MathematicS In Action

A simple mathematical model for the growth and division of cells

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Abstract. In this paper, we derive an electrostatic-electrodynamic model of the exchanges of ions between a cell and its exterior during its growth, as well as a model of exchange of ions within the cell. Observations show that, in the phase G1, the growth of the volume explains the variation of density of ions (by dilution), hence explains the change of electrostatic potential inside the cell. The potential encounters a threshold at the beginning of phase S, and the ion channels open (the conductance of the membrane increases). This afflux of ions leads to a change of potential, which will trigger the disappearance of the nucleus double membrane (through the calcium channels).
From these remarks on the electric phenomena in the cell, one deduces a simple mathematical model, which is a generalization of the Hodgkin-Huxley model for the axons, for the cell cycle.

1. Introduction and electrical model of a growing cell

Recent trends in biology and medecine recognize the wide role of interdisciplinary analysis of biological phenomena, namely the role of physical modeling, chemical [8] and thermodynamical explanations [10], mechanical analysis in understanding microbiology phenomena [5], [9], to name a few. It is then necessary to be able to understand the mutual influence of these different fiels, and be able to see if a more global model can be proposed.
However, the complexity of all the phenomena involved prevent scientists to write a complete, understandable, and usable model. In other words, complete and understandable models exist (coupling two disciplinary fields at most) and have been widely proposed, but their complexity renders the analysis quite complicated, or even impossible. One may also use a precise modeling of a specific phenomenon, and one may deduce results from this. This has been done quite often, but in this case one lacks the global understanding in the view of other physical domains of the solutions of such explicit models.
Experimental studies have been performed for the study of the mechanical behavior of the tissues by the authors [6], which confirm the influence of a repeated mechanical stress on the modification of the structure of the brain. We rely in this paper on experiments conducted by various authors for the electrical potentials and ionic exchanges in the cell [2], but we did not perform such experiments ourselves.
In this paper, we propose a mathematical model, using on one side other models of electric interactions between a cell and the difference of potential across its membrane, which can explain the mitosis of a cell as well as the role of the electric currents in this mitosis, and on the other side classical mechanics analysis of such bodies. We rely on a few ideas, which may be considered as simple; henceforth this model must bee seen as a first approach of the study of this fundamental biological phenomenon. We only rely here on static equations, but one may as well introduce the corresponding dynamical equations (laws of motion for an ion inside an electric field, Mawxell

equations for the behavior of the induced electromagnetic field, classical laws of fluid mechanics including deformation of physical boundaries under pressure forces, ...). Of course, this model is far from being complete and accurate; it has to be seen as a 'simple' model, allowing to understand the equations with mathematical tools.
We will use only, among all the phenomena, the following ideas

(1) The exchange of ions between the interior and the exterior of a cell does not depend on the cell,

(2) When a cell grows, the number of ionic channels which allow (or not) the ions to move between the interior and the exterior depends on the surface of the cell. The number of ionic channels by unit surface is a characteristic of the cell,

(3) Usual laws of electrostatic potential and electrodynamic equations are valid in a cell,

(4) A cell grows in the direction in which there is no resistance, which means inside a region where there is no other cell, otherwise it grows with no privilegied direction,

(5) the nucleus of a cell obeys the same electrodynamic laws.

The first item allows us to use the celebrated model that Hodgkin and Huxley introduced for the giant squid axon [4]. We assume that **all membranes have the same electrostatic behavior**.
Namely, recall that the Hodgkin-Huxley equations express the ionic currents across the membrane for any type of ion as

$$I(x,t) = \bar{g}p(V(x,t) - E_{eq}), (x,t) \in \mathbb{R} \times \mathbb{R}R_+$$

where E_{eq} is the equilibrium potential of the considered ion, $\bar{g}$ is the maximum value of the ionic conductance of the membrane, and p can be seen as the probability that the considered ion crosses the membrane (whatever direction has the ion). The ions exit the cell if the potential $V(x,t)$ is smaller than E_{eq} and enter the cell otherwise.
In this equality, $\bar{g}$ has the dimension of a conductance by unit of surface, $V(x,t)$ is in volt and I is a surface density current.
Such a model of conductivity is not specific to the giant squid axon, it is general for cells (see [7]).
In their analysis, Hodgkin and Huxley [4] introduced for potassium ions $p = n^4$ and obtained an equation on n by experimental analysis of the form

