

# Periodic oscillations of a model for membrane permeability with fluctuating environmental conditions

Pedro J. Torres \*

Departamento de Matemática Aplicada,  
Universidad de Granada, 18071 Granada, Spain.  
E-mail: ptorres@ugr.es

## Abstract

We perform an analytical study of the dynamics of a multi-solute model for water transport across a cell membrane under periodic fluctuations of the extracellular solute molalities. The presence or not of non-permeating solute in the cell influences the dynamical behavior of the water volume oscillations in a notable way. The proofs are based on classical tools from the qualitative theory of differential equations, namely Brouwer degree, upper and lower solutions and comparison arguments.

*Keywords:* Cell volume, membrane transport, periodic oscillation, stability, Brouwer degree

## 1 Introduction

Cells may experience volume changes as a result of water transport across the cell membrane by osmosis. Living organisms count on homeostatic processes for regulation of cell volume, but this equilibrium can be altered by changing extracellular conditions. A good understanding of the dynamics of cell volume is critical in the study of the physiology of biological tissues, in particular in evolving areas like pharmacokinetics or cryobiology.

In a realistic situation, there are a large number of chemical species that can permeate across the cell membrane. In the recent paper [3], the authors propose a general model capable to describe the basic aspects of the dynamics of cell volume produced by active and passive transport of water and an arbitrary number of solute species across the cell membrane. The proposed model is the following system of ordinary differential equations

$$\begin{aligned} \dot{w}_1 &= \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n M_i(t), \\ \dot{w}_k &= b_k \left( M_k(t) - \frac{w_k}{w_1} \right), \quad k = 2, \dots, n. \end{aligned} \tag{1}$$

Here,  $w_1(t)$  is the water volume and  $w_k(t)$ ,  $k = 2, \dots, n$  are the amount of non-negative solute species inside the cell. The parameter  $x_{np} \geq 0$  represents the amount of non-permeating intracellular solute species (salts) and  $b_k > 0$  are the relative decrease rates of permeating solutes.

---

\*Partially supported by Spanish MICINN Grant with FEDER funds MTM2011-23652.

Finally,  $M_1 : \mathbb{R} \rightarrow [0, +\infty)$  models the extracellular concentration of non-permeating solute and  $M_k : \mathbb{R} \rightarrow [0, +\infty)$   $k = 2, \dots, n$  represent variations of the extracellular concentrations of permeating solute species.

System (1) is the natural extension of a previous model by Hernández [8] that considered only the interplay between water volume and one permeating solute. As discussed in [8], the model unifies a variety of relevant examples of solute–solvent transmembrane flux models presented in the literature, see for instance [2, 3, 10, 11, 12] and the references therein.

As pointed out in [3], for the case of constant molalities  $M_k$ ,  $k = 1, \dots, n$ , system (1) is autonomous and its study can be reduced to an equivalent linear system, just multiplying by  $w_1$  all the components of the vector field. This operation is equivalent to a time rescaling and does not modify the geometry of the orbits. By using this reduction, the authors in [3, Section 2] prove that system (1) has a unique equilibrium which is globally asymptotically stable. The reparametrization to a linear system is also useful when the functions  $M_k(t)$  are piece-wise constant and was used in [3, Section 3] to implement an optimal control scheme. Nevertheless, this argument is not valid for more general cases on variable functions  $M_k(t)$ .

In spite of the variety of homeostatic processes in living organisms, biological parameters are not static. As a matter of fact, there is extensive evidence of the existence of a circadian rhythm in plasma ion concentration in animals [1, 6, 9, 15]. Periodic water intake or pharmacological treatments may influence on such periodic fluctuations as well. On the other hand, the interaction of circadian clocks and solute concentration plays an important role in the physiology of plants [7]. In this paper, we are interested in the case when the extracellular environment experiences periodic fluctuations. From now on, we assume that  $M_k : \mathbb{R} \rightarrow [0, +\infty)$  are continuous and  $T$ -periodic functions, that is, there exists  $T > 0$  such that

$$M_k(t + T) = M_k(t), \quad k = 2, \dots, n$$

for every  $T$ . In this context, it is natural to look for  $T$ -periodic solutions and their properties.

