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Mathematical modeling of the intracellular protein dynamics: The importance of active transport along microtubules

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HIGHLIGHTS

- We propose a generic model of intracellular protein and mRNA dynamics.
- The model accounts for the active transport of molecules along the microtubules.
- We assume that the regulation of protein synthesis acts as a negative feedback.
- We give a hypothesis on the oscillations of protein and mRNA concentrations.

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ABSTRACT

In this paper we propose a mathematical model of protein and mRNA transport inside a cell. The spatio-temporal model takes into account the active transport along microtubules in the cytoplasm as well as diffusion and is able to reproduce the oscillatory changes in protein concentration observed in many experimental data. In the model the protein and the mRNA interact with each other that allows us to classify the model as a simple *gene regulatory network*. The proposed model is generic and may be adapted to specific signaling pathways. On the basis of numerical simulations, we formulate a new hypothesis that the oscillatory dynamics is allowed by the mRNA active transport along microtubules from the nucleus to distant locations.

1. Introduction

The first symptoms of diseases such as cancer are almost always clinical, but the responsible mechanisms begin with alterations to a cell's DNA. Therefore in order to better understand the disease and make desirable changes in its dynamics, we must look more closely at processes appearing at the intracellular level. In particular, we should focus on the functioning of signalling pathways which are cascades of biochemical reactions that lead to signal transduction from receptors located on the cell surface to the cell nucleus, see Bellomo et al. (2008).

These signalling pathways constitute natural regulatory systems that on one hand preserve cell homeostasis, see Gérard et al. (2013), and on the other hand ensure a proper response to external forcing, see Szymańska and Zylicz (2009). Abnormalities in these intra-cellular pathways are the characteristic feature of major diseases and other pathological conditions including cancer, see Bennet et al. (1999), Toledo and Wahl (2006), and Zilfou and Lowe (2009). The proper modeling of signaling pathways, more precisely specific signal transduction pathways known to be important in cancer progression, is an efficient tool to understand the initial dysfunction, and to develop more effective therapeutic protocols.

Over the recent years, mathematical modeling of signalling pathways has become a scientific objective for many research groups and there are now many well established models for important pathways such as NF-κ B, Hsp70, and p53-Mdm2, see e.g. Szymańska and Zylicz (2009), Gordon et al. (2009), Lipniacki et al. (2004), and Puszynski et al. (2009).

Most of the models have neglected the important spatial aspect, focusing solely on the reaction kinetics, see Agrawal et al. (2009), Momiji and Monk (2008), and Monk (2003). In these models, the regulation of the protein synthesis by the signalling pathways is obtained by a negative feedback loop. Using time delays parameters, the authors have observed oscillatory dynamics which corresponds to the experimental evidence, see

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Geva-Zatorsky et al. (2006), Hirata et al. (2002), Nelson et al. (2004), and Shankaran et al. (2009).

Few studies take into account the spatial effects. Initially, the transport of molecules was only modeled by diffusion inside the cell, see Busenberg and Mahaffy (1985), Glass and Kauffman (1972), Mahaffy (1988), Mahaffy and Pao (1984), and Shymko and Glass (1974). Recently, a new mathematical model was proposed to take into account the active transport of molecules by the importin–cargo complex along cytoplasmic microtubules, see Cangiani and Natalini (2010).

The main objective of our work is to contribute to a better understanding how spatial distribution influences the dynamics of protein synthesis. We look for a spatial explanation of the oscillatory dynamics usually obtained by artificial time delay parameters. Before we propose the new model we refer to two recent works which in our opinion present the most advanced models of intracellular protein dynamics. One of them emphasizes the importance of active transport (Cangiani and Natalini, 2010) while the second one focuses on the negative feedback loop (Sturrock et al., 2011).

Since the time delay is linked to the spatial transport of molecules, the concentration evolutions are strongly dependent on spatial processes. In 2010 Cangiani et al. proposed a systems of partial differential equations considering diffusion process as well as active transport along microtubules, see Cangiani and Natalini (2010). In order to give a realistic description of transport processes inside the cell, the authors introduced several new variables, for instance the Ran protein.

In 2011 Sturrock et al. proposed a system of partial differential equations to capture the evolution in space and time of the species, mRNA and proteins, in the Hes1 and p53-Mdm2 systems, see Sturrock et al. (2011). The authors showed that the proposed reaction–diffusion models are able to produce sustained oscillations both spatial and temporal, using negative feedback loop and localization of production of mRNA and proteins. They estimated ranges of parameters where sustained oscillations are observed. In particular they emphasized the essential role of the localization of proteins' production at a significant distance from the nuclear envelope.

