Averaging in Biological Systems Letter to Tony Watts, February 11, 2012

Dear Tony

You should not apologize for asking profound questions.

We have worried about the averaging in ion channels (and proteins etc) for many years (We = me + a series of superb collaborators, e.g., Wolfgang Nonner, Doug Henderson, Chun Liu, Allen Horng, and some I have no doubt forgotten to mention) and only recently think we understand what is going on, in the case of ion channels, and proteins with a well defined function.

I will try to be careful to separate what we know, and what we suppose, in what I write below.

First, let's deal with the biological problem, which by the way is identical to an engineering problem. Let's start with a system where we know there is a well-defined, reasonably robust reduced description essential for the survival of the species, to use some ancient but appropriate language. Something like a sodium channel where we know the molecular even atomic details of function directly determine conduction velocity and thus the ability of the species to survive among the fittest.

The issue is the same for engineering devices like an amplifier (or even as simple as a diode or as complex as shift register or other digital circuit) where a reduced description like a gain function captures all that is needed to interconnect the device with others and make a machine.

In these cases, the issue is not whether an averaged description is possible. The issue is how to derive that averaged description. ***We know ahead of time that an averaged description is possible.***

In the case, of proteins we know that the averaged description allows small groups of atoms, sometimes one atom can change function dramatically. In some systems the smallest atom, a "proton" has a profound effect as it separates and makes a neutral carboxyl group into a negatively charged carboxylate anion.

So atomic scale distances change macroscopic function. **Obviously, we cannot average (in space) over such structures and preserve their functional role in the resulting space averaged description.**

So the averaging we need to understand biological systems is not over space.

Our (pre-existing) reduced models arise from averaging in time not space.

How this averaging occurs is beyond my understanding. Indeed, I do not know anyone who understands how atomic scale phenomena can average in time over time scales of 10^{17} or more to make EXACT macrocscopic laws.

Let us not forget that some conservation laws (e.g., particle number) are exact mathematics (not science). Other conservation laws are exact science as close as we can tell (mass, energy, and charge are the ones I know about). And Maxwell's equations and Schroedinger's equations (I like to think of Schroedinger as a coupled Poisson and wave equation) are essentially exact, as I am told, are special relativity and some flavor of general relativity.

The essential issue here is how do atomic motions on a 10^{-16} time scale manage to produce an exact result (to one part in 10^{-20}) law like Kirchoff's current law in the Maxwell equations?

The physical image here is breathtaking. Imagine a metal wire starting in New York, connected to a vacuum capacitor in Philadelphia, then to polyethylene tube filled with 1 M NaCl extending to Pittsburgh, and to a semiconductor diode and then a carbon resistor and whatever kind of wire you wish to Chicago.

In each of those very different physical devices very different atomic motions occur. Yet current flow (suitably defined as in the Maxwell equations, not as in elementary circuit theory) is exactly equal everywhere to fantastic precision.

No human being I know can imagine how that happens.

But it happens.

This kind of situation is of course familiar to one class of scientists and mathematicians (at least), namely those who create or use (computational) fluid mechanics. Here it has long been obvious that no person can begin to feel comfortable with (i.e., 'explain') the complexities of air flow over a wing, or how that will change when even small changes are made to the wing (think of the flaps at the ends of modern airplane wings, or the little rectangles of metal on the top of the airfoils). The equations compute the results with essentially perfect accuracy, but the solutions of the equations are beyond our understanding.

So that I think is the answer to your question. **The averaging in the biological systems we consider (where we know ahead of time that there is a well determined reasonably stable and robust reduced equation) is in time**.

Now, this side steps the issue you were really thinking of, which is the general physical problem of averaging in any system.

Here the answer should be sought by a classical technique of mathematics. Mathematicians use counter examples to cast a searing searchlight into our ignorance.

As soon as you try to create counter examples, it is obvious that one can create systems in which averaging in time will lead to incorrect and bizarre results. (Just imagine a system with an old fashioned resonance of the type we were all taught in

elementary physics, mass, dashpot, and spring, or RLC circuit, or the optical equivalent). Even this simple linear resonance can dominate the behavior of a system. If there is threshold detector, the resonance can do anything when it passes the threshold. So time averaging must respect the resonance and get its details right. If we do not know the resonance exists, or 'where' it is located (in phase space), we cannot possibly average it in a way that preserves its essential behavior.

So the answer to your question is that in some systems you can average in time, and in others you cannot.

How can we tell which type of system we are dealing with?

We guess and check (the essence of science).

We 'guess' (in as informed a way as possible) a mechanism, we compute its consequences, and we compare with the real system OVER AS WIDE A RANGE OF CONDITIONS AS POSSIBLE.

If the guess works, it is good enough for engineering and biological purposes (usually to allow a reduced model that can be a component in a larger machine).

Note the enormous importance of doing the computation correctly. If the computation itself introduces uncertainty, we cannot tell if our guess is any good, and the social process of science that I just described does not converge to a useful result.

In my view, variational methods of the type introduced by Chun Liu, more than anyone else, that use both energy functionals (Hamiltonian) and dissipation functionals (Rayleigh Onsager) are the only methods that are guaranteed to handle forces and boundary conditions selfconsistently with minimal free parameters. This is because they DERIVE (by algebra alone, with no further assumptions beyond those in the model) the partial differential equations that describe the motions of the system rather than assume them.