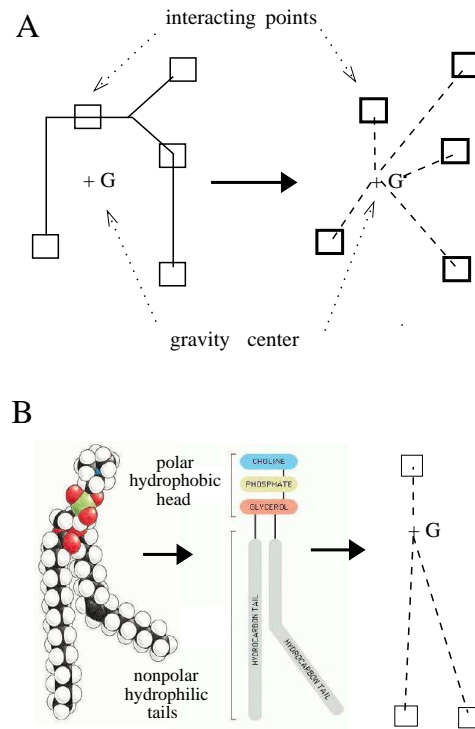


Fig. 3. A: abstracted 3D structure. B: application to a phospholipid.

Modeling internal dynamics could be important parameters in enzymatic reactions. For example, an already filled active site will not be able to react with another metabolite. A lot of enzymes interact with more than one metabolite, in a certain order or randomly, before transforming them into new products. The enzyme conformation could evolve after the binding of a first substrate, revealing a second active site for a second type of substrate. Our model allows these flexible movements.

Even if their freedom is limited, the interacting points can be seen as agents and thus molecules as communities of linked agents.

Each pair of interacting points defines one direction with two types of interaction - attraction/repulsion. Therefore, n interacting points could induce $2n(n - 1)$ forces with intensity depending on the distance between agents. As shown in Fig.4, the interactions between phospholipids can be given by 4 forces f_1, f_3, f_4, f_5 that describe hydrophobia, another one f_2 for hydrophilic and electrostatic charges, and the two last ones f_6, f_7 for the molecular incompressibility.

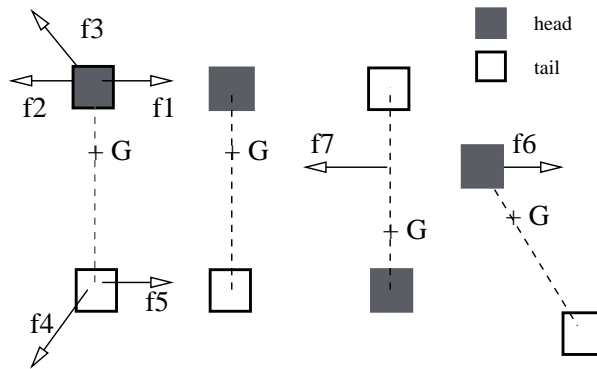


Fig. 4. Example of interaction forces for phospholipids.

As a first step, we have implemented simple functions with three parameters (Fig.5 A): a_k - maximal magnitude value of f_k , r_k - the radius value under which f_k magnitude is maximal - and r'_k - the radius value over which f_k is null. A second step will be to study the impact of the choice of functions over phospholipid structure formation that would emerge from MAS simulations. Fig.5 B shows another function possibility.

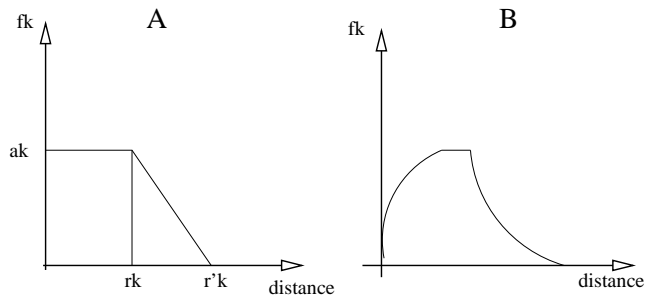


Fig. 5. Forces intensities are function of the distance. A: simple ramp function. B: example of other function available.

With this approximation, the interactions between agents are reduced to a set of forces. For a molecule i in interaction with its neighbors, the compound force is:

$$\vec{F}_i(t) = \underbrace{a_{lin} \sum_h \sum_{j \neq i} \sum_k \vec{f}_{h,k}(t)}_{\alpha_{lin}} + \underbrace{b_{lin} \overrightarrow{rand}_{lin}(t)}_{\beta_{lin}} - \underbrace{c_{lin} \vec{V}_i(t)}_{\gamma_{lin}}$$

where:

- ▷ α_{lin} is the forces from the neighborhood (forces from the k interacting points of the molecule j acting upon the h interacting points of the molecule i),
- ▷ β_{lin} is the thermal effects depending on molecule type,
- ▷ γ_{lin} is the friction (\vec{V}_i = molecule velocity) depending on molecule type.