We distinguish two situations depending if non-permeating solute is present ( $x_{np} > 0$ ) or not ( $x_{np} = 0$ ) in the cell. The first case is studied in Section 2, whereas Section 3 is devoted to the second case. Finally, Section 4 presents some conclusions and further remarks.

In the rest of the paper,  $C_T$  is the space of continuous and  $T$ -periodic functions. For a given  $h \in C_T$ , we denote  $\|h\|_\infty = \max_{[0, T]} h(t)$ . The mean value of a given  $h \in C_T$  is denoted by

$$\bar{h} = \frac{1}{T} \int_0^T h(t) dt.$$

Throughout the paper,  $T$ -periodic solutions of (1) are understood in the classical sense, that is, a set  $w_1, \dots, w_n$  of  $T$ -periodic functions with continuous derivatives satisfying (1) for all  $t$ . We only consider  $T$ -periodic solutions in the range of physically consistent values, that is,  $w_1(t) > 0$  and  $w_k(t) \geq 0$   $k = 2, \dots, n$  for all  $t$ .

## 2 The case $x_{np} > 0$ .

In the model under consideration,  $x_{np} > 0$  accounts for the presence of non-permeating solute species in the cell. Our main result is as follows.

**Theorem 2.1** *Assume that  $x_{np} > 0$ . Then, system (1) has a  $T$ -periodic solution if and only if  $\bar{M}_1 > 0$ .*

The following lemma, which has interest by itself, plays a key role in the proof of Theorem 2.1. For simplicity, let us define the function

$$\gamma(t) = \sum_{i=1}^n M_i(t).$$

**Lemma 2.1** *Assume that  $x_{np} > 0$  and  $\overline{M}_1 > 0$ . Any eventual  $T$ -periodic solution  $w = (w_1, \dots, w_n)$  of system (1) satisfies the following bounds*

$$\begin{aligned} \frac{x_{np}}{\|\gamma\|_\infty} &\leq w_1(t) < \frac{x_{np}}{\overline{M}_1} + T\overline{\gamma}, \\ \frac{x_{np}}{\|\gamma\|_\infty} \min_{[0,T]} M_k(t) &\leq w_k(t) < \left( \frac{x_{np}}{\overline{M}_1} + T\overline{\gamma} \right) \|M_k\|_\infty, \quad k = 2, \dots, n \end{aligned}$$

for every  $t \in [0, T]$ .

**Proof.** Let  $w = (w_1, \dots, w_n)$  be a  $T$ -periodic solution of system (1). We divide the proof into several steps

**Step 1:**  $w_1(t) > 0$  for every  $t$ . Write the system as

$$\begin{aligned} \dot{w}_1 &= \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n M_i(t), \\ \frac{1}{b_k} \dot{w}_k &= M_k(t) - \frac{w_k}{w_1}, \quad k = 2, \dots, n. \end{aligned}$$

Adding all the equations, we get

$$\dot{\varphi} = \frac{x_{np}}{w_1} - M_1(t)$$

where  $\varphi = w_1 + \sum_{k=2}^n \frac{w_k}{b_k}$  is  $T$ -periodic. Therefore, integrating over  $[0, T]$ ,

$$x_{np} \int_0^T \frac{1}{w_1(t)} dt = \overline{M}_1 T > 0. \quad (2)$$

By the integral mean value theorem, there exists  $t_0$  such that  $w_1(t_0) > 0$ . Besides, due to the singular term  $\frac{x_{np}}{w_1}$ , a solution  $w_1$  must have a constant sign. In conclusion,  $w_1(t)$  is always positive.