$$\partial_t n(x,t) = -\frac{n - n_\infty(V(x,t))}{\tau(V(x,t))}$$

where $\tau(V)$ is a time rate of decay depending on the potential V, and $n_\infty(V)$ is the limit number of ions passing through the membrane at the potential V. For a fixed constant potential V_*, the quantity $n(t)$ converges exponentially to the limit $n_\infty(V_*)$ at the rate $\tau(V_*)$. The work of Hodgkin and Huxley was to measure, for all potentials V, the values of the limit and of the rate of convergence (see Figure 1 for the value of the limit probability for all potentials). This model for the exchange of ions across a membrane has not been contradicted since then; even theoretical proofs of such behaviors (using Nernst's laws for example) have been published in the literature [1]. This model has also been used in other mathematical models for cells (see [7] for example). The curve given here shows a treshold for the value of the current of ions around the value -80mV of the potential. From the curves on $n_\infty(V)$ and $\tau(V)$, this is easily explained ($n_\infty(V)$ converges exponentially in V to its limit 1 at $V \to -\infty$ and to its limit 0 at $V \to \infty$, and the time for teaching the equilibrium value goes to 0 exponentially in both cases.

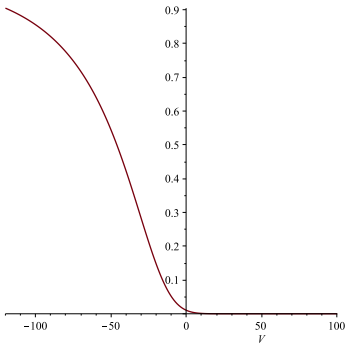

FIGURE 1. *Potassium conductance probability for an axon*

2. Influence of the volume on the potential

2.1. General remarks

The second item of our ideas is related with the growth of the cell, and more precisely to the relative growth of the cell versus its surface. We shall illustrate this on two examples

(1) the volume of a sphere is $\frac{4}{3}\pi(R(t))^3$, the surface of a sphere is $4\pi(R(t))^2$

(2) the volume of an ellipsoid of parameters $a(t), b(t), b(t)$ is $\frac{4}{3}a(t)b(t)^2$ and its surface is $2\pi(b(t))^2 + 2\pi a(t)b(t)\frac{\phi(t)}{\sin\phi(t)}$, where $\cos\phi(t) = \frac{b(t)}{a(t)}$.

In the first case, the evolution of the concentration of ions can behave as $\frac{N_{ic}4\pi(\frac{3}{4\pi}V(t))^{\frac{2}{3}}}{V(t)} = N_{ic}4\pi(\frac{3}{4\pi})^{\frac{2}{3}}(V(t))^{-\frac{1}{3}}$.
In the second case, the evolution of the concentration of ions behave as

$$N_{ic}\frac{2\pi(b(t))^2 + 2\pi a(t)b(t)\frac{\phi}{\sin\phi}}{\frac{4}{3}\pi a(t)(b(t))^2} = \frac{3}{2}N_{ic}\frac{1}{b(t)}(\cos\phi(t) + \frac{\phi(t)}{\sin\phi(t)})$$

This second case is a cigar-like cell (ellipspoidic).
Recall the following classical Theorem, dating back to Dirichlet in its first version:

Theorem 2.1. *Let Ω be a bounded open set with smooth boundary. The problem*

$$-\Delta V = f, in\Omega, V|_{\partial\Omega} = V_0$$

has a unique solution for $f \in L^2(\Omega)$. This solution belongs to $H^1(\Omega)$.

2.2. The case of a sphere with an uniform distribution of ions

In this section, we study two cases where we have an explicit value of the potential inside a spherical cell of changing volume. We assume that the exterior potential is always the same, uniform, equal to V_0, and that the cell is spherical, of radius $R(t)$.

