Comments and opinions on editorials, articles, and research in Bio/Technology *are welcome. Letters to the Editor may be addressed to: 65 Bleecker Street, New York, NY 10012, fax: 212 254 9493, (e-mail: gins@pipeline.com).*

Is virtual spectroscopy real?

To the editor:

It is hard to see how the physicochemical approach of Irena Cosic could work, at least on the basis of the information as presented in the article "Virtual Spectroscopy for Fun and Profit" (*Bio/Technology* **13**:236-238, February). The method plots protein sequence profiles in a manner typical of hydrophobicity plots but based on the electron ion interaction potential describing the average energy states of electrons in each amino acid. This sequence profile is then processed by a fast Fourier transform into a frequency spectrum (which effectively highlights the inherent periodicities in the sequence profile). Similar spectra between ligand and receptor and even protein product and its gene are taken as indicative of "a kind of resonance between interacting molecules that might form the basis of mutual recognition." Not least, it proposes a physical basis in that "charge moving through the backbone and passing through different energy stages caused by different amino acid side groups can produce sufficient conditions for the specific electromagnetic radiation of absorption. It is the frequency of this electromagnetic irradiation or absorption that emerges in the RRM spectra."

There is room for useful coincidence. It is possible that some kind of relevant information is actually implied by this process, say another less heretical protein sequence property like hydrophobicity which relates to polarity and chemical polarizability. I suspect that if there is anything in this at all, it is because the numbers do relate in some way to sidechain polarity, and this could explain the "resonance" since hydrophobic patches of helix and sheet do dock together between ligand and receptor, and since DNA bases do have physical properties which have some correlation with the polarity of residues for which they code. Possibly, it might represent a degree of fortuitous agreement with some single set of numbers which might be obtained by principle coordinate analysis or multidimensional scaling of a whole set of physical descriptors. Again possibly, the method might simply "label" amino acid residues in a rather arbitrary quantitative way which can be used to reflect certain periodic features of sequence. Who knows, a useful set of numbers might indeed have been discovered by this physically tortuous route!

The physical *explanations* given, however, do not correspond to any known phenomenon for protein systems that I am aware of, and seem not to inhabit the right energy and frequency domains for the processes we currently understand. If true, these explanations would not only be featured on the front page of *Nature*, but would revolutionize most of biology and chemistry and quite a bit of physics. To be fair, some of the resonance idea seems to smack of something that the brilliant physicist Penrose might have come up with in "The Emperor's New Mind," but then he is entitled to get away with it. As the method and its rationale stands at present in the eyes of we poor timorous earthbound mortals, it just seems unearthly. As Scottie says as the *Enterprise* is strained into some intolerable domain of hyperspace, "Ye canna break the laws of physics!" It's worse than that, it's dead, Jim.

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Irena Cosic replies:

Regarding the comments of Barry Robson on my paper, I would like to point out that I understand the difficulties one can have in accepting, immediately, a completely new concept in any science. However, it is well known that protein structure-function models that have already been accepted are not powerful enough to explain how a protein biological function is written in the amino acid sequence. Thus alternative approaches, that might be revolutionary, should be considered.

Regarding the RRM, there is not much room for "useful coincidence," as Dr. Robson suggested because model was tested on thousands of proteins showing that each functional group of proteins is characterized by a unique frequency component. Additional tests have shown that amino acids that contribute mostly to the characteristic frequency are also related to the active sites of protein. Finally, peptides designed only from the characteristic frequency and without any homologies with the native proteins have biological function related to that frequency.

The electron-ion interaction potential is related to the side-chain polarizability. However, when polarizability is used within the RRM, the characteristic frequencies are not so well defined. The other amino acid indices (270 tested so far) do not show consistent results in terms of a unique characteristic for each biological function. Multidimensional analysis of a whole set of physical parameters is in progress and will be published soon.

I do not know which part of the physical explanation was difficult for Dr. Robson to accept. Charge and energy transfer along proteins is a process that is already accepted. The fact that laser irradiation of selective frequencies can influence particular biological processes and protein activities naturally leads to the proposition that these processes act at the same energy levels. The concept of resonant recognition between interacting macromolecules is not unusual, keeping in mind that these interactions are very selective and that selective processes are generally resonant in nature.

The articlepresents results of exact mathematical and physical computations performed on a significant number of examples. Conclusions are obvious from the results obtained. This model does not break any physical law. For more details readers can consult other publications on the RRM.