

A Stochastic Approach of Mitochondrial Dynamics

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Abstract—Mitochondria are dynamic organelles, capable to interact with each other. While the number of mitochondria in a cell varies, their quality and functionality depends on the operation of fusion, fission, motility and mitophagy. Nowadays, several researches declare as an important factor in neurodegenerative diseases the disruptions in the regulation of mitochondrial dynamics. In this paper a stochastic model in BioAmbients calculus is presented, concerning mitochondrial fusion and its distribution in the renewal of mitochondrial population in a cell. This model describes the successive and dependent stages of protein synthesis, protein's activation and merging of two independent mitochondria.

Keywords—Mitochondrial Dynamics, P-Calculus, Stochastic Modeling.

I. INTRODUCTION

THE number of mitochondria in a cell is regulated to match the cell's requirements for ATP, while fusions and fissions play a functional role in maintenance of proper inner membrane electrical potential. Without the mitochondrial dynamics, the mitochondrial population consists of autonomous organelles that have impaired function [1]. In a wild-type cell, high rates of fusion and fission are independent events, which constantly change the identity of individual mitochondria. Fusion is likely to protect function by providing a chance for mitochondria to mix their contents, thus enabling protein complementation, mtDNA repair and equal distribution of metabolites, helping the isolation of damaged mitochondrial segments and promoting their autophagy [2]. In contrast, fission acts in order to facilitate equal segregation of mitochondria into daughter cells during cell division and to enhance distribution of mitochondria along cytoskeletal tracks. The failure in this biological machinery may also promote apoptosis [3]. A further two important aspects of mitochondrial dynamics beyond fusion and fission is the motility of mitochondria and mitophagy. It has been proved that perturbations in mitochondrial dynamics can lead to distinctive defects in neurons [4]. The large tangle of highly interconnected mitochondria in fission-deficient cells prevents

efficient movement, especially into small pathways such as neuronal processes [5]-[6]. While mitophagy denotes the degradation of mitochondria through autophagy, recent findings indicate that mitophagy can selectively degrade defective mitochondria [7]. Finally the mitochondrial motility is critically important, distributing their population evenly within the cell body. Recent studies have shown that mitochondria are significantly reduced in Alzheimer's disease (AD), supporting a topographic and probably temporal relationship between neuronal oxidative damage and mitochondrial abnormalities [8]. While AD can be genetically classified as familiar or sporadic, researchers proposed that the case of sporadic AD is not caused by the accumulation of amyloid- β ($A\beta$), but instead is a consequence of a decline in mitochondrial function with age [9]-[10]. Additionally, the overexpression of $A\beta$ causes an alteration in the mitochondrial fission and fusion proteins resulting in mitochondrial dysfunction, mitochondrial fragmentation, increase in reactive oxygen species (ROS) and ATP production and reduced mitochondrial membrane potential [11]. In the brain, mitochondrial function declines with age and this functional decline associates with increased mitochondrial biogenesis. In various neurodegenerative disease states brain mitochondrial function declines even further, perhaps to the point where mitochondrial biogenesis can no longer compensate for functional declines [12]. The mitochondrial fusion can be represented as an artificial parallel system where several units operate at the same time. These units can interact with each other and thus mutually affect their behaviour. Formal models are used to model real-world parallel systems, like complex molecular and biological systems or work flow in business management. Formal models of parallel systems use precise mathematical methods to capture overall or specific behaviour of a selected system. Different formal models are designed to achieve different aims. In this paper we concentrate solely at process calculi which constitute one of the possible approaches to model concurrent systems. Specifically, a stochastic model in BioAmbients calculus is presented, concerning mitochondrial fusion and its distribution in the renewal of mitochondrial population in a cell.

II. MITOCHONDRIAL DYNAMICS

Mitochondria provide most of the ATP for cellular reactions. ATP production in mitochondria is coupled to an electron transport system in which the passage of electrons down the various electron carriers is associated with the transport of protons from the matrix into the inter membrane space. The majority of these protons re-enter the

