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Comment on the Comment by Dr. Marino and Dr. Frilot on "Proposed Test for Detection of Nonlinear Response in Biological Preparations Exposed to RF Energy"

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In their *Comment* on the paper of Balzano [2002] on the detection of nonlinear responses, Marino and Frilot [2003] state that certain possible biological systems with a response described by "non linear differential equations" can respond (chaotically) to an interaction that is "arbitrarily small, say $kT/10^6$." This is correct but does not lead to the conclusion that significant biological effects can be generated by signals that are much smaller than kT. Indeed voltage gated ion channels, the best understood nonlinear biological system, have long been known to respond to such infinitessimal signals [Koch, 1999], but the biological effects of such channels are still severely limited by thermal noise. Though a very small signal impulse can generate a response, overwhelmingly, those responses will also be generated by noise impulses swamping the responses from the directed signal.

I present a specific example: from numerical simulations using the Hodgkins and Huxley [1952] equations to describe ion channel dynamics, I find that a transmembrane pulse of +6.905 mV applied to an area of a squid giant axon populated by ion channels *never generates* action pulses while a pulse of +6.906 mV *always* does. This change of 0.001 mV represents an energy transfer of about $2.4 \cdot 10^{-4}$ kT in each sodium channel and a little less in the potassium channels. However, the generation of an action pulse follows with equal efficiency from noise impulses and exogenous signals and neither voltage gated channel systems nor the hypothetical systems suggested by Marino and Frilot can discriminate between signal and noise impulses.

Hence, when I include the thermally dependent noise chatter of channel openings and closings from $M_{N\alpha} \approx 300\,000$ $N\alpha$ channels and $M_K \approx 36\,000$ K channels that occupy an axon area of $1000\ \mu^2$, the probability of a channel opening from a signal impulse of ≈ 6.9 mV is approximately one-half and the opening probability changes gradually from near zero to near one over a signal impulse range of about 1 mV, or about ± 0.25 kT per channel. Hence, with thermal noise considered, effects of a signal $S \ll kT/(\sqrt{M_{N\alpha}+M_K}\,) \approx 0.05$ mV (a conservative estimate of the noise for signals coherent over M elements) added to an appropriate bias voltage, will not be distinguishable from noise effects.

In Balzano's reply [Balzano, 2003], he says that the nonlinear effects he would investigate can cause "biological responses that are not limited by the thermal noise level, kT." That statement can be misread to imply that nonlinear systems in general are especially immune to kT noise limitations and that Balzano's ingenious experiment will be sensitive to all such systems. This is not the case.

When voltage gated ion channels are exposed to 900 MHz radiation, those systems will not reradiate 1800 MHz photons at a level detectable by the procedure outlined by Balzano. The voltage sensitive elements of the systems (probably an alpha helix element in the S4 sectors of each of the four domains that largely make up the channel protein), which are accelerated by the 900 MHz incident fields, have masses in excess of 1000 Da. Thus the accelerations of the charged elements are small, they radiate very little, and Balzano's proposed experiment would not detect that nonlinearity.

However, any nonlinearity that led to the reports of rectification of RF radiation that Balzano cited would presumably involve electron currents involving very

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large numbers, N, of electrons acted upon coherently. Such electrons would radiate copiously and the purely thermal effects, of the order of $kT/N^{1/2}$ per electron, could be small.

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