In the first case, the number of ions in the cell does not change (potential $V(t)$). In the second case, the density of ions does not change (potential $W(t)$). Equations:

$$-\Delta V(t) = \frac{\rho(t)}{\epsilon_0}, x \in B(0,R(t)), V(t)|_{\partial B(0,R(t))} = V_0.$$

$$-\Delta W(t) = \frac{\rho}{\epsilon_0}, x \in B(0,R(t)), W(t)|_{\partial B(0,R(t))} = V_0.$$

As one has $\rho(t) = \frac{N}{\frac{4}{3}\pi R(t)^3}$, (which is the mathematical translation of the fact that the number of ions is constant in $B(0,R(t))$, one finds

$$V(r,t) = V_0 + \frac{N}{8\pi\epsilon_0 R(t)^3}(R(t)^2 - r^2), W(r,t) = V_0 + \frac{\rho}{6\epsilon_0}((R(t))^2 - r^2).$$

and thus

$$V(R(t),t) - V(0,t) = -\frac{N}{8\pi\epsilon_0 R(t)}, W(R(t),t) - W(0,t) = -\frac{\rho}{6\epsilon_0}(R(t))^2$$

We can thus propose the following observation:
A change of volume of the cell alone may induce a change of the potential. It can be either when the number of ions in the cell is constant or when the density of ions in the cell is constant.
Note that the variation of the potential is not similar in both cases: when the number of ions is constant, the depolarization decreases, while when the density of ions is constant, the depolarization increases.
We can generalize the first result, by assuming that the change of the number of ions is linked with the ions which flow inside or outside the cell through the ion channels, driven by the potential at the boundary V_0.

2.3. **The homothetic case**

Consider now the case of an open set Ω_1, strictly convex, star shaped, called Ω_1 and assume that, for $\rho_1(x,y,z)$ a C^0 function supported in Ω_1 (which is the density distribution of a certain type of ions in the cell), we have found the unique solution $V_1(x,y,z)$ of

$$-\Delta V_1 = \frac{\rho_1}{\epsilon_0}, V_1|_{\partial\Omega_1} = V_0.$$

Consider $\Omega_2 = \{(x,y,z) \in \mathbb{R}^3, (\lambda^{-1}x, \lambda^{-1}y, \lambda^{-1}z) \in \Omega_1\}$. One can say, for example, that if Ω_1 is a sphere of radius R_1, then Ω_2 is a sphere of radius R_2, both centered at $(0,0,0)$.
Introduce $\rho_2(x,y,z) = \lambda^{-3}\rho_1(\lambda^{-1}x, \lambda^{-1}y\lambda^{-1}z)$ for $(x,y,z) \in \Omega_2$.
The number of ions is thus conserved in Ω_2, thanks to

$$\int_{\Omega_2} \rho_2(X,Y,Z)dXdYdZ = \int_{\Omega_1} \rho_1(x,y,z)dxdydz.$$

Consider, on Ω_2, the problem

$$-\Delta V_2 = \frac{\rho_2}{\epsilon_0}, V_2|_{\partial\Omega_2} = V_0.$$

Consider $W_1(X,Y,Z) = V_2(\lambda X, \lambda Y, \lambda Z)$, such that, for all $(X,Y,Z) \in \Omega_1$, $(\lambda X, \lambda Y, \lambda Z) \in \Omega_2$. One gets

$$-\Delta W_1 = -\lambda^2 \Delta V_2(\lambda X, \lambda Y, \lambda Z) = \lambda^2\lambda^{-3}\frac{\rho_1(X,Y,Z)}{\epsilon_0} = \frac{1}{\lambda}\frac{\rho_1}{\epsilon_0},$$

along with the same boundary condition for W_1 as for V_1.
However, the source term is not identical, hence the solution at $(0,0,0)$ for example is distinct from $V_1(0,0,0)$. One just proved:

Lemma 2.2. *If one considers an homothetic transformation of a cell, according to its growth, and if one assumes the number of ions inside the cell does not change, then the potential changes inside the cell.*

