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

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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 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 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.

Keywords: Parabolic hyperbolic coupled model, Intracellular dynamic, Negative feedback, Microtubule, Active transport

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 [1].

These signalling pathways constitute natural regulatory systems that, on one hand preserve cell homeostasis, see [2], and on the other hand ensure a proper response to external forcing, see [3]. Abnormalities in these intra-cellular pathways are the characteristic feature of major diseases and other pathological conditions including cancer, see [4, 5, 6]. 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-κB, Hsp70, and p53-Mdm2, see e.g. [3, 7, 8, 9].

Most of the models have neglected the important spatial aspect, focusing solely on the reaction kinetics, see [10, 11, 12]. 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 [13, 14, 15, 16].

Few studies take into account the spatial effects. Initially, the transport of molecules was only modeled by diffusion inside the cell, see [17, 18, 19, 20, 21]. 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 [22].

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 [22] while the second one focuses on the negative feedback loop [23].

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 [22]. 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 [23]. 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 [24, 25], authors presented models of the transcription factor Hes1 and Mdm2 inhibition of p53 transcriptional activity. The authors considered nucleus, cytoplasm and microtubule-organising centre 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 proteins 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 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 lays 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 can not 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 [23, 24, 25] but by the active transport along microtubules. Close to the nuclear envelope, 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 can't move back to the nucleus. Similarly, the protein molecules are transported from the cytoplasm to the nucleus and can't 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 info account more complex signalling pathways, i.e. pathways containing more types of proteins and mRNA. We would like to emphasis that the proposed model is deterministic. However it is known that some stochastic aspects of the gene regulation process may be important [26, 27, 28]. 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 characteristics 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 nuclear pores through which nucleus-cytoplasm exchange occurs. Smaller molecules simply diffuse through the nuclear pores, whereas 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 [29]. A typical mammalian cell will have about 3000 - 4000 pores. In mammalian cells, the average diameter of the nucleus is approximately 6 micrometers (μm), i.e. nucleus occupies about 10% of the total cell volume [30].

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 micrometres 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 [31]. The major microtubule motor proteins are kinesin and dynein. Movement along microtubules is of average speed of about $3\mu m/$s [30]. Experimental studies have shown a linear decrease in microtubule density from about 100% at the cell centre to about 15% at the cell edge [32]. Th outer diameter of a microtubule is approximately $25nm$ [30].

The translation process, i.e. protein synthesis, occurs at molecular complexes called ribosomes. A typical cell contains millions of ribosomes in the cytoplasm [30]. Ribosomes are either "free" or bound to the rough endoplasmic reticulum. The membrane of the rough endoplasmic reticulum forms large double membrane sheets that are located near, and continuous with, the outer layer of the nuclear envelope [33]. Free ribosomes can be found anywhere in the cytoplasm except from the cell nucleus and other organelles.

The transport of proteins to the nucleus is mediated by a nuclear localization signal (NLS), and can be divided into at least two steps, (i) targeting proteins to the nuclear envelope and (ii) translocation through this membrane. NLS mediation provides that the process of translocation through the nuclear envelope occurs in one direction [34].

Proteins are able to rapidly move through the mammalian cell nucleus. Diffusion coefficients for inert molecules have been measured and estimated to be in the range 10-100 $\mu m^2 \cdot s^{-1}$ depending on the size and shape of the molecule. The overall mobility of biologically active molecules is reduced by a factor of 10-100. The motion of molecules, both inert and biologically active, is generally energy-independent and occurs by anomalous diffusion in which the free motion of molecules is obstructed by the presence of structural elements such as chromatin fibers and nuclear bodies [35].

Nuclear DNA encodes genetic information that is read by copying stretches of DNA into the related mRNA molecule in a transcription process. Afterwards the mRNA molecules are transported outside the nucleus to the cytoplasm where, in the ribosomes, they are used as a template for determining the correct sequence of amino acids of a particular protein (translation process). In the cytoplasm, proteins perform their assigned functions. Some of them influence the level of synthesis of new proteins. To this end they have to be transported to the nucleus where they influence transcription.

It is known from experimental data, that most mRNA molecules are rapidly exported from the nucleus after their synthesis. Newly synthesized, fully processed mRNA molecules can be detected in the cytoplasm within a few minutes after their generation. This fact inspired the notion that their movement within the nucleus might be directed in order to increase transport efficiency. However the notion of directed, energy-dependent transport of mRNA within the cell nucleus has now largely been debunked. Several independent studies demonstrated the energy-independent diffusional motion of mRNA within the cell nucleus and a diffusion coefficient of 0.03-0.1 $\mu m^2 \cdot s^{-1}$ was determined [35].

Recent analysis indicates that active transport of mRNA to distinct intracellular regions requires a functional cytoskeleton as well as motor proteins that move along these cytoskeletal filaments [36, 37]. In general, microtubules appear to be involved in the long-distance transport in large cells, whereas microfilaments are involved in mRNA targeting in smaller cells [38].

3. Mathematical modeling

3.1. Space decomposition

Let Ω be a (nonempty) convex bounded and smooth domain in $\mathbb{R}^d$, $d \geq 1$, corresponding to the cell. The cell membrane corresponds to its boundary denoted Γ_c. Let $\mathcal{N}$, nucleus, be a (nonempty) bounded and smooth sub-domain in Ω. Its boundary Γ_n corresponds to the nuclear envelope. We assume that the nucleus is completely embedded in the cell such that the boundaries are not connected, i.e. $\Gamma_n \cap \Gamma_c = \emptyset$. From now on, we denote by $m_n(t,x)$ (resp. $p_n(t,x)$) the concentration of mRNA (resp. the concentration of protein) on the nucleus for any $x \in \mathcal{N}$ with $t \geq 0$ the time variable.

We introduce the cytoplasm as the complement of the nucleus in the cell, i.e. $\mathcal{C} = \Omega \backslash \mathcal{N}$. Since microtubules are thin but numerous we propose their continuous representation through the function $0 \leq \xi(x) \leq 1$ defined on $\mathcal{C}$, see Figure 1. The function ξ could be interpreted as the local density of microtubules. In part of the domain where no microtubules are present, the function ξ is equal to 0, and similarly if the whole elementary volume is occupied by microtubules, the function ξ is equal to 1. The movement of molecules in the cytoplasm depends on whether the molecules are bound (using motor proteins) to the microtubules or not. Therefore, in the cytoplasm, both species, protein and mRNA are divided into those associated with microtubules, from now on called the linked molecules, and those not associated, from now on called the free molecules. We

denote, for any $x \in \mathcal{C}$, by $m_l(t,x)$ (resp. $p_l(t,x)$) the concentration of mRNA (resp. the concentration of protein) linked to the microtubules and by $m_f(t,x)$ (resp. $p_f(t,x)$) the concentration of mRNA (resp. the concentration of protein) not linked (free) to the microtubules.

