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History of Physical Models of Ions in Channels centered at Rush

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Dear Claudio

The history is of course not known to you until it is known.
And history is a random walk, so it has lots of twists and turns
that are hard to see from afar.

But once you know the history, it is your responsibility to get it right.
Documentation can easily be found for most of this by
searching my CV (attached) for the relevant names.
The papers and relevant abstracts should be easy
to download.

Briefly

1) the need for dealing with Brownian motion of ions in
channels was realized first (as far as I know) by Kim
Cooper a graduate student of Eric Jakobsson, who
got the idea from a course with Peter Wolynes (all
at the Univ of Illinois Urbana Champaign). Peter was
a leader in the field of the Kramers problem, which
occupied a good fraction of physical chemists in
the 1980's (see famous review by Hanggi)

2) Kim came to work with me because Eric was
disinterested and running for the United States
Congress.

3) I realized Brownian motion needed to be dealt
with by mathematics not just simulation. We did
a range of simulations in the Barcilon, Chen,
Eisenberg, Ratner paper and then moved to
analysis with a world leader in stochastic differential
equations Zeev Schuss. We DERIVED the displaced
Maxwellian for the first time in the study of flux
over barriers (a HUGE field in chemical physics
a generalization of the Kramers problem)

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and understood its implications. We derived
ANALYTICAl EXPRESSIONS for rate constants
etc..

4) I realized that the electric field had to be dealt with consistently, ie. by computing it from the charges not by assuming it. This could not (and still cannot) be done analytically with stochastic differential equations so I moved to PNP

5) Chen and I created PNP of channels (previous work had ignored the crucial role of permanent charge, had not used the Gummel iteration or equivalent and so basically had not solved the equations, and **had ignored the crucial device orientation that arose from the analogy with transistors**. thus the name PNP. This is all documented in the early abstracts I sent you 1992-3 in Biophysical Journal and even before that in the Journal of General Physiology.

Chen Jerome and I extended PNP to include a consistent treatment of heat flow and other effects in the hydrodynamic model.

6) Eventually Wolfang Nonner and I realized that finite diameter had to be involved and so we created what I am now calling the all spheres model.

7) I presented a bit of this at Brigham Young where (at the same time) I met Doug Henderson. (David Busath had invited me to give the talk). Doug strongly objected to the use of MSA by Wolfgang and me (he was surely right) and was very skeptical of our approach. He preferred (he may have been right!!!) what he and Paul Crozier had done.

BUT Doug had the absolute integrity to check our ideas with simulations of toy models with Dezso.

The simulations showed the basic idea of crowded charge was right and he and Dezso then addressed the original all sphere model with their powerful MC methods.

You probably have a decent idea of the subsequent history: I introduced Dirk and Wolfgang to DFT and Rosenfeld, Dirk carried on from there. Dezso has led an enormous expansion of knowledge using MC and now extending MC to deal with flow.

I brought back the kernel of the ICC idea from Cambridge UK (JP Hansen and his student Allen) and Dirk greatly improved it and used it very very well.

8) Fully consistent calculations are now possible (for the FIRST time) because variational methods can be used to derive consistent Euler Lagrange equations that can be solved or simulated. This work started with Chun Liu (who created the variational methods) and YunKyong Hyon (also Yoichiro Mori) and now involves Tia Chia Lin, Allen Horng, and Jinn Liang Liu. Jinn Liu has introduced the Poisson Fermi equation as a way of dealing with crowded charge in channels using the all sphere model.

Dezso and Dirk are extending the all spheres model using different approaches to nonequilibrium, starting from the chemical tradition of simulation reaching towards electrostatics. That approach heads down "the street" from one end. The EnVarA approach starts down the start from the other end.

9) In a parallel path, arising from stochastic work, I interested Peter McClintock's group (Lancaster: Kaufmann, Tindjong, Luchinsky) in channels.

This has now produced simulations showing "quantized" conduction (as a function of the density of permanent charge) for calcium channels

10) In another parallel path, enzymes were shown to have as high a density of permanent charge in their active sites as channels (work with David Jimenez-Morales and Jie Liang) suggesting that the electic field created by these charges has a dominant role in catalysis.

11) Fred Cohen and Rolf Ryham are using the variational approach to (in my opinion) revolutionize the computation of membranes and structural changes involving membranes. They can calculate the shapes membranes assume (WITHOUT assuming them) and how they evolve during biological processes of immense importance

I hope this is helpful and I have not left out too much nor distorted things too badly. Corrections are of course solicited and will be made!!!!

As ever
Bob

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> Dear Bob
>
> ..... I just wanted to reference some work in which mobile charges were used.
> But I didn't know all the story and where this model come from.
>
> My knowledge of the bibliography is (of course) much smaller than yours and I am comforted that you review our work paying so much attention on the references. It helps enormously to make the paper much more solid.
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> Claudio
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> _____
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