Further extensions of the Sturrock et al. model were proposed to describe more precisely the spatial transport. In Chaplain et al. (2012) and Sturrock et al. (2012), authors presented models of the transcription factor Hes1 and Mdm2 inhibition of p53 transcriptional activity. The authors considered nucleus, cytoplasm and microtubule-organizing center with more realistic cell geometries by using an imported image of a real cell as computational domain. The active transport along microtubules was simply modeled by a drift term in the equations. However, the localization of protein' production at some distance from the nuclear envelope was still needed to recover the oscillatory dynamics.

In the present paper, we propose a spatio-temporal model of intracellular transport taking into account active transport along the microtubules and the microfilaments. The model describes the spatial structures and their functions, i.e. mRNA is produced in the nucleus (transcription), moves across the nuclear envelope into the cytoplasm where it is translated into protein (synthesis). Protein is then able to perform its assigned functions in the cytoplasm and to move back into the nucleus where it may suppress the mRNA production, thereby creating the negative feedback loop.

The first novelty of our work lies in the distinction between the molecules that are linked to microtubules and those that are free to diffuse in the cytoplasm. More precisely, we assume that the molecules cannot be at the same time bound to microtubules and ribosomes. The mRNA molecule must be released from the microtubule before the start of the translation process. In this way we can explain the experimentally observed oscillations, not by the spatial distribution of ribosomes in the cytoplasm, as suggested by some authors (Sturrock et al., 2011; Chaplain et al., 2012; Sturrock et al., 2012), but by the active transport along microtubules. Close to the nuclear envelope, the high density of microtubules makes the concentration of free mRNA in the cytoplasm too low to make the translation process significant. Further in the cytoplasm, the density of microtubules decreases and the concentration of free mRNA becomes large enough to increase proteins' production.

The second main novelty of the present model lies in the boundary conditions for the nuclear envelope. We propose a boundary conditions reflecting the non-reversible nature of the membrane, such that the mRNA molecules are transported from the nucleus to the cytoplasm and cannot move back to the nucleus. Similarly, the protein molecules are transported from the cytoplasm to the nucleus and cannot move back to the cytoplasm.

The proposed model is generic, i.e. we consider a simple loop involving a single pair mRNA/protein. The model and its mathematical properties can be easily adapted in order to take into account more complex signalling pathways, i.e. pathways containing more types of proteins and mRNA. We would like to emphasize that the proposed model is deterministic. However it is known that some stochastic aspects of the gene regulation process may be important (Gamba et al., 2005; Sturrock et al., 2013; de Franciscis and d'Onofrio, 2013). Nonetheless the given distribution of microtubules may cover some stochastic features of the phenomenon.

The present paper is organized as follows. In Section 2 we describe the biological background of the process and the characteristic values of parameters are discussed. In Section 3 we introduce the mathematical model. In Section 4, we present the numerical simulations. We illustrate the capacity of the model to describe oscillatory dynamics without assumptions on the protein production localization. Eventually, we present discussion and conclusions in Section 5. Appendix contains some details of numerical simulations.

2. Biological background

The main internal structural features of a eukaryotic cell are the nucleus which is embedded within the cytoplasm. The nucleus contains DNA whereas the extant organelles are located in the cytoplasm. The nucleus is separated from the cytoplasm by a so-called nuclear envelope which is a lipid bilayer. The nuclear envelope contains many protein complexes named as nuclear pores through which nucleus–cytoplasm exchange occurs. Smaller molecules simply diffuse through the nuclear pores, whereas the larger ones in order to pass through require the assistance of proteins building up the nuclear pore. A nuclear pore can actively conduct 1000 translocations per complex per second, see Yang et al. (2004). A typical mammalian cell will have about 3000–4000 pores. In mammalian cells, the average diameter of the nucleus is approximately 6 μm, i.e. nucleus occupies about 10% of the total cell volume (Alberts et al., 2004).

Eukaryotic cells create internal order and ensure the efficient transport of molecules in the cytoplasm using the so-called microtubules. Microtubules are polar, tubular polymers that can grow as long as 25 μm and are highly dynamic. Microtubules perform many functions in the cell, in particular they provide platforms for intracellular transport. The high degree of spatio-temporal organization of molecules and organelles inside the cell is achieved by protein machines that transport components to various destinations within the cytoplasm (Vale, 2003). The major microtubule motor proteins are kinesin and dynein. Movement along microtubules is of average speed of about 3 μm/s (Alberts et al., 2004). Experimental studies have shown a linear decrease in