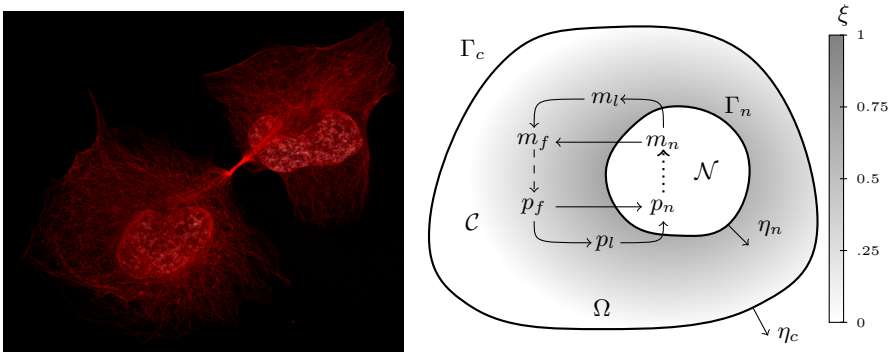

Figure 1: Cell structure. On the left, human non-small cells lung carcinoma (H1299 cells) in the final stage of cell division with colored microtubules. Courtesy of Marta Małuszek from IIMCB. On the right, scheme of the space decomposition of the cell.

3.2. The system of equations

In the nucleus, the particle motion is governed by diffusion, with a diffusion coefficient $\kappa_n > 0$. The degradation of mRNA (resp. the degradation of protein) is proportional to a decay parameter $\lambda_m > 0$ (resp. $\lambda_p > 0$). The equations read

$$\text{on } \mathcal{N} \quad \begin{cases} \partial_t m_n - \nabla \cdot (\kappa_n \nabla m_n) = -\lambda_m m_n + \dfrac{\alpha_m}{1 + \left(\frac{p_n}{\overline{p}}\right)^{\gamma}}, & \text{(1a)} \\ \partial_t p_n - \nabla \cdot (\kappa_n \nabla p_n) \ = -\lambda_p p_n, & \text{(1b)} \end{cases}$$

where $\alpha_m > 0$ is the mRNA transcription rate, $\overline{p} > 0$ is the critical concentration of protein above which an effective inhibition of transcription occurs and $\gamma > 0$ is the Hill parameter governing the strength of inhibition, see [23].

In the cytoplasm, the free particles also satisfy a reaction-diffusion equation, with a diffusion coefficient $\kappa_c > 0$. We assume that the rate of translation is proportional to the free mRNA concentration with the factor $\alpha_p > 0$. The linked mRNA, analogously the linked protein, is drifted along the microtubules at the speed $\nu_m \geq 0$, analogously $\nu_p \geq 0$. More precisely, we define the unit vector field $\mathbf{v} : \mathcal{C} \in \mathbb{R}^d$ such that the microtubules are tangent to $\mathbf{v}$ and oriented from the nuclear envelope to the cell membrane. Protein is drifted in direction of nucleus whereas mRNA is drifted in the opposite direction. We introduce two new functions $\beta_m(\xi) > 0$ and $\beta_p(\xi) > 0$, from now on called the exchange

parameters, modeling the release (resp. the binding) of mRNA (resp. protein) by the kinesin molecules to microtubules. The chance for proteins to get bound to the microtubules increases with the volume occupied by microtubules, i.e. β_p is an increasing function of ξ. Similarly, we assume that the chance for mRNA to be released from microtubules increases with the volume not occupied by microtubules, i.e. β_m) is a decreasing function of ξ. We propose the following equations

$$\text{on } \mathcal{C} \quad \begin{cases} \partial_t m_f - \nabla \cdot (\kappa_c \nabla m_f) = -\lambda_m m_f + \beta_m m_l, & \text{(2a)} \\ \partial_t m_l + \nabla \cdot (\nu_m m_l \ \mathbf{v}) = -\lambda_m m_l \ - \beta_m m_l, & \text{(2b)} \\ \partial_t p_f - \nabla \cdot (\kappa_c \nabla p_f) = -\lambda_p p_f \ - \beta_p p_f + \alpha_p m_f, & \text{(2c)} \\ \partial_t p_l - \nabla \cdot (\nu_p p_l \ \mathbf{v}) = -\lambda_p p_l \ + \beta_p p_f. & \text{(2d)} \end{cases}$$

Macromolecules such as mRNA and proteins are too big to diffuse freely through the pores of the nuclear envelope. To pass through, those molecules require the assistance of other proteins, see [30] for more details about transport through the nuclear envelope. We assume that the transport through the nuclear envelope is possible only in one direction depending on the particles.

We assume that mRNA passes only through the nuclear envelope to exit the nucleus with speed $\mu_m > 0$. Then, the mRNA population is split into the two sub-populations linked and free mRNA (resp. m_l and m_f) according to the density of microtubules ξ close to the nuclear envelope:

$$\text{on } \Gamma_n \begin{cases} \eta_n \cdot (\kappa_n \nabla m_n) = -\mu_m m_n, \\ -\eta_n \cdot (\kappa_c \nabla m_f) = (1-\xi)\, \mu_m m_n, \\ \eta_n \cdot \mathbf{v} \ \nu_m m_l = \xi \mu_m m_n, \end{cases} \tag{3}$$

where η_n is the unit vector normal to the nuclear envelope outward of the nucleus, see Figure 1.

Two processes contribute to the pass of proteins through the nuclear envelope. We assume that free protein molecules passes only through the nuclear envelope to enter the nucleus with speed $\mu_p > 0$. This phenomenon is represented by term $\mu_p p_f$. We also take into account the proteins linked to microtubules p_l that are released directly in the nucleus. This phenomena is represented by term $\eta_n \cdot \mathbf{v} \ \nu_p p_l$. It leads to the following boundary conditions

$$\text{on } \Gamma_n \begin{cases} \eta_n \cdot (\kappa_n \nabla p_n) = \mu_p p_f + \eta_n \cdot \mathbf{v} \ \nu_p p_l, \\ -\eta_n \cdot (\kappa_c \nabla p_f) = -\mu_p p_f, \end{cases} \tag{4}$$

where η_n again is the unit vector normal to the nuclear envelope outward of the nucleus, see Figure 1.