**Step 2**  $w_k(t) > 0$  for all  $t$ ,  $k = 2, \dots, n$ . For a given  $k$ , let  $t_0 \in [0, T]$  be such that  $w_k(t_0) = \min_{[0,T]} w_k(t)$ . Obviously,  $\dot{w}_k(t_0) = 0$ . Hence, the  $k$ -th equation reads

$$0 = M_k(t_0) - \frac{w_k(t_0)}{w_1(t_0)},$$

that is,

$$w_k(t_0) = M_k(t_0)w_1(t_0) \geq 0. \quad (3)$$

**Step 3**  $w_1(t) \geq \frac{x_{np}}{\|\gamma\|_\infty}$  for every  $t$ . Take  $t_0 \in [0, T]$  such that  $w_1(t_0) = \min_{[0, T]} w_1(t)$ . Evaluating in the first equation

$$0 = \frac{x_{np}}{w_1(t_0)} + \sum_{j=2}^n \frac{w_j(t_0)}{w_1(t_0)} - \gamma(t_0).$$

Then, by using Step 2,

$$\frac{x_{np}}{w_1(t_0)} = \gamma(t_0) - \sum_{j=2}^n \frac{w_j(t_0)}{w_1(t_0)} \leq \|\gamma\|_\infty,$$

and the conclusion follows.

**Step 4**  $w_k(t) \geq \frac{x_{np}}{\|\gamma\|_\infty} \min_{[0, T]} M_k(t)$  for all  $t$ ,  $k = 2, \dots, n$ . Trivial from (2) and Step 3.

**Step 5**  $\min_{[0, T]} w_1(t) \leq \frac{x_{np}}{\overline{M}_1}$ . Coming back to (2), by the integral mean value theorem, there exists  $t_0$  such that

$$\frac{x_{np}}{w_1(t_0)} = \overline{M}_1.$$

Then,  $\min_{[0, T]} w_1(t) \leq w_1(t_0) = \frac{x_{np}}{\overline{M}_1}$ .

**Step 6**  $w_1(t) < \frac{x_{np}}{\overline{M}_1} + T\overline{\gamma}$  for every  $t$ . By periodicity, we can take  $t_1 < t_2 < t_1 + T$  such that  $w_1(t_1) = \max_{[0, T]} w_1(t)$ ,  $w_1(t_2) = \min_{[0, T]} w_1(t)$ . From the first equation of the system,

$$\dot{w}_1(t) > -\gamma(t).$$

Integrating on  $[t_1, t_2]$  we get

$$w(t_2) - w(t_1) > \int_{t_1}^{t_2} \gamma(t) dt > -T\overline{\gamma}.$$

Therefore,

$$\max_{[0, T]} w_1(t) = w_1(t_1) < w_1(t_2) + T\overline{\gamma},$$

and the conclusion follows directly from Step 5.

**Step 7**  $w_k(t) < \left(\frac{x_{np}}{\overline{M}_1} + T\overline{\gamma}\right) \|M_k\|_\infty$  for all  $t$ ,  $k = 2, \dots, n$ . For a given  $k$ , take  $t_1 \in [0, T]$  such that  $w_k(t_1) = \max_{[0, T]} w_k(t)$ . Evaluating on the  $k$ th equation,

$$0 = M_k(t_1) - \frac{w_k(t_1)}{w_1(t_1)}.$$

Thus,

$$w_k(t_1) = w_1(t_1) M_k(t_1) \leq w_1(t_1) \|M_k\|_\infty,$$

and the proof is finished by Step 6.

□

To prove Theorem 2.1, we use a well-known continuation theorem by Capietto-Mawhin-Zanolin, which is stated below for the reader's convenience.

**Proposition 1 ([4])** *Let  $\Omega$  be a domain contained in  $\mathbb{R}^n$ . Let us consider a continuous homotopy  $f = f(t, x; \lambda) : [0, T] \times \Omega \times [0, 1] \rightarrow \mathbb{R}^n$  such that  $F(t, x) = f(t, x; 1)$  and  $f_0(x) = f(t, x; 0)$ , where  $f_0 : \Omega \rightarrow \mathbb{R}^n$  is a given continuous function. Assume that there is a compact set  $K \subset \Omega$  containing all the  $T$ -periodic solutions of the homotopic system*

$$x' = f(t, x; \lambda)$$

and suppose that  $\{z \in \mathbb{R}^n : f_0(z) = 0\} \subset K$ . Assume that

$$d_B(f_0, G, 0) \neq 0$$

where  $G \subset \mathbb{R}^n$  is an open subset containing  $K$ . Then, system  $x' = F(t, x)$  has at least one  $T$ -periodic solution with values in  $K$ .