2.4. **Change of volume and of number of ions**

A third result in what follows is the influx of ions. Let i_{ep} a unit current of ions through a channel, N_s the density of channels by unit of surface of the cell. We assume that the density of channels by unit of surface does not change during the growth of the cell. The current i_{ep} depends on the potential V and can be expressed, following Hodgkin and Huxley, for the potassium channels $i_{ep}^K(V,t) = \bar{g}_k n^4(V - V_K)$, where n is given by an ODE identical to the ODE that one can find in [4], namely $\partial_t n = -\frac{n-n_\infty(V)}{\tau_K(V)}$. The total pore current is $\sum i_{ep}^S(V,t)N_s^S = i(V,t)$, and the ion flux is thus

$$I(t) = i(V,t)\text{mes}(\partial\Omega(t)).$$

The variation of the number of ions during a time Δt is thus, for a cell considered as a sphere

$$N(t) + 4\pi(R(t))^2 i(V,t)\Delta t.$$

This implies that the density of ions inside the cell after Δt is

$$\frac{N(t) + 4\pi(R(t))^2 i(V,t)\Delta t}{\frac{4}{3}\pi(R(t)+\Delta R)^3}.$$

We have then

$$\rho(t+\Delta t) - \rho(t) = \frac{N(t) + 4\pi(R(t))^2 i(V,t)\Delta t}{\frac{4}{3}\pi(R(t)+\Delta R)^3} - \frac{N(t)}{\frac{4}{3}\pi(R(t))^3} = \frac{3\Delta t}{R(t)}[i(V,t) - \rho(t)\frac{\Delta R}{\Delta t}] + O((\Delta t)^2).$$

As a consequence, the influence of the ion channels and the simultaneous growth of the cell give rise to a change in the density of ions inside the cell.
All these remarks led us to propose an somewhat refined model for the analysis of the electrostatic potential inside the cell, coupling the electrodynamic equations of the cell with its mechanical behavior, including for example the characteristic dimensions of the cell (namely volume and surface).

3. **A new model of the cell**

This model of the cell can explain the change in potentials uniquely linked with the growth of the cell. The equations that we propose could be:

(1) Equation for the potential inside the cell: $-\Delta V = \frac{\rho(t)}{\epsilon_0}$, on $\Omega(t)$. Boundary condition $V(t,x) = \mathcal{V}(t,x), x \in \partial\Omega(t)$

(2) Equation for the electroporation, or transfert of ions inside the cell

$$C_m\partial_t[\mathcal{V}] + S_m([\mathcal{V}])[\mathcal{V}] = \sigma_c\partial_n V_{\partial\Omega-} + I_{ep}$$

(3) Equation for the density of ions inside the cell (spherical cell in this equation)

$$\rho'(t) = \frac{3}{R(t)}[i(t,V) - \rho(t)\frac{\Delta R}{R(t)}]$$

(4) Guess for the general equation of density of ions inside the cell

$$\rho'(t) = -\rho(t)\frac{d}{dt}\ln(Vol(\Omega(t))) + \frac{Vol(\Omega(t))}{Area(\Omega(t))}i(t,V)$$

(5) Expression of the electroporation current I_{ep}:

$$I_{ep} = i(V,t)Area(\Omega(t))$$

with $\sum i_{ep}^S(V,t)N_s^S = i(V,t)$, $i_{ep}^S = \bar{g}_S(V - V_S)P^S(t,V)$, where $\bar{g}_S$ is the conductivity of the species of ions S, V_S is the threshold current, P^S is the probability of opening of channels. In the seminal paper of Hodgkin and Huxley, it is n^4 for the potassium ions, m^2h for the sodium ions.

