Dear Paul,

We have now answered the new criticism of reviewer III below. We hope that in the present form, our manuscript is now suitable for publication in the J. of Nonlinear Science.

With Best Regards,

Jerome Cartailler, Zeev Schuss and David Holcman

**Reviewer #3:** I am very very sorry to have to change my recommendation about this paper. There are real strengths here and the paper addresses an important issue. But the authors state clearly (cut and paste)

"Indeed, we constructed the present model as an extreme case dominated by positive charges only. In reality, the chloride ions should be used and they diminish the excess of positive charges."

> **ANSWER:** We have written this sentence in response to reviewer 3, but not in the manuscript. Our goal was to explain that it is hard at this stage to relate the parameter lambda to the positive or negative charge. This sentence was here misinterpreted: our aim is not to justify that we have not modelled negative charges. We recall that we already mentioned in the discussion that we have made the assumption about modeling positive charge only, due to net clear unbalance toward positive charges:

“Cytoplasmic ions are characterized by the following concentrations Na$^+$ = 148ml, K$^+$ = 10ml and Cl$^-$ = 4ml. There is a clear unbalance toward positive charges, however there are probably molecules of various sizes with negative charges to re-balance the charges.”
We have also added that “There is a clear unbalance toward positive charges, however there are probably molecules of various sizes with negative charges to re-balance the charges. However, the motility of these proteins should be driven by a diffusion coefficient smaller than the one of the ions.”

The fact is that one must not assume that an extreme case dominated by mobile positive charges only ever exists in an environment like that inside a cell.

>ANSWER: Our assumption of neglecting negative charge is legitimated by the concentration (positive) $158\text{ml} > > 4\text{ml}$ (negative).

It is not safe to make that assumption even inside a single 1 nm diameter channel (the coions still often have significant effects) or in heavily doped semiconductors (where minority carriers often have crucial effects despite being very very much in the minority.

>ANSWER: We do not deal here with nm diameter channel, where indeed negative charges can play a critical role. Here we deal with hundreds of nm, which is very different from the nano-meter channel.

I encourage the authors to revise their work to deal with a reasonable concentration of coions (anions in their case). But NOT an identically zero concentration of mobile anions.

>ANSWER: To validate our assumption, we can use a regulation expansion of the solution with two species with total charge positive $Q_+$ and negative $Q_-$ and

$$\text{eps} = Q_-/Q_+ << 1.$$

The steady state PNP is

$$-\Delta u = (Q_+) e^{-u} \int e^{-u} - (Q_-) e^u \int e^u$$

we obtain PNP with two charges, when there is enough mixing (not in ionic channel).

Clearly, the solution can be expanded using a regular expansion:

$$u = u_0 + \text{eps} u_1 + ..,$$

where $u_0$ is solution of the PNP with a single positive charge and $u_1$ is solution of a linear equation that depends nonlinearly on $u_0$. 
This expansion shows that the limit when the total negative $Q_-$-charges (or $\varepsilon$) goes to zero, converges to the solution when $Q_- = 0$ (with no negative charge). We have now added this regular expansion in the appendix.

This regular expansion shows that although we may miss some effects, as mentioned in our discussion, what we get does not seem to contradict physiological laws at the cellular level. There is precious little theory around that does not miss some phenomenology, e.g. classical Hodgkin-Huxley, etc... Also Newton's mechanics misses many effects, such as, for example, all stat. phys.

We have made here a simplifying assumption that can over-simplify the model. The need for the simplifying assumption is to gain some insight into the model, as we actually do. Finally, we have now added the following sentence to explain that adding negative charge would be relevant for ionic channels:

“Finally, we note that we did not consider here nanometer structures, such as ionic channels, where a negative ionic charge can affect the motion of the other ions in the channel pore.”

We thank the reviewer for raising the question.