We focus our attention on the intracellular transport neglecting the exchange between cell and surrounding environment. Therefore, on the cell membrane we impose no-flux boundary condition. For proteins, this means that no particles can cross the cell membrane either by diffusion or by active transport along microtubules. Since the mRNA can not leave the cell, mRNA molecules, which are transported along microtubules are released into the cytoplasm before it

reaches the cell membrane. This leads to the formation of free mRNA incoming flux so that the total number of mRNA molecules in the cell is preserved. As a result, we obtain the following boundary conditions

$$\text{on } \Gamma_c \begin{cases} \eta_c \cdot (\kappa_c \nabla m_f) = \eta_c \cdot \mathbf{v}\ \nu_m m_l, \\ \eta_c \cdot (\kappa_c \nabla p_f) = 0, \quad \text{and} \quad \eta_c \cdot \mathbf{v}\ \nu_p p_l = 0, \end{cases} \tag{5}$$

where η_c is the unit vector normal to the cell membrane outward of the cell, see Figure 1. We would like to emphasize that our model refers to intracellular proteins which are not released outside the cell. In case of proteins, which are released outside the cell, this boundary condition should be modified.

Remark 1. *To better reflect biological reality some parameters of the model should depend on the density of microtubules ξ and then on the space variable. In particular:*

- *The concentrations of linked molecules, mRNA or protein, should tend to 0 when the density of microtubules approaches 0 (no microtubules);*
- *The concentrations of free molecules should tend to 0 when the density of microtubules approaches 1 (no space for diffusion).*

To ensure the aforementioned properties, we should assume that

- *β_m and β_p tend to ∞ and 0, respectively, as ξ approaches 0;*
- *β_m and β_p tend to 0 and ∞, respectively, as ξ approaches 1.*

The vector field $\mathbf{v}$ which is tangent to the microtubules should avoid on the regions of cytoplasm without microtubules ($\xi = 0$).

Remark 2. *The proposed model is deterministic. Further development of the model should take into considerations the stochastic effects. As shown by recent works in the field stochastic behaviour may deeply affect spatiotemporal intracellular dynamics [39, 40, 41, 26, 27, 28].*

Theorem 1. *For the parameters smooth enough and non-negative initial data, there exist a global solution of (1)-(2) with the boundary condition (3)-(4)-(5). In addition the solution is non-negative.*

The details of the proof as well as some generalizations will be presented in a separate paper in preparation [42].

4. Numerical results

In this section we present simulations of protein and mRNA concentration dynamics. We performed the simulations based on the parameters found elsewhere in the literature. Summary of parameters used in the model together

with the appropriate units and references can be found in Table 1. We tried to adjust the parameters to Hes1 pathway. To simplify the computation and the notation, we consider the two–dimensional case and we represent nucleus and cell volumes as a concentric balls with respective radius R_n and R_c. For simplicity microtubules are represented by straight tubes running from the nuclear envelope to the cell membrane. In this case the spherical coordinates are better suitable to perform the numerical simulations, therefore any point x is described by its radius R and its angle Θ. We approximate the drift on the microtubules as well as the drift through the nuclear envelope with an explicitly "up-wind" volume finite scheme. On the other hand, the diffusion operators are treated with an implicit scheme. We use a finite volume method where the gradients at the interface are reconstructed using finite difference between the centers of the control volumes around the interface. The decay terms and the exchange between linked and free particles are treated implicitly. Finally, we use an explicit scheme to approximate the source terms of mRNA and protein productions. Proceeding in this way, we can treat equations separately and we limit the computational costs in time and in memory, and we ensure the stability and positivity under the Courant-Friedrichs-Lewy condition (CFL condition), c.f. [43], which is not too restrictive. More details about the numerical simulations are presented in Appendix.

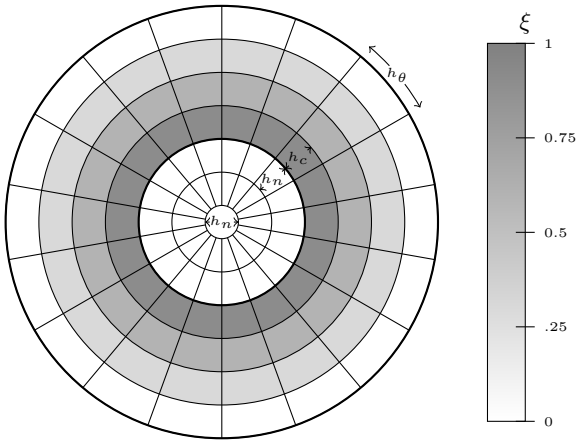

Figure 2: Numerical grid and discretization of the density of microtubules function ξ.

The behavior of cells is subjected to cyclical changes, which are regulated by the intracellular concentration of the respective proteins. In the following part we discuss the impact of microtubules on the formation of these oscillations.

Parameter	Description	Value in simulation	Unit	Reference
R_c	Cell radius	10^2	μm	[30]
R_n	Nucleus radius	10^1	μm	[30]
κ_n, κ_c	Diffusion coefficients	10^1	$\mu m^2 \cdot s^{-1}$	[44]
λ_m, λ_p	Decay rates	10^{-3}	s^{-1}	[14]
μ_m, μ_p	Passing rate through nuclear envelope	10^{-1}	$\mu m \cdot s^{-1}$	[45]
ν_m, ν_p	transport cargo speed	10^{-1}	$\mu m \cdot s^{-1}$	[45]
α_m	mRNA transcription	10^{-3}	$\mu M \cdot s^{-1}$	[25]
α_p	Protein translation	10^{-2}	s^{-1}	[46]
$\overline{p}$	Critical protein concentration	10^{-1}	μM	[47]
γ	Hill parameter	3		[12]

Table 1: Description of model parameters: values used in simulations and references

Results without microtubules

Let us start with simulations without microtubules ($\xi = 0$). We set the model parameters in order of magnitude of biological values, according to the literature see Table 1, and we start simulations with the vanishing initial condition, i.e. $m_n(0,x) = p_n(0,x) = m_f(0,x) = m_l(0,x) = p_f(0,x) = p_l(0,x) = 0$. We fix the radial and angular mesh size to $h_n = h_c = 5 \cdot 10^{-1} \mu m$ and $h_\theta = 1\ rad$ and we set the time step to satisfy the CFL condition ensuring positivity of the solution, see Proposition 1 in the Appendix. See Figure 2 and the Appendix for description of the numerical parameters.

Figure 3 shows the total concentration of mRNA and protein molecules in the nucleus and in the cytoplasm as functions of time. After a transition period from the initial condition (about 5 hours), the concentrations of molecules does not change with time. Figure 4 shows the spacial distribution at the steady state (t=12h). The mRNA molecules produced in the nucleus pass through the nuclear envelop and is diffused in the cytoplasm. Due to the decay of mRNA, the concentration close to the nuclear envelop is more important than at the cell membrane. It leads that the production of protein essentially occurred in the vicinity of the nuclear envelope. However, the concentration of protein is quite homogeneous in the cytoplasm since the molecules of protein close to the nuclear envelope are actively transported into the nucleus.