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mitochondrial matrix by the ATP syntheses, thereby generating ATP. From a geometrical point of view, it is quite obvious that a number of (un) correlated factors can affect the mitochondrial shape. There is a more complex problem, as morphological changes in mitochondrial structure are associated with biological dysfunctions and electrophysiology problems. These effects are directly or indirectly correlated with human neurodegenerative diseases. While fusions and fissions contribute to the wide variety of mitochondrial morphologies, a discrete mitochondrion at one point in time will be changed at a later time by the addition of new mitochondrial material through fusion or by the removal of material through division. It is a logical consequence of high probability that after a certain period of successful events (fusions and fissions) the inner structure will totally lose its initial characteristics in a non-reversible way, restricting the inner space and reducing the corresponding area and energy. It is obvious that any failure in inner membrane mitochondrial fissions can easily generate unstable electric potential, effecting functionality and reduce voltage gradient [13]. For the mitochondrial fusion three different mammalian proteins are required. Mfn1 and Mfn2 for outer membrane fusion, and OPA1 for inner membrane fusion [14]-[16]. Mutations in these proteins can impact several kinds of nerves. On the other hand, mitochondrial fission in mammals is mediated by a dynamin-like protein, Drp1 [14]. Drp1 is a predominantly cytosolic protein that is recruited to mitochondria during fission. Recent studies have identified another tail-anchored outer membrane protein, Mff, which is involved in mitochondrial fission [17]. In yeast, latest studies proved also the importance of the mitochondrial outer membrane protein Fis1 for the operation of fission [18]. Fusion is likely to protect function by providing a chance for mitochondria to mix their contents, thus enabling protein complementation, mtDNA repair and equal distribution of metabolites. Fission likely acts instead to facilitate equal segregation of mitochondria into daughter cells during cell division and to enhance distribution of mitochondria along cytoskeletal tracks [4].

III. MODELING USING BIOAMBIENTS CALCULUS

In this section a case study for the application of pi-calculus algebra in parallel biological is presented. More specific, a model for the mitochondrial fusion in BioAmbients calculus, which is one of the first process calculi with an explicit notion of compartments [19], is proposed. A BioAmbient system, which contains the communicating processes, is seen as a hierarchy of nested ambients that generally abstracts compartments. These compartments introduce a notion of location. The boundary surrounding the ambient defines what is inside and what is outside it. Various kinds of action involving compartments can be easily represented, such as transport of molecules across compartments. Ambients can be nested within other ambients, with each ambient harboring a collection of sub-ambients, with their content. Ambient moves as a whole with its component processes and sub-ambients. The processes inside an ambient control it by instructing it to

move. Compartment movement occurs when an entire compartment moves with respect to the other compartments in the system. The most typical event is the merge of two membrane-bound compartments, in which two separate compartments become one, with their contents shared. In other cases, compartments may enter or exit one another, in cases such as mitophagy or entry of a complex molecule (a molecular compartment) into an organelle (a membrane-bound compartment). Capabilities can change the ambient hierarchy by allowing ambient entry, exit, or merge. All capabilities are synchronized in pairs, using named channels. Ambient boundaries restrict communication between processes. The proposed stochastic model initially creates the proteins Mfn1-Mfn2 in the outer mitochondrial membrane and OPA1, in the inner mitochondrial membrane, respectively. Then, an interaction phase is taken place in order to activate OPA1 by the Mfn1- Mfn2. Finally, the merge of two independent mitochondria is occurred for the completion of mitochondrial fusion. Mitochondria, membranes, nucleic acids, genes and proteins are the biological data of this problem.

For better comprehension, the simulation can be formulated through the following steps (Figure 1):

- 1) We assume as M1 and M2 the two independent mitochondria and we represent as two separate ambients the outer and the inner membranes, named OuterMembraneOfM1&M2 and InnerMembraneOfM1&M2 respectively.
- 2) Two genes, gene Mfn1-Mfn2 and OPA1 gene are represented as two ambients, the GeneMfn1-Mfn2 and the GeneOPA1 respectively.
- 3) The transcribed DNA of genes (mRNA) is presented as two ambients RNAMfn1-Mfn2 and RNAOPA1 in the ambients GeneMfn1-Mfn2 and GeneOPA1 respectively
- 4) Protein Mfn1-Mfn2 is represented by an ambient named ProteinMfn1-Mfn2 which is contained in the ambient RNAMfn1-Mfn2, while OPA1 protein is represented by an ambient named ProteinOPA1 which is contained in ambient RNAOPA1.
- 5) The ambients Transcr and Transl contribute to the transcription and translation process respectively.
- 6) The inactive status of the protein Ku is represented as an ambient named BountKu in the ambient ProteinKu.
- 7) The active status of the protein OPA1 is represented as an ambient named ActiveOPA1 in the BountOPA1
- 8) Ambients RNAdeg and Proteindeg contribute to the destruction of mRNA and protein respectively.
- 9) Kinase, which is responsible for the activation of the protein Ku, is represented as an ambient named Kinase in the ProteinMfn1-Mfn2.

The modeling process for the creation of the protein Mfn1-Mfn2 begins with the transcription of DNA into mRNA, which has two sub steps. It consists of a (sibling) communication in the channel basal between GeneTLC1 and Transcr, followed by a (exit/expel) communication in channel a between GeneMfn1-Mfn2 and RNAMfn1-Mfn2, which has

resulted in the elimination of the RNAMfn1-Mfn2 from GeneMfn1-Mfn2. At this point RNAMfn1-Mfn2 is able to react with Transl. The mRNA translation is completed in two steps: a (sibling) communication in the channel utr between RNAMfn1-Mfn2 and Transl is done, followed by a (exit/expel) communication in channel b between RNAMfn1-Mfn2 and ProteinMfn1-Mfn2, which has resulted in the elimination of the ProteinMfn1-Mfn2 from RNAMfn1-Mfn2. The last action represents the creation of protein Mfn1-Mfn2 after the translation of RNAMfn1-Mfn2. The production of protein OPA1 is a similar process. The production process of the above two proteins is independent.