Here,  $d_B(f_0, G, 0)$  is the Brouwer topological degree of the vector field  $f_0$  (one can consult for instance [5, 13] for the formal definition and main properties). To apply Proposition 1, first we have to embed system (1) into a suitable homotopic system. To this aim, we define the functions

$$M_{k,\lambda}(t) = \lambda M_k(t) + (1 - \lambda) \overline{M}_k, \quad k = 1, \dots, n$$

with  $\lambda \in [0, 1]$ . Then, the homotopic system

$$\begin{aligned} \dot{w}_1 &= \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n M_{i,\lambda}(t), \\ \dot{w}_k &= b_k \left( M_{k,\lambda}(t) - \frac{w_k}{w_1} \right), \quad k = 2, \dots, n. \end{aligned} \tag{4}$$

defines a continuous deformation from the original system (1) for  $\lambda = 1$  into the autonomous system

$$\begin{aligned} \dot{w}_1 &= \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n \overline{M}_i, \\ \dot{w}_k &= b_k \left( \overline{M}_k - \frac{w_k}{w_1} \right), \quad k = 2, \dots, n \end{aligned} \tag{5}$$

for  $\lambda = 0$ . Moreover, note that

$$\overline{M}_{k,\lambda} = \overline{M}_k,$$

$$\min_{[0,T]} M_k(t) \leq \min_{[0,T]} M_{k,\lambda}(t) \leq \|M_{k,\lambda}\|_\infty \leq \|M_k\|_\infty$$

for all  $\lambda \in [0, T]$ ,  $k = 1, \dots, n$ . This fact implies that the uniform bounds given by Lemma 2.1 remain valid for the  $T$ -periodic solutions of the whole homotopic system (4). Therefore, to conclude the proof it remains to check that the Brouwer degree of the vector field  $f_0(w)$  given by system (5) is different from zero.

In our case,  $\Omega = \mathbb{R}^+ \times \mathbb{R}^{n-1}$  and  $K$  is the closed box in  $\Omega$  defined by the lower and upper bounds given in Lemma 2.1. The vector field  $f_0 : \Omega \rightarrow \mathbb{R}^n$  is defined by

$$f_0(w) = \left( \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n \overline{M}_i, b_2 \left( \overline{M}_2 - \frac{w_2}{w_1} \right), \dots, b_n \left( \overline{M}_n - \frac{w_n}{w_1} \right) \right).$$

For regular vector fields, the simplest way to compute the degree is the following *linearization principle*: if  $f$  is of class  $C^1$  and has a finite number of zeroes in  $G$ , say  $f^{-1}(0) = \{\xi_1, \dots, \xi_m\}$ , then the Brouwer degree is explicitly given by the formula

$$d_B(f, G, 0) = \sum_{i=1}^m \operatorname{sgn}(\det Jf(\xi_i)), \quad (6)$$

where  $Jf$  is the Jacobian matrix of  $f$ . In our case,  $f_0 \in C^1(\Omega)$  and the unique point such that  $f(\xi) = 0$  is

$$\xi = \frac{x_{np}}{\overline{M}_1} (1, \overline{M}_2, \dots, \overline{M}_n).$$