(6) Equation for the growth of the cell

$$\nabla.\vec{\phi}(x,t) = 1, x \in \Omega(t), \vec{\phi}(x,t).\vec{n}(x,t)|_{\partial\Omega(t)} = i(x,t)|_{\partial\Omega(t)}, \vec{\phi}(x,t) = 0, x \notin \Omega(t).$$

The last equation is equivalent to the following equation in the distribution sense

$$\nabla.\vec{\phi}(x,t) - i(x,t)\delta_{\Sigma(t)} = 0 \tag{3.1}$$

In particular, this equation implies

$$\mathcal{V}(\Omega(t)) = \int_{\Omega(t)} dx = \int_{\Sigma(t)} i(x,t)d\sigma(x,t) = I(t). \tag{3.2}$$

In the case of this model, one has

Lemma 3.1. *The potential V inside the cell is coupled with the volume of the cell and namely with the variation of the ratio 'surface over volume'.*

Further investigations are needed to see it there is a threshold for a certain augmentation of the volume of the cell.
Observations by Boonstra et al [2] confirm the electrical behavior as well as the decrease of the density of charges when the number of ions is constant while the volume of the cell grows (dilution of the ions).

4. Growth of the cell and its division

The last set of equations is about free boundaries and free surfaces. Minimization principles show that, if the boundary of the cell is considered to be an equilibrium under the pressure forces (the classical equilibrium equation for the mechanical behavior of the boundary is the equality of pressures on both sides of $\Omega(t)$, and it MUST not be considered as equivalent to the osmotic pressure, which is linked with chemical reactions of molecules), then a boundary which receives only pressure forces from the substract moves more freely than a boundary which has a contact with another cell, which exerts a reaction force through the constraints tensor.
In order to have a better understanding of the complete cycle, one needs to know how the DNA replicates and divides This is the aim of the last paragraph, where one stresses the importance of the electrical behavior of the membrane of the cell.

4.1. Growth of the cell as a mechanical equilibrium

For the first point (free surface), the proposed set of equations follows:
Namely, the equilibrium equation is

$$p_1 + \sum_i \sigma_{ij}^1 n_i n_j = p_2 + \sum_i \sigma_{ij}^2 (-n_i)(-n_j),$$

where σ^p is the constraints tensor of the object p (this tensor being nonzero if and only if it is another cell).
This equation proves that the free boundary of the growing surface moves in a direction where there is no cell; either in the boundary of the bunch of cells or in place of a dead cell.

4.2. **Understanding the DNA expansion and duplication**

We already studied the influence of the dilution (initial growth of a cell) on the electrostatic potential inside the cell, which induces (thanks to the increase of the value of the potential) the opening of ionic channels. The number of positive ions grows, hence the electrostatic potential inside the cell decreases.
As a result, the jump of the electrostatic potential between the inside and the outside of the nucleus of the cell increases (see [3]). As the ions Ca^{2+} are located between two membranes of the nucleus of the cell, the two membranes disappear simultaneously, freeing the chromosomes from the nucleus (uncondensing them). The chromosomes then follows the well known movement towards the spindle poles, following a dipole field generated by all the ions in the cell, which accumulate near the membrane inside the cytoplasm. As seen in [3], the calcium-signaling system (transient increase in intracellular calcium concentration) is observed. It is coherent with the disparition of the membrane of the kernel (which contains these ions Ca^{2+}). As the ion channels are still open, ions continue to flow in the cell, and this increases again the jump of potential through the membrane of the cell in the phase before mitosis. The duplication of DNA is then a mechanical effect (not electrical).

4.3. **Summary of the equations**

Let $\Omega(t)$ be the cell, $\omega(t)$ being its nucleus (when it exists). The potential in the cell satisfies the equation

$$-\Delta V = \frac{\rho(x,t)}{\epsilon_0}, x \in \Omega(t) - \omega(t), t < T_{ANA}$$

$$-\Delta V = \frac{\rho^*(x,t)}{\epsilon_0}, x \in \Omega(t), t > T_{ANA}$$

where $\int_{\Omega(T_{ANA})}(\rho^*(T_{ANA}) - \rho(T_{ANA}))dx = N_{Ca^{2+}}$,
supplemented by the boundary conditions

$$V|_{\partial\omega(t)} = V_{int}, C_m\partial_t V(t) = \sigma_c\partial_n V|_{\partial\Omega_-} + I_{ep} + g(t, V|_{\partial\Omega})V|_{\partial\Omega(t)} - S(t, V|_{\partial\Omega}),$$