Without assuming the active transport along the microtubules, the oscillatory dynamic never appears using model (1)-(2)-(3)-(4)-(5). Sturrock at al. suggest that the oscillations in protein concentration inside the cytoplasm could not be stable if the protein production occurs close to the nucleus [23, 25]. They assume that the production of proteins is a function of space and the appropriate parameter - λ_p - vanishes in the vicinity of the nuclear envelope. In our opinion, this parameter should be proportional to the concentration of ribosomes which is quite homogeneous in the cytoplasm. In the present section we show how the

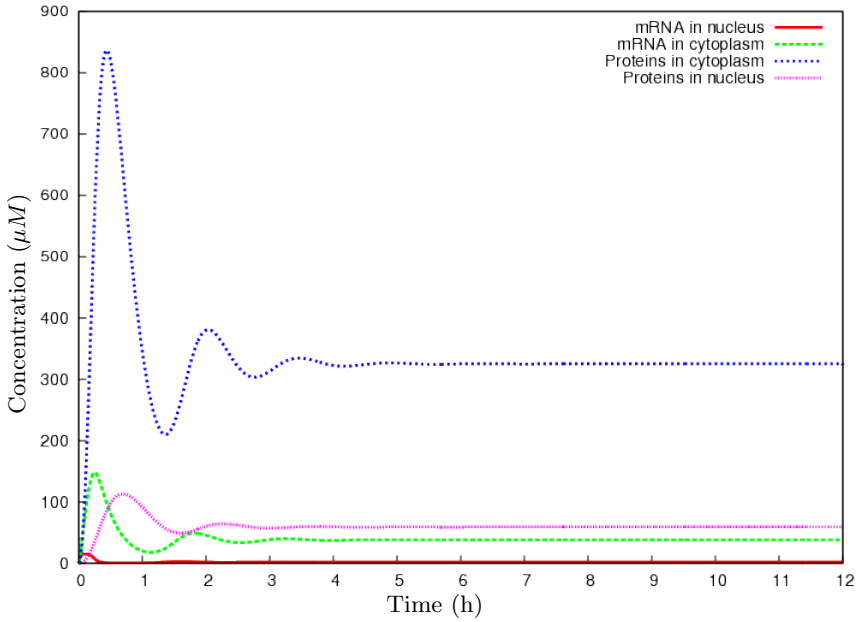

Figure 3: Total concentrations of molecules as functions of time in nucleus and cytoplasm in the case without microtubules. Parameters are given in Table 1 and the initial condition vanishes. The red solid line stands for the concentration of mRNA in the nucleus and the green dashed line stands for the concentration of mRNA in the cytoplasm. The blue dotted line stands for the concentration of protein in the cytoplasm and the pink thinly dotted line stands for the concentration of protein in the nucleus.

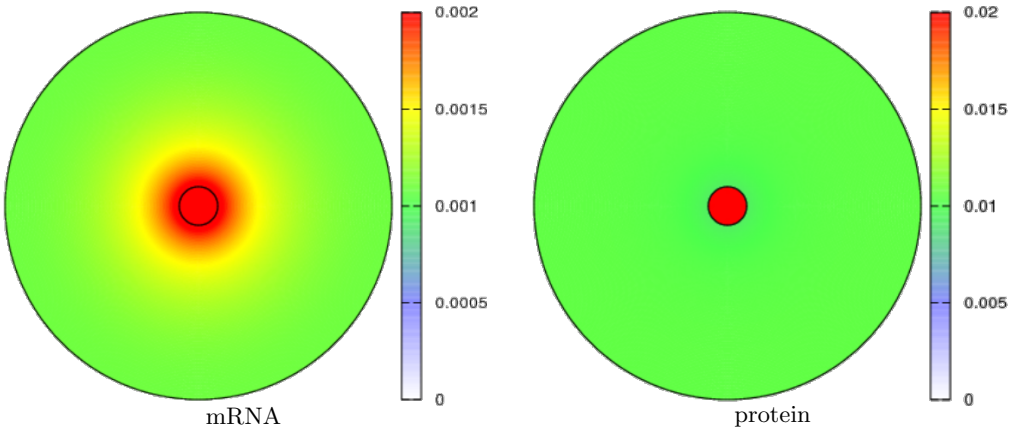

Figure 4: Spacial distribution of mRNA (left) and protein (right) at steady state (t=12h) in the case without microtubules ($\xi = 0$). Parameters are given in Table 1 and the initial condition vanishes.

active transport along the microtubules makes the protein production close to the nuclear envelope less significant, and leads to oscillatory dynamics.

In 2012 the same authors introduce the active transport along microtubules by adding i) an advection term into the equations describing the protein dynamics in the cytoplasm; and ii) a particular boundary conditions at the nuclear envelope [25]. However, since the particles are still diffusing through the nuclear envelope, it seams to us that the oscillatory dynamics are not recovered for large enough time.

Results with microtubules

In the current section, except that we are considering active transport along microtubules, we use the same parameters as used in the previous section (described in Table 1). The density of microtubules ξ could be approximated as a linear decreasing function of the radius, see [32, Figure 7.D]. More precisely, in the current paper we set

$$\xi(R,\Theta) = 1 - \frac{\arctan\left(10^2\left(R-\overline{r}(\Theta)\right)\right) - \arctan\left(10^2\left(R_n-\overline{r}(\Theta)\right)\right)}{\pi} \quad \text{with} \quad \overline{r}(\Theta) = \frac{80+5\cos(\Theta)+10\cos(20\Theta}{100}$$

and we consider the following probability of linking

$$\beta_m(\xi) = \frac{1-\xi}{\xi}\,\overline{\beta}_m \qquad \text{with} \qquad \overline{\beta}_m = 10^{-4}s^{-1} \qquad \text{and} \qquad \beta_p(\xi) = \frac{\xi}{1-\xi}\,\overline{\beta}_p \qquad \text{with} \qquad \overline{\beta}_p = 10^{-7}s^{-1}$$

such that the conditions of Remark 1 are fulfilled.