Computing the Jacobian matrix of  $f_0$  and evaluating in  $\xi$ , after simple row manipulation on the determinant, we get

$$\begin{aligned} \det Jf(\xi) &= \left( \frac{\overline{M}_1}{x_{np}} \right)^n b_2 \cdots b_n \det \begin{pmatrix} -\sum_{k=1}^n \overline{M}_k & 1 & 1 & \cdots & \cdots & 1 \\ \overline{M}_2 & -1 & 0 & \cdots & \cdots & 0 \\ \overline{M}_3 & 0 & -1 & 0 & \cdots & 0 \\ \vdots & & & & & 0 \\ \overline{M}_n & 0 & 0 & \cdots & 0 & -1 \end{pmatrix} \\ &= \left( \frac{\overline{M}_1}{x_{np}} \right)^n b_2 \cdots b_n \det \begin{pmatrix} -\overline{M}_1 & 0 & 0 & \cdots & \cdots & 0 \\ \overline{M}_2 & -1 & 0 & \cdots & \cdots & 0 \\ \overline{M}_3 & 0 & -1 & 0 & \cdots & 0 \\ \vdots & & & & & 0 \\ \overline{M}_n & 0 & 0 & \cdots & 0 & -1 \end{pmatrix} \\ &= (-1)^n \overline{M}_1 \left( \frac{\overline{M}_1}{x_{np}} \right)^n b_2 \cdots b_n. \end{aligned}$$

In consequence,  $d_B(f_0, G, 0) = (-1)^n \neq 0$ , where  $G$  is an open and bounded set such that  $K \subset G \subset \overline{G} \subset \Omega$ . Thus, the sufficient part of Theorem 2.1 is proved.

To complete the proof of Theorem 2.1, it remains the “only if” part, that is, if system (1) has a  $T$ -periodic solution then  $\overline{M}_1 > 0$ . To prove it, we write system (1) as

$$\begin{aligned} \dot{w}_1 &= \frac{x_{np}}{w_1} + \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n M_i(t), \\ \frac{1}{b_k} \dot{w}_k &= M_k(t) - \frac{w_k}{w_1}, \quad k = 2, \dots, n. \end{aligned}$$

Then, if there exists a  $T$ -periodic solution, adding all the equations and integrating over a period, we get

$$\overline{M}_1 = \frac{1}{T} \int_0^T \frac{x_{np}}{w_1(t)} dt > 0,$$

and the proof is done.

### 3 The case $x_{np} = 0$ .

In this section, we analyze the dynamics of system (1) when  $x_{np} = 0$ , that is, when the cell does not contain non-permeating solute species. In this case, the system can be written as

$$\begin{aligned} \dot{w}_1 &= \sum_{j=2}^n \frac{w_j}{w_1} - \sum_{i=1}^n M_i(t), \\ \frac{1}{b_k} \dot{w}_k &= M_k(t) - \frac{w_k}{w_1}, \quad k = 2, \dots, n. \end{aligned}$$

Adding all the equations,

$$\dot{\varphi} = -M_1(t),$$

where  $\varphi = w_1 + \sum_{k=2}^n \frac{w_k}{b_k}$ . Remember that  $M_1 : \mathbb{R} \rightarrow [0, +\infty)$  is the extracellular concentration of non-permeating solute. Therefore,

$$\varphi(t) = \varphi(0) - \int_0^t M_1(s) ds.$$

In consequence, if  $\overline{M}_1 > 0$  then

$$w_1(t) \leq \varphi(t) = \varphi(0) - \int_0^t M_1(s) ds \rightarrow -\infty \quad \text{as } t \rightarrow +\infty.$$

But remember that  $w_1(t)$  is the water volume inside the cell, so physically if  $\overline{M}_1 > 0$  the water volume is zero at a finite time, regardless the initial conditions. Therefore, a necessary condition for the existence of periodic states is  $M_1(t) \equiv 0$ . The next result considers a particular case where such condition is also sufficient.

**Theorem 3.1** *Assume that  $x_{np} = 0$ ,  $M_1(t) \equiv 0$  and*

*(H<sub>1</sub>) there exists  $b > 0$  such that  $b = b_k$  for every  $k = 2, \dots, n$ .*

*Then, system (1) has infinitely many  $T$ -periodic solutions.*

In the proof, we will need the following basic result for a first order scalar equation with a singular nonlinearity.