Linear and rotational accelerations are thus given by Newton's Second Law - the fundamental law of dynamics: the acceleration of an object of constant mass is proportional to the resultant force acting upon it ($\vec{F}_i(t) = m \vec{a}$). This compound force is used in the power series (order 2) of the position function $\vec{X}_i(t)$:

$$\begin{aligned} \vec{X}_i(t + \delta t) &= \vec{X}_i(t) + \frac{d\vec{X}_i(t)}{dt} \delta t + \frac{d^2\vec{X}_i(t)}{2dt^2} \delta t^2 + o(\delta t^2) \\ \Leftrightarrow \Delta \vec{X}_i(t + \delta t) &= \vec{V}_i(t) \delta t + \frac{1}{2} \vec{a}_i(t) \delta t^2 + o(\delta t^2) \\ \Leftrightarrow \Delta \vec{X}_i(t + \delta t) &= \vec{V}_i(t) \delta t + \frac{1}{2m} \vec{F}_i(t) \delta t^2 + o(\delta t^2) \end{aligned}$$

Each time step of the simulation requires for the linear movement:

$$\begin{cases} \Delta \vec{V}_i(t + \delta t) \approx \frac{1}{m} \vec{F}_i(t) \delta t \\ \Delta \vec{X}_i(t + \delta t) \approx \vec{V}_i(t) \delta t + \frac{1}{2m} \vec{F}_i(t) \delta t^2 \end{cases}$$

where:

- ▷ m is the molecule mass,
- ▷ \vec{X}_i is the vector position of the gravity center of the molecule (i.e.: the origin of the local frame).

The forces applied by neighboring molecules induce torques. The compound torque is:

$$\vec{T}_i(t) = \underbrace{a_{rot} \sum_h \sum_{j \neq i} \sum_k \vec{\tau}_{h,k}(t)}_{\alpha_{rot}} + \underbrace{b_{rot} \overrightarrow{rand}_{rot}(t)}_{\beta_{rot}} - \underbrace{c_{rot} \vec{W}_i(t)}_{\gamma_{rot}}$$

where:

- ▷ α_{rot} is the torques from the neighborhood (torques from the k interacting points of the molecule j acting upon the h interacting points of the molecule i),
- ▷ β_{rot} is the thermal effects depending on molecule type,
- ▷ γ_{rot} is the rotational friction depending on molecule type.

In the same way, each time step of the simulation requires for the angular movement:

$$\begin{cases} \Delta \vec{W}_i(t + \delta t) \approx \frac{1}{I} \vec{T}_i(t) \delta t \\ \Delta \vec{\Theta}_i(t + \delta t) \approx \vec{W}_i(t) \delta t + \frac{1}{2I} \vec{T}_i(t) \delta t^2 \end{cases}$$

where:

- ▷ I is the rotational inertia linked to the molecule size,
- ▷ $\vec{\Theta}_i$ is the vector perpendicular to the rotation plan, oriented so that the rotational movement is positive and which has a norm corresponding to the angular variation.

This model with interaction points and gravity center seems to be a right way to take into account the internal dynamics, the 3D structure and the space orientation of the different biological molecules. Moreover the possibility to adapt the agent granularity gives the possibility to design heterogeneous molecules.

4 Application to the mitochondrial membranes and mitochondrial metabolism

In a first attempt, we used this model to design mitochondrial membranes. Two embedded membranes appear as an important characteristic of mitochondria. The inner membrane is the more irregular one. As can be seen in Fig.1 one can understand that giving a mathematical definition of this form will be rather difficult. On the other hand, using an emergent property of MAS (analogous to natural membrane formation) can presumably be a better solution. It can take into account the diversity of phospholipids constituting the bilayer and the fact that the inner mitochondrial membrane is also composed of a large amount of proteins complexes.

MAS also appear well suited to simulate the respiratory chain reactions, particularly the electron transport, which occurs inside the inner membrane and the proton transport which occurs across it. In principle, the mitochondrial application of our MAS model should allow the natural emergence of the complex electron transport by CoenzymeQ (CoQ) described under the name of "Q-cycle" [8], based on the reactions rules described for each CoQ site on complexIII.

There is another field, in which MAS would certainly have a great interest ; it is the field of mitochondrial diseases due to deficiencies in respiratory complexes. Mitochondrial diseases are a group of complex pathologies, which can affect

different unrelated tissues with an unexpected association of symptoms ([5], [10]).

The disturbance in the distribution of the various CoQ species due to mutations in respiratory chain complexes (giving sometimes only mild respiratory chain deficiency) seems to be at the origin of (severe) mitochondrial diseases [9]. Our MAS model easily describes the distribution of the various redox CoQ species during the evolution of the reactions, for any state of the respiratory complexes. It thus will give a strong help to describe the plausible properties of the system and to design new experiments allowing us to better understand these complex pathologies.

Finally reduced CoQ is an antioxidants [3]. Chemical derivatives of this molecule are studied in order to reinforce its antioxidant properties and to treat the oxidative stress in some mitochondrial diseases or during aging. Our MAS model will help specifying the relevant targets of these molecules, to keep them in their antioxidant form and thus help designing their properties.

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