Figure 5 shows the concentration of mRNA and protein molecules in the nucleus and in the cytoplasm as functions of time during the first 24 hours. The first line shows result initialized by the vanishing initial condition, i.e. $m_n(0,x) = p_n(0,x) = m_f(0,x) = m_l(0,x) = p_f(0,x) = p_l(0,x) = 0\mu M$. The second line shows result initialized by homogeneous concentration, i.e. $m_n(0,x) = \frac{5}{\pi R_n^2}\mu M$, $p_n(0,x) = \frac{70}{\pi R_n^2}\mu M$, $m_f(0,x) = m_l(0,x) = \frac{15}{\pi(R_c^2-R_n^2)}\mu M$ and $p_f(0,x) = p_l(0,x) = \frac{35}{\pi(R_c^2-R_n^2)}\mu M$. The third line shows result initialized by the steady state of the model without microtubules, i.e. result plotted in Figure 4. Note that the initial condition have a significative impact on the asymptotic behavior, in particular on the amplitude of the oscillations. However, with the set of parameters given in Table 1, we always observed a stable oscillatory dynamic after a transition period of about 12 hours. Below we describe the oscillatory dynamics for the case with vanishing initial condition case, i.e. first line of Figure 5. Note that, the right pictures of Figure 5 present about one cycle of the negative feedback and the period of the oscillation is between 1.5h and 2h which corresponds to the order of experimental observations, see [14]. At the beginning of the cycle (t=21.5h), the concentration of mRNA in the cytoplasm decreases, and soon the concentration of protein also begins to decrease due to decay of molecules.Then, the amount of protein which passes

through the nuclear membrane and enters the nucleus decreases (t=22 h), which together with the decay of molecules, cause the diminution of the protein concentration in the nucleus. Soon after, because of the reduced protein-mediated inhibition (the negative feedback) the concentration of mRNA in the nucleus increases. The concentration of mRNA in the cytoplasm starts to increase little after. Eventually, the concentration of proteins in the cytoplasm increases after a delay (t=22.5 h).The extremes of the evolution of the protein concentration in the nucleus, of the mRNA concentration in the nucleus and the mRNA concentration in the cytoplasm are almost synchronous, whereas the extremes of the evolution of protein concentration in the cytoplasm have clearly marked delays. These delays correspond to the active transport along the microtubules of the mRNA (delay before the inflection of the concentration of protein in the cytoplasm) and of the protein (delay after the inflection of the concentration of protein in the cytoplasm).

We performed several simulations corresponding to a large set of patterns describing the microtubules density ξ. We have noticed that the regularity of the microtubules density does not seem to have significant impact on the results, particularly in case of large diffusion. The parameters that significantly affect the oscillatory dynamics are the density of the microtubules close to the nuclear membrane and the probability of release of the mRNA molecule by microtubules. More precisely, the necessary condition of oscillatory dynamics is that the microtubule density near the nuclear membrane is sufficiently large, i.e. $\xi\left(R_n, Theta\right) \approx 1$, and the probability of release of the mRNA molecule by microtubules is small enough, i.e.: $\overline{\beta}_m < 10^{-3} s^{-1}$.

5. Conclusions

In this paper we proposed a generic model of intracellular protein dynamics that accounts for the active transport of molecules (both mRNA and protein) along the microtubules. The model assumes that the regulation of protein synthesis acts as a negative feedback, i.e. protein produced in the cytoplasm in the process of translation, acts also as self-inhibitor. The newly synthesized protein enters the nucleus where it inhibits transcription of its mRNA. In this way, the level of the protein is limited. Although the proposed regulatory pathway is generic, there are proteins that are inhibitors of its own transcription, both directly like Hes1 protein [23, 25] or indirectly like of Hsp70 [3].

On the basis of the numerical simulations we performed, we formulate a hypothesis on the oscillations of protein and mRNA concentrations. Since the ribosomes can be found even close to the nucleus we believe it is not justified to make any assumption on their localisation in cytoplasm. We argue that the presence of microtubules and active transport of mRNA from the nucleus to the cytoplasm explain the existence of oscillations in the concentration of protein and mRNA.

The proposed model is general and can be extended in many directions. One possible extension of the model is to consider the mRNA production not in the whole nucleus, but at a certain place inside the nucleus which would correspond

to the mRNA production in a specific site on DNA. One possible approach to that problem is suggested in [25].

Further extensions that will bring the model closer to the reality may account for the rearrangements in microtubules structure. This extension may particularly play a role when half life of the microtubules is in the same range as the half life of considered molecules.

The proposed model is generic and the main purpose of that work was to provide a methodology for future models of specific regulatory networks. Bearing in mind that the ultimate goal is the construction of models based on specific biological questions that could have a significant impact on our understanding of many biological processes, even as complex as cancer, we propose a universal methodology that is likely to significantly facilitate the creation of models of various regulatory pathways.

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Appendix

We now present the numerical scheme in details. Let us first introduce some notations to present more precisely the numerical computation. Let N_n and N_c be the number of point on the numerical grid on the radial direction respectively on the nucleus and on the cytoplasm. In addition, let N_θ be the number of points on the angular direction. We design by h_n (resp. h_c) the radius step on nucleus (resp. on cytoplasm), by h_θ the angular step and by h_t the time step of the numerical grid, see Figure 2. We have

$$h_n = \frac{R_n}{N_n + \frac{1}{2}}, \qquad h_c = \frac{R_c - R_n}{N_c}, \qquad h_\theta = \frac{2\pi}{N_\theta}, \qquad \text{and} \qquad h_t > 0.$$

On the nucleus, we design by $m_n^s[0]$ (resp. $p_n^s[0]$) the approximation of the mean concentration of mRNA $m_n(t, R, \Theta)$ (resp. of proteins $p_n(t, R, \Theta)$) at time $t = sh_t$ on the control volume $V_0 = \{(R, \Theta) \text{ such that } R < h_n/2\}$ of surface $S_0 = \frac{\pi h_n^2}{4}$. Then for any $\theta \in [\![1, N_\theta]\!]$ and any $r \in [\![1, N_n]\!]$, where $[\![a, b]\!] = [a, b] \cap \mathbb{Z}$, we design by $m_n^s[r, \theta]$ (resp. $p_n^s[r, \theta]$) the approximation of

the mean concentration of mRNA $m_n(t,R,\Theta)$ (resp. of proteins $p_n(t,R,\Theta)$) at time $t = sh_t$ on the control volume

$$V_n[r,\theta] = \left\{ (R,\Theta) \text{ such that } \begin{array}{l} \left(r-\frac{1}{2}\right)h_n \leq R < \left(r+\frac{1}{2}\right)h_n \\ \left(\theta-\frac{1}{2}\right)h_\theta \leq \Theta < \left(\theta+\frac{1}{2}\right)h_\theta \end{array} \right\},$$

of surface $S_n[r] = rh_n^2 h_\theta$.

On the cytoplasm, for any $\theta \in [\![1, N_\theta]\!]$ and any $r \in [\![1, N_c]\!]$ we design by $m_f^s[r,\theta]$ and $m_l^s[r,\theta]$ (resp. $p_f^s[r,\theta]$ and $p_l^s[r,\theta]$) the approximation of the mean concentration of free and linked mRNA $m_f(t,R,\Theta)$ and $m_l(t,R,\Theta)$ (resp. of proteins $p_f(t,R,\Theta)$ and $p_l(t,R,\Theta)$) at time $t = sh_t$ on the control volume

$$V_c[r,\theta] = \left\{ (R,\Theta) \text{ such that } \begin{array}{l} R_n + (r-1)h_c \leq R < R_n + rh_c \\ \left(\theta-\frac{1}{2}\right)h_\theta \leq \Theta < \left(\theta+\frac{1}{2}\right)h_\theta \end{array} \right\},$$

of surface $S_c[r] = \left(R_n + \left(r-\frac{1}{2}\right)h_c\right)h_c h_\theta$.