**Lemma 3.1** *For any  $h \in C_T$  with  $h_m := \min_{[0,T]} h(t) > 0$  and  $a > 0$ , the first order equation*

$$\dot{w}_1 = \frac{a}{w_1} - h(t) \tag{7}$$

*has a unique  $T$ -periodic solution  $w_1(t)$ . Moreover,  $w_1$  satisfies the explicit bounds*

$$\frac{a}{\|h\|_\infty} \leq w_1(t) \leq \frac{a}{h_m} \quad \text{for all } t. \tag{8}$$

**Proof.** To prove the existence, we make use of the classical method of upper and lower solutions (see for instance [14]). According to the definition in [14],  $\alpha = \frac{a}{\|h\|_\infty}$  is an upper solution and  $\beta = \frac{a}{h_m}$  is a lower solution for eq. (7). By [14, Theorem 2.2], (7) has a  $T$ -periodic solution with values between  $\alpha$  and  $\beta$ .

To prove the uniqueness, let us assume by contradiction that there exist two different solutions  $w_1, \hat{w}_1$  of eq. (7). For a first order equation with regular nonlinearity on its domain of definition, the flux is ordered, that is, two solutions do not cross each other, as a consequence of the uniqueness of solution for the initial value problem. Hence, we can assume  $w_1(t) > \hat{w}_1(t)$  for all  $t$ . If  $d(t) = w_1(t) - \hat{w}_1(t)$ , by subtracting the respective equations,

$$\dot{d} = \frac{a}{w_1} - \frac{a}{\hat{w}_1} < 0, \quad \text{for all } t.$$

Now, an integration on  $[0, T]$  leads to contradiction.  $\square$

**Proof of Theorem 3.1.** By repeating the argument at the beginning of this section, we have that  $\dot{\varphi} = 0$ , where  $\varphi(t) = w_1(t) + \frac{1}{b} \sum_{k=2}^n w_k(t)$ . In consequence,  $\varphi(t)$  is a conserved quantity of the system, that is, there exists  $C > 0$  such that  $\varphi(t) = C$  for all  $t$ .

Now, we will use the conserved quantity to decouple the first equation. From  $\varphi(t) = C$  we get

$$\sum_{k=2}^n w_k(t) = b(C - w_1(t)) \quad \text{for all } t. \quad (9)$$

Inserting this summation into the first equation of system (1), one gets the decoupled equation

$$\dot{w}_1 = \frac{bC}{w_1} - b - \sum_{i=2}^n M_i(t). \quad (10)$$

Now, we apply Lemma 3.1 with  $a = bC$  and  $h(t) = b + \sum_{i=2}^n M_i(t)$ . For any  $C > 0$ , there exists a unique  $T$ -periodic solution  $w_{1,C}$  of (10), such that

$$\frac{bC}{b + \|\sum_{i=2}^n M_i(t)\|_\infty} \leq w_{1,C}(t) \leq \frac{bC}{b + \min_{[0,T]} \sum_{i=2}^n M_i(t)} \quad \text{for all } t. \quad (11)$$

Once  $w_{1,C}$  is fixed, the rest of equations of the system are written as

$$\dot{w}_k + \frac{b}{w_{1,C}(t)} w_k = bM_k(t), \quad k = 2, \dots, n, \quad (12)$$

and can be solved as linear equations. In effect, By Fredholm's alternative, eq. (12) has a unique  $T$ -periodic solution  $w_{k,C}$ ,  $k = 2, \dots, n$ .

In conclusion, we have demonstrated the existence of a uniparametric family  $w_C = (w_{1,C}, \dots, w_{n,C})$  of  $T$ -periodic solutions with  $C > 0$ .  $\square$

In the previous result, the first component  $w_{1,C}(t)$  of the uniparametric family  $T$ -periodic solutions of system (1) represents periodic oscillations of the water volume. In the final result of this section, it is proved that the water volume determined by arbitrary initial conditions of the system tends asymptotically to one of these periodic oscillations.