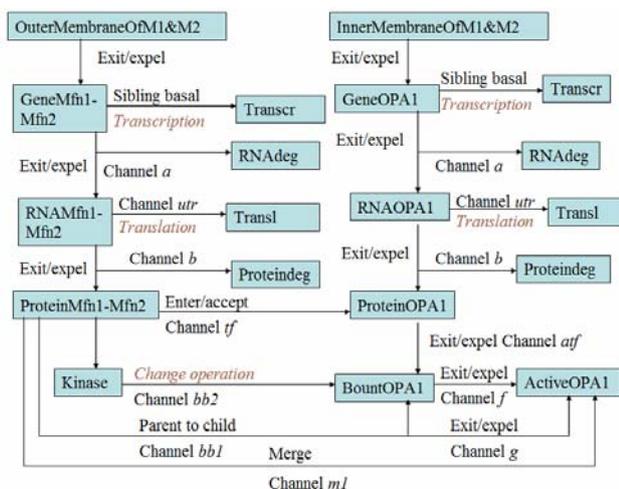


Fig. 1 Diagrammatic representation of the proposed model, where M1 and M2 are two independent mitochondria of the same cell

The process of activating the protein OPA1 follows these steps (Figure 1): Initially, the protein Mfn1-Mfn2 binding protein OPA1 with a (enter/accept) communication in channel tf, between ProteinMfn1-Mfn2 and ProteinOPA1. Then ProteinOPA1 eliminate the BoundOPA1 with an exit/expel communication in channel atf. Kinase alters the function of BoundOPA1 by a (sibling) communication in the channel bb2, followed by a parent to child communication in channel bb1 between ProteinMfn1-Mfn2 and BoundOPA1. Finally, by an exit/expel communication in channel f between ActiveOPA1 and BoundOPA1, and an exit/expel communication in channel g between ActiveOPA1 and ProteinMfn1-Mfn2, ActiveOPA1 come to the surface, which as mentioned is represented the active form of protein OPA1.

Finally, the modeling of the above problem in BioAmbients calculus is as follows:

X1:=(s2s basal?{x2}.expel a.X1 + s2s pa?{x1}.expel a.X1)
X2:=exit a.(s2s utr?{x4}.expel b.X2 + s2s degm?{x3}.0)
X3a:=p2c bb1!{d}.(expel g.X3 + X3)
X3b:=s2s degp?{x6}.p2c bb3!{d}.p2c bb3!{d}.0
X3c:=s2s degp?{x7}.p2c bb3!{d}.0
X3:=accept tf.(X3a + X3b + X3c)
X4:=(s2s bb2!{d}.X4 + c2p bb3?{x5}.0)
X5:=(s2s basal?{y2}.expel c.X5+ s2s pa?{y1}.expel c.X5)
X6:=exit c.(s2s utr?{y4}.expel e.X6 + s2s degm?{y3}.0)

X7:=(s2s ptail!{d}.X7 + s2s degp?{y10}.0)
X8:=(s2s basal!{d}.X8+s2s ptail?{z1}.s2s pa!{d}.X8)
X9:=s2s utr!{d}.X9
X10:=s2s degm!{d}.X10
X11:=s2s degp!{d}.X10
X12a:= c2p bb1?{y9}.enter atf.0
X12b:=c2p bb3?{y8}.0
X12c:=s2sbb2?{y7}.(c2pbb1?{y6}.expelf.0+c2p
bb3?{y5}.0)
X12:=(X12a+X12b+X12c)

GeneMfn1Mfn2[GM:X1|RnaMfn1Mfn2[RM:X2|ProteinMfn1Mfn2 [PM:exitb.X3|Kinase [K1:X4]]]
GeneOPA1[GOPA1:X5|RnaOPA1[ROPA1:X6|ProteinOPA1[POPA1:exit e.enter tf.expel atf.accept atf.0 m1.merge |BoundOPA1[BOPA1:exitatf.X12|ActiveOPA1[AOPA1:exit f.exit g.X7]]]]
Transcr[Tr1:X8]
Transl[T11:X9]
RnaDEG[RDEG1:X10]
ProteinDEG[PDEG1:X11]

IV. CONCLUSION

Mitochondrial fusion and fission play prominent roles in controlling mitochondrial shape and function. Since many neurodegenerative diseases cause mitochondria to malfunction, it may be important to focus on developing methods to repair and restore mitochondria. In this paper a theoretic stochastic model in BioAmbients calculus is presented, using the most common commands of a BioAmbient Machine simulator. Experimental results will be published in future work.

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