We performed a scheme using an explicit drift on microtubules and through the nuclear envelope to make a good compromise between numerical diffusion and time computation. The time iteration of the numerical scheme could be summarized in four steps. Note that each step (1 to 4) of the scheme could be solved in parallel.

1. **mRNA in nucleus (1a).** Since we approach the inhibition of protein with an explicit scheme Eq. (1a) leads to the solution of a reaction-diffusion equation, i.e. the concentration on the nucleus is given by

$$\left((1+h_t\lambda_m)\,\mathtt{I_d} + h_t\mathtt{M_n}\right)m_n^{s+1} = \left(\mathtt{I_d} - h_t\frac{R_n h_\theta}{S_n}\mu_m \mathtt{B}_{N_n}\right)m_n^s + \frac{h_t\alpha_m}{1+\left(\frac{p_n^s}{\bar{p}}\right)^\gamma}, \tag{6}$$

with the loss of particles through the nuclear envelope is highlighted by the boundary indicator $\mathtt{B}_{N_n}[r]$

$$\mathtt{B}_q[r] = \left\{ \begin{array}{ll} 1, & \text{if } r = q \\ 0, & \text{else.} \end{array} \right.$$

$\mathtt{I_d}$ is the identity matrix and $\mathtt{M_n}$ is the matrix of diffusion on the nucleus i.e. in the spherical grid we write at centrum

$$\left(\mathtt{M_n} m_n^{s+1}\right)[0] = \frac{\kappa_n}{S_0}\left(\pi m_n^{s+1}[0] - \frac{h_\theta}{2}\sum_{\theta=1}^{N_\theta} m_n^{s+1}[1,\theta]\right),$$

for any $\theta \in [\![1, N_\theta]\!]$ and any $r \in [\![1, N_n - 1]\!]$

$$\left(\mathtt{M_n} m_n^{s+1}\right)[r,\theta] = \frac{\kappa_n}{S_n[r]}\Bigg(\left(2rh_\theta + \frac{2}{rh_\theta}\right)\ m_n^{s+1}[r,\theta]$$

$$-\left(r-\tfrac{1}{2}\right)h_\theta\ \ m_n^{s+1}[r-1,\theta] - \left(r+\tfrac{1}{2}\right)h_\theta\ \ m_n^{s+1}[r+1,\theta]$$

$$-\ \frac{m_n^{s+1}[r,\theta-1]+m_n^{s+1}[r,\theta+1]}{rh_\theta}\Bigg)$$

and at the nuclear envelope

$$\left(\mathtt{M_n} m_n^{s+1}\right)[N_n,\theta] = \frac{\kappa_n}{S_n[N_n]}\Bigg(\left(\left(N_n-\frac{1}{2}\right)h_\theta + \frac{2}{N_n h_\theta}\right)\ m_n^{s+1}[N_n,\theta]$$

$$-\left(N_n-\tfrac{1}{2}\right)h_\theta\ \ m_n^{s+1}[N_n-1,\theta] - \ \frac{m_n^{s+1}[N_n,\theta-1]+m_n^{s+1}[N_n,\theta+1]}{N_n h_\theta}\Bigg).$$

2. **mRNA in cytoplasm (2a)-(2b).** The solution the cytoplasm can be to realized in two step. First we approximate the drift of linked mRNA on cytoplasm (2b) using an explicit "up-wind" finite volume method, i.e. for any $\theta \in [\![1, N_\theta]\!]$ the boundary condition at the nuclear envelope (3)-(4) leads to

$$m_l^{s+1}[1,\theta] = \frac{\left(1-\dfrac{h_t h_\theta}{S_c[1]}(R_n+h_c)\nu_m\right)m_l^s[1,\theta] + \dfrac{h_t h_\theta}{S_c[1]}\overline{\xi}[\theta]\, R_n\mu_m m_n^s[N_n,\theta]}{1+h_t(\lambda_m+\beta_m[1,\theta])}, \tag{7}$$

while for any $r \in [\![2, N_c]\!]$ we have

$$m_l^{s+1}[r,\theta] =$$

$$\frac{\left(1-\dfrac{h_t h_\theta}{S_c[r]}(R_n+rh_c)\nu_m\right)m_l^s[r,\theta] + \dfrac{h_t h_\theta}{S_c[r]}(R_n+(r-1)h_c)\nu_m m_l^s[r-1,\theta]}{1+h_t(\lambda_m+\beta_m[r,\theta])}.$$

We assume that microtubules are straight lines from nuclear envelope to cell membrane, thus $\mathbf{v}\cdot e_r = 1$. Then, since the concentration of linked mRNA on the cytoplasm at time $t = (s+1)h_t$ is already known, we are able to approach the concentration of free mRNA (2a) by a reaction-diffusion equation with explicit source terms, i.e.

$$((1+h_t\lambda_m)\,\mathtt{I_d} + h_t\mathtt{M_c})\,m_f^{s+1} = m_f^s + h_t\beta_m m_l^{s+1} + \left(1-\overline{\xi}\right)h_t\frac{R_n h_\theta}{S_c}\mu_m m_n^s[N_n,.]\,\mathtt{B}_1 + h_t\frac{R_c h_\theta}{S_c}\nu_m m_l^s \mathtt{B}_{N_c} \tag{8}$$

with particles coming from the nucleus through the nuclear envelope is highlighted by the boundary indicator $\mathtt{B}_1[r]$ and particles leaving the microtubules at the cell membrane is highlighted by the boundary indicator $\mathtt{B}_{N_c}[r]$. $\mathtt{M_c}$ is the matrix of diffusion on the cytoplasm i.e. for any $\theta \in [\![1, N_\theta]\!]$ close to the nuclear envelope

$$\left(\mathtt{M_c} m_f^{s+1}\right)[1,\theta] = \frac{\kappa_c}{S_c[1]}\Bigg(\left(\frac{(R_n+h_c)h_\theta}{h_c} + \frac{2h_c}{\left(R_n+\frac{h_c}{2}\right)h_\theta}\right)\ m_f^{s+1}[1,\theta]$$

$$-\tfrac{(R_n+h_c)h_\theta}{h_c} m_f^{s+1}[2,\theta] - \frac{h_c}{\left(R_n+\frac{h_c}{2}\right)h_\theta}\left(m_f^{s+1}[1,\theta-1]+m_f^{s+1}[1,\theta+1]\right),$$