**Theorem 3.2** *Assume the conditions of Theorem 3.1. Let  $w(t, w_0) = (w_1(t, w_0), \dots, w_n(t, w_0))$  the unique solution of system (1) with initial condition  $w(0) = w_0 = (w_1^0, \dots, w_n^0)$ . Then,*

$$\lim_{t \rightarrow +\infty} |w_1(t, w_0) - w_{1, C_0}(t)| = 0,$$

$$\text{where } C_0 = w_1^0 + \frac{1}{b} \sum_{k=2}^n w_k^0.$$

For the proof, repeating the arguments at the beginning of the proof of Theorem 3.2, it is shown that  $w_1(t, w_0)$  verifies eq. (10) with  $C = C_0$ . On the other hand,  $w_{1, C_0}(t)$  is the unique  $T$ -periodic solution of (10) with  $C = C_0$ , by Lemma 3.1. Then the proof is finished once the following lemma is proved.

**Lemma 3.2** *Let be  $h \in C_T$  with  $h_m := \min_{[0, T]} h(t) > 0$  and  $a > 0$ . Then, the unique  $T$ -periodic solution of eq. (7) given by Lemma 3.1 is globally asymptotically stable.*

**Proof.** The argument is similar to that used to prove the uniqueness. Let  $w_1$  be the unique  $T$ -periodic solution and  $\hat{w}_1$  any other solution of eq. (7). We have to prove that  $d(t) = w_1(t) - \hat{w}_1(t)$  tends to zero as  $t \rightarrow +\infty$ .

Again by the order of the flux, we can assume  $w_1(t) > \hat{w}_1(t)$  for all  $t$  (the reciprocal inequality is handled analogously). By subtracting the respective equations,

$$\dot{d} = \frac{a}{w_1} - \frac{a}{\hat{w}_1} < 0, \quad \text{for all } t. \quad (13)$$

Therefore,  $d(t)$  is a positive and strictly decreasing function, so in consequence it tends to a constant and  $\dot{d}(t) \rightarrow 0$  as  $t \rightarrow +\infty$ . For (13), we can write

$$d(t) = -\frac{1}{a} w_1(t) \hat{w}_1(t) \dot{d}(t),$$

and passing to the limit, the proof is concluded.  $\square$

## 4 Conclusions and final remarks.

We have studied the dynamical behavior of a general model recently proposed in the literature for the evolution of water transport accross a cell membrane under the influence of an arbitrary number of permeating solutes, when the extracellular solute molalities change periodically. We have shown that the situation is different depending if the cell contains non-permeating solute species (salts) or not. In the first case ( $x_{np} > 0$ ), the system has at least one periodic solution if and only if the extracellular molality of non-permeant solute ( $\bar{M}_1$ ) is positive (Theorem 2.1). Moreover, we have provided explicit bounds of the oscillations of water volume and solute concentrations (see Lemma 2.1). For constant extracellular molalities, such periodic solution corresponds to the unique asymptotically stable equilibrium found in [3]. Our main result only guarantees the existence of periodic solution, thus the question of uniqueness and stability (even in the case  $n = 2$ ) remains as an interesting open problem.

On the other hand, in the absence of non-permeating solute ( $x_{np} = 0, M_1(t) \equiv 0$ ), we have proved the existence of an infinite number of  $T$ -periodic solutions when the rate constants  $b_k$  are the same for all the permeating solutes (hypothesis ( $H_1$ )). Furthermore, for any initial

condition the water volume variation is asymptotically periodic (Theorem 3.2), and we have explicit bounds on the asymptotic periodic profile depending on the initial conditions, see (11). Note that by means of (11),  $w_{1,C}(t)$  tends uniformly to  $+\infty$  (resp. 0) if  $C \rightarrow +\infty$  (resp. 0). Therefore, we can modulate the asymptotic periodic profile of water volume attending to the initial conditions. Of course, for the case  $n = 2$ ,  $(H_1)$  is always valid. In the general case of an arbitrary number of solutes with different rates  $b_k$ , it is not clear if results analogous to those of Section 3 can be proved.