by an equation for the growth of the cell (ρ_m is the density of mass inside the cell, we express that the variation of the density of mass is negligible, hence the volume of the cell is proportional to the mass of the cell, the mass of the cell increases by the entrance of water and nutriments quantized by $N(t)$. As the density of the cell is constant, the pressure can be deduced from this constraint (and this pressure is the osmotic pressure),

$$\partial_t\rho_m(t,x) + \mathrm{div}(\rho_m(t)\vec{u}(t)) = N(t), \int_{\Omega(t)}\rho_m(t,x)dx = \rho_m\int_{\Omega(t)}dx$$

the shape of the cell being studied through the function $\vec{\phi}(x,t)$ solution of

$$\nabla.\vec{\phi}(x,t) = i(x,t)\delta_{\Sigma(x,t)}, \vec{\phi}(x,t)1_{\Omega(t)^c} = 0,$$

and finally by the equations for $g(t, V|_{\partial\Omega}), S(t, V|_{\partial\Omega})$:

$$g(t,V) = \bar{g}_K(n_\infty(V))^4 + \bar{g}_{Na}(m_\infty(V))^3h_\infty(V) + \bar{g}_l,$$
$$S(t,V) = \bar{g}_K(n_\infty(V))^4V_K + \bar{g}_{Na}(m_\infty(V))^3h_\infty(V)V_{Na} + \bar{g}_lV_l.$$

5. **Conclusion**

We proposed in this paper a theoretical model for the growth of cells, deduced from the electrical properties of the membrane of the cell as well as the electrical properties of the membrane of the nucleus, as well as mechanical equilibrium relations. We use well known facts of biology to propose this new set of equations. It is still to be tested on models, and understood numerically.

It is a prospective analysis which can help to promote interdisciplinary science with the aim of having a simplified model. Namely, one relies on the flux of ions in and out a cell (using for a general cell the model developed for an axon), the flux of water in and out a cell (for studying the shape of the cell, which induces changes in volume and in surface, and thus driving modifications of the potential), the mechanical behavior of the cell (pressure laws for instance), thresholds in the electric potential in the cell (which play the same role as switches in everyday electricity at the microbiology level). As many phenomena are coupled, we advocate to study at first this simple model to draw general conclusions on its validity.

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Bibliography

[1] J. Boonstra et al. Cation transport and growth in neuroblastoma cells, modulation of k^+ transport and electrical membrane properties during the cell cycle. *Journal of cellular physiology*, 1981.

[2] L. Groigno and M. Whitaker. An anaphase calcium signal controls chromosome disjunction in early sea urchin embryos. *Cell*, 92:193–204, 1998.

[3] A.L. Hodgkin and A.F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerves. *Journal of Physiology*, 117:500–544, 1952.

[4] Cronin J. *Mathematical aspects of Hodgkin-Huxley neural theory*. Cambridge University Press, 1987.

[5] Rafelski S.M. Jayashankar V., Mueller I.A. Shaping the multiscale architecture of mitochondria. *Current opinion in cell biology*, 38:45–51, 2016.

[6] Levy Noriega M. Lafitte O. Steyaerts J.M. Bakardjan H. Dubois B. Hampel H. Schwartz L. Mechanical stress related to brain atrophy in alzheimer's disease. *Alzheimer's and Demential*, 12(1):11–20, January 2016.

[7] C. Poignard et al O. Kavian. Classical electropermeabilization modelling at the cell scale. *Journal of theoretical biology*, 68(1-2)(1-2):235–265, 2014.

[8] L. Schwartz. *Cancer, un traitement simple et non toxique*. Thierry Souccar Collection 'Medecine', 2016.

[9] Fleury V. Schwartz L. Diffusion limited aggregation from shear stress as a simple model of vasculogenesis 1999. *Fractals*, 7(1):33–39, 1999.

[10] E. Desmond-Le Quéméner T. Bouchez. A thermodynamic theoriy of microbial growth. *The ISME Journal*, 8:1747–1751, 2014.

[11] Mummery C. Van Zoelen E. Membrane regulation of the na^+, k^+-atpase during the neuroblastoma cell cycle: correlation with protein mobility. *J. Cellular Biochemistry*, 21:77–91, 1983.