for any $r \in [\![2, N_c - 1]\!]$

$$\begin{aligned}\left(\mathtt{M_c} m_f^{s+1}\right)[r,\theta] = \frac{\kappa_c}{S_c[r]}\Bigg(&\left(\frac{(2R_n + (2r-1)\,h_c)\,h_\theta}{h_c} + \frac{2h_c}{\left(R_n + \left(r - \frac{1}{2}\right)h_c\right)h_\theta}\right) m_f^{s+1}[r,\theta] \\ &- \frac{(R_n + (r-1)\,h_c)\,h_\theta}{h_c} m_f^{s+1}[r-1,\theta] - \frac{(R_n + r h_c)\,h_\theta}{h_c} m_f^{s+1}[r+1,\theta] \\ &- \frac{h_c}{\left(R_n + \left(r - \frac{1}{2}\right)h_c\right)h_\theta}\left(m_f^{s+1}[r,\theta-1] + m_f^{s+1}[r,\theta+1]\right)\Bigg),\end{aligned}$$

and at the cell membrane

$$\begin{aligned}\left(\mathtt{M_c} m_f^{s+1}\right)[N_c,\theta] = \frac{\kappa_c}{S_c[N_c]}\Bigg(&\left(\frac{(R_n + (N_c-1)\,h_c)\,h_\theta}{h_c} + \frac{2h_c}{\left(R_n + \left(N_c - \frac{1}{2}\right)h_c\right)h_\theta}\right) m_f^{s+1}[N_c,\theta] \\ &- \frac{(R_n + (N_c-1)\,h_c)\,h_\theta}{h_c} m_f^{s+1}[N_c-1,\theta] \\ &- \frac{h_c}{\left(R_n + \left(N_c - \frac{1}{2}\right)h_c\right)h_\theta}\left(m_f^{s+1}[N_c,\theta-1] + m_f^{s+1}[N_c,\theta+1]\right)\Bigg).\end{aligned}$$

3. **Protein in cytoplasm (2c)-(2d).** To approach the concentration of protein in the cytoplasm, we proceed similarly to the step 2, except we follow the biological process by solving firstly the concentration of free protein molecules (2c), then the concentration of linked protein (2d). More precisely we start by approaching (2c) considering the system

$$\left((1 + h_t(\lambda_p + \beta_p))\,\mathtt{I_d} + h_t \mathtt{M_c}\right) p_f^{s+1} = \left(1 - h_t \frac{R_n h_\theta}{S_c}\mu_p \mathtt{B}_1\right) p_f^s + h_t \alpha_p m_f^s \tag{9}$$

with particles leaving the cytoplasm to the nucleus through the nuclear envelope is highlighted by the boundary indicator $\mathtt{B}_1[r]$. Then, since the concentration of free protein on the cytoplasm at time $t = (s+1)\,h_t$ is already known, we are able to approach the concentration of linked protein (2d), i.e. for any $r \in [\![1, N_c - 1]\!]$ we have

$$p_l^{s+1}[r,\theta] = \frac{\left(1 - \frac{h_t h_\theta}{S_c[r]}(R_n + (r-1)\,h_c)\,\nu_p\right) p_l^s[r,\theta] + \frac{h_t h_\theta}{S_c[r]}(R_n + r h_c)\,\nu_p p_l^s[r+1,\theta] + \beta_p[r,\theta]\, p_f^{s+1}[r,\theta]}{1 + h_t \lambda_p}$$

while at the cell membrane

$$p_l^{s+1}[N_c,\theta] = \frac{\left(1 - \frac{h_t h_\theta}{S_c[N_c]}(R_c - h_c)\,\nu_p\right) p_l^s[N_c,\theta] + \beta_p[N_c,\theta]\, p_f^{s+1}[N_c,\theta]}{1 + h_t \lambda_p}. \tag{10}$$

4. **Protein in nucleus (1b).** Similarly to the motion of mRNA on nucleus, we approach the concentration of protein (1b) on nucleus by the following

scheme

$$\left(\left(1+h_t\lambda_p\right)\mathtt{I_d}+h_t\mathtt{M_n}\right)p_n^{s+1}=p_n^s+h_t\frac{R_nh_\theta}{S_n}\left(\nu_p p_l^s\left[1,.\right]+\mu_p p_f^s\left[1,.\right]\right)\mathtt{B}_{N_n}, \tag{11}$$

where the last term is the concentration of protein coming to the nucleus through the nuclear envelope.

Proposition 1. *For any non-negative initial condition, the numerical approximation is non-negative under the CFL condition*

$$h_t\leq\min\left(\frac{S_n\left[N_n\right]}{R_nh_\theta\mu_m},\frac{S_c\left[1\right]}{R_nh_\theta\mu_p},\min_{r\in[\![1,N_c]\!]}\left(\frac{S_c\left[r\right]}{\left(R_n+rh_c\right)h_\theta\nu_m},\frac{S_c\left[r\right]}{\left(R_n+\left(r-1\right)h_c\right)h_\theta\nu_p}\right)\right).$$

Proof. We easily check that for any $a\geq 0$ the matrices $\mathtt{I_d}+a\mathtt{M_n}$ and $\mathtt{I_d}+a\mathtt{M_c}$ are M-matrix, i.e. the non-diagonal terms are strictly negative while the diagonal terms are strictly positive and strictly dominant. Therefore the matrices are invertible, positive and definite. We conclude by remark that under the CFL condition of Proposition 1, the right member of equations (6)-(7)-(8)-(9)-(10)-(11) are non-negative. ∎