As a final remark, we have chosen the extracellular concentrations  $M_k(t)$  as continuous functions for simplicity, but exactly the same arguments can be developed with minor modifications for piece-wise continuous functions, by considering the solutions of (1) in the Carathéodory sense (that is, in the space  $W_{loc}^{1,1}$ ).

## References

- [1] Bernardi, M., DePalma, R., Trevisani, F., Capani, F., Santini, C., Baraldini, M., Gasbarrini, G.: Serum potassium circadian rhythm. Relationship with aldosterone, *Hormone and Metabolic Research*, vol. 17, no. 12, p. 695, (1985)
- [2] Benson, J.D., Chicone, C.C., Critser, J.K.: Exact solutions of a two parameter flux model and cryobiological applications, *Cryobiology*, **50** (3), 308–316 (2005)
- [3] Benson, J.D., Chicone, C.C., Critser, J.K.: A general model for the dynamics of cell volume, global stability and optimal control, *Journal of Mathematical Biology*, **63** (2), 339–359 (2011)
- [4] Capietto, A., Mawhin, J., Zanolin, F.: Continuation theorems for periodic perturbations of autonomous systems, *Trans. Amer. Math. Soc.* **329**, 41–72 (1992)
- [5] Deimling, D.: *Nonlinear Functional Analysis*. Springer-Verlag, Berlin (1985)
- [6] Fijorek, K., Puskulluoglu, M., Polak, S.: Circadian Models of Serum Potassium, Sodium, and Calcium Concentrations in Healthy Individuals and Their Application to Cardiac Electrophysiology Simulations at Individual Level, *Computational and Mathematical Methods in Medicine*, vol. 2013, Article ID 429037, 8 pages, (2013)
- [7] Haydon, M.J., Bell, L.J., Webb, A.A.R.: Interactions between plant circadian clocks and solute transport, *J. Exp. Bot.* **62** (7), 2333–2348 (2011)
- [8] Hernández, J.A.: A general model for the dynamics of the cell volume, *Bulletin of Mathematical Biology* **69** (5), 1631–1648 (2007)
- [9] Kanabrocki, E.L., Scheving, L.E., Halberg, F.: Circadian variations in presumably healthy men under conditions of peace time army reserve unit training, *Space Life Sciences* **4**, no. 2, 258–270, (1973)
- [10] Katkov, I.: A two-parameter model of cell membrane permeability for multisolute systems, *Cryobiology*, **40** (1), 64–83 (2000)
- [11] Katkov, I.: The point of maximum cell water volume excursion in case of presence of an impermeable solute, *Cryobiology*, **44** (3), 193–203 (2002)

- [12] Kleinhans, F.W.: Membrane permeability modeling: Kedem–Katchalsky vs a two-parameter formalism, *Cryobiology* **37** (4), 271–289 (1998)
- [13] Krasnoselskii, M.A., Zabreiko, P.P.: Geometrical methods of nonlinear analysis. Springer-Verlag, Berlin (1984)
- [14] Nkashama, M.N.: A generalized upper and lower solutions method and multiplicity results for nonlinear first-order ordinary differential equations, *Journal of Mathematical Analysis and Applications* **140**, Iss. 2, 381–395 (1989)
- [15] Sennels, H.P., Jørgensen, H.L., Goetze, J.P., Fahrenkrug, J.: Rhythmic 24-hour variations of frequently used clinical biochemical parameters in healthy young malesthe Bispebjerg study of diurnal variations, *Scandinavian Journal of Clinical & Laboratory Investigation*, vol. 72, pp. 287–295, (2012)
- [16] Sothorn, R.B., Vesely, D.L., Kanabrocki, E.L. et al.: Circadian relationships between circulating atrial natriuretic peptides and serum sodium and chloride in healthy humans, *American Journal of Nephrology*, vol. 16, no. 6, pp. 462–470, (1996)