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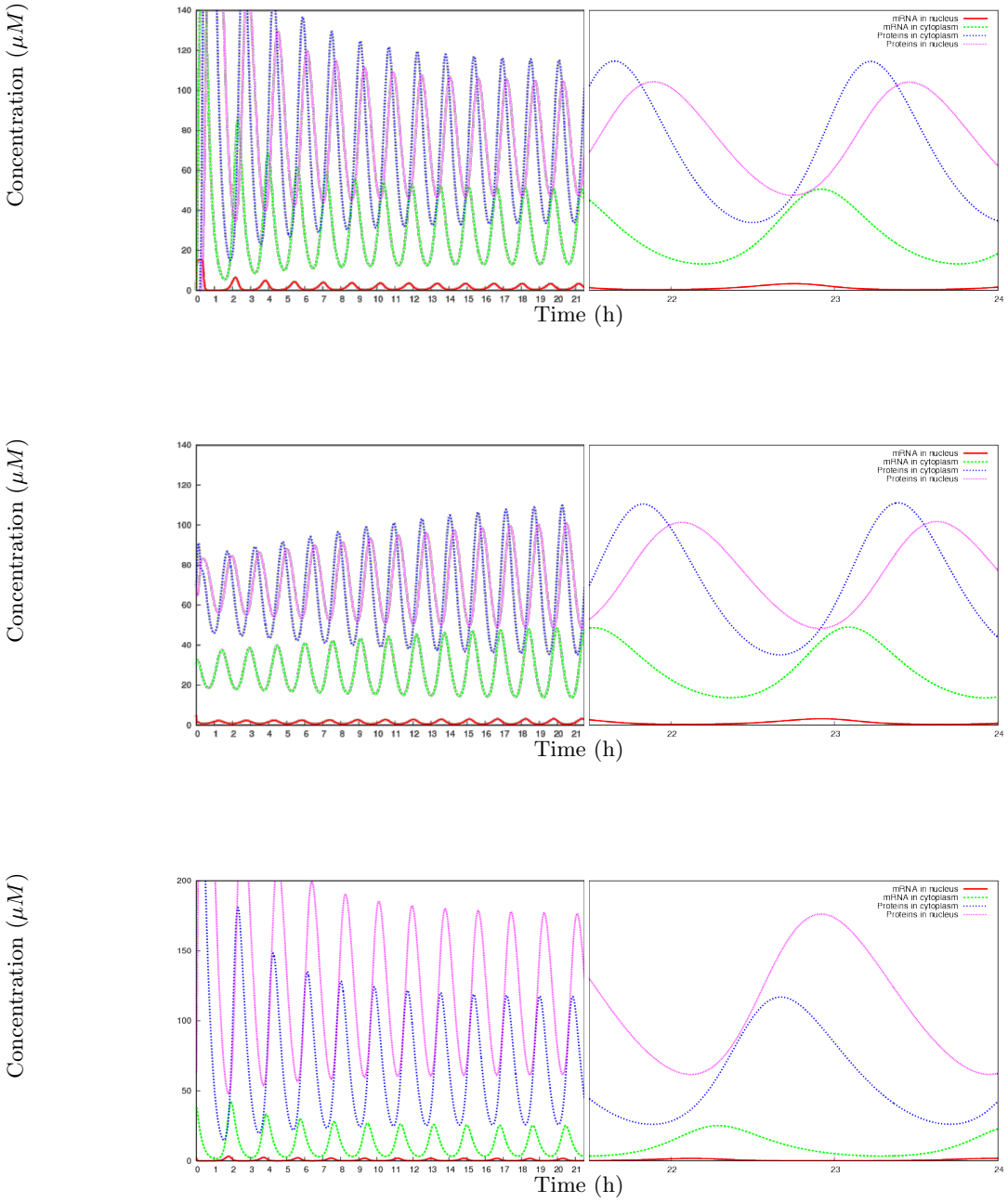

Figure 5: Total concentrations of molecules as functions of time in nucleus and cytoplasm in the case with microtubules. Parameters are given in Table 1 with vanishing initial condition (first line), homogeneous initial condition and steady initial condition (third line). The red solid line stands for the concentration of mRNA in the nucleus and the green dashed line stands for the concentration of mRNA in the cytoplasm. The blue dotted line stands for the concentration of protein in the cytoplasm and the pink thinly dotted line stands for the concentration of protein in the nucleus.

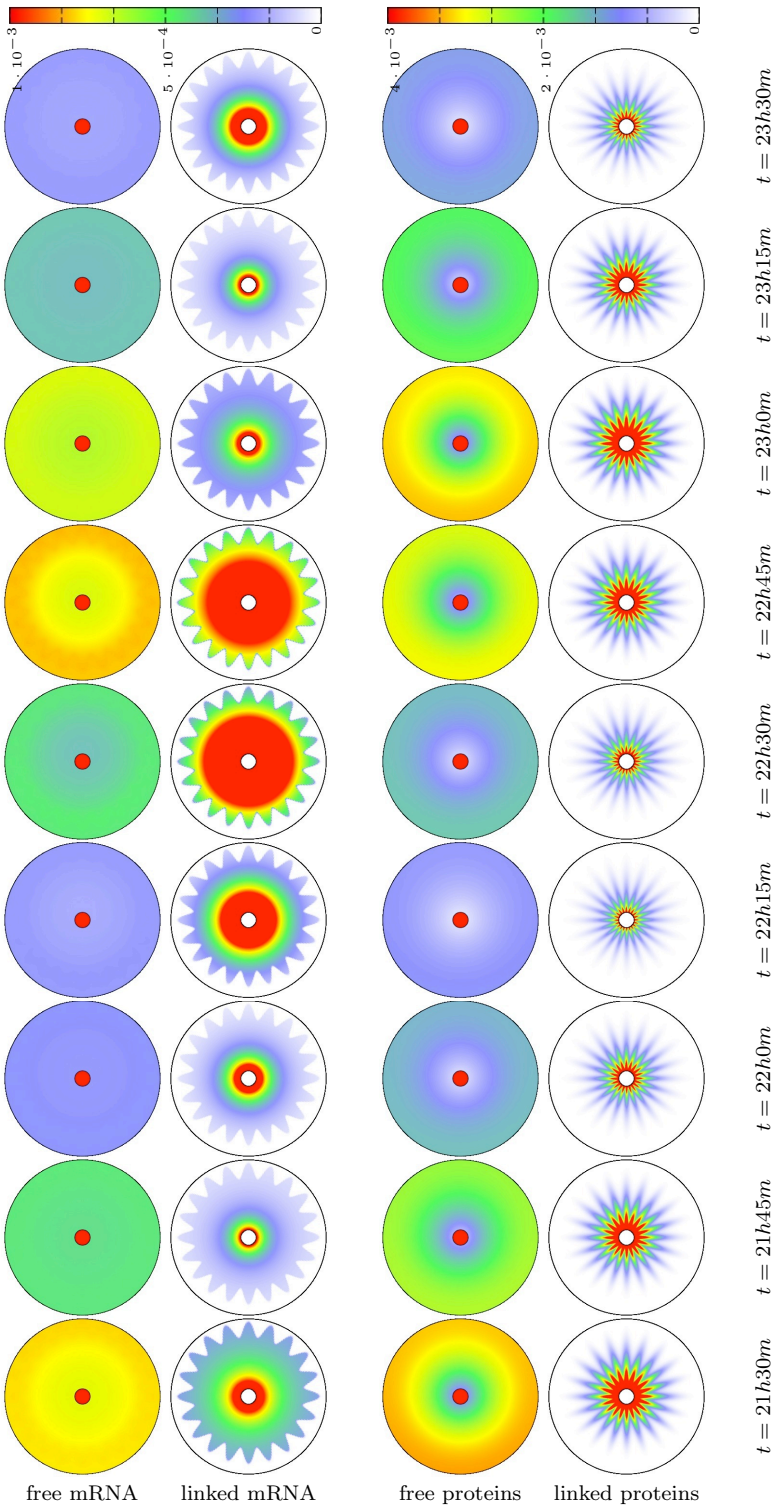

Figure 6: Spacial distribution of free mRNA (first column), linked mRNA (second column), free protein (third column) and linked protein (fourth column) at different times in the case with microtubules. Parameters are given in Table 1 with vanishing initial condition.