

An Ultra Simple Model of Protoplasm to Test the Theory of Its Long-range Coherence and Control So Far Tested (and Affirmed) Mostly on Intact Cell(s)

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Abstract: According to the association-induction hypothesis, the core of living phenomena lies in the long-range, one-on-many connectedness among all three major components of living protoplasm: protein, water and K^+ (and the controlling agents, called the cardinal adsorbents.) This article describes simple experimental models that could cogently test the theory of this connectedness and its control by drugs and other cardinal adsorbents.

IN VOLUME, the largest component of all living cells is water; the next is proteins. In number, the largest component is again water; but the next largest is K^+ . From these, one concludes that the living cell is largely an assembly of water, proteins and K^+ .

As part of what became known later as Ling's fixed charge hypothesis (LFCH) (Ling 1962, p. 218), I first suggested in 1952 that on *statistical mechanical* and *energy* grounds, K^+ in living cells is not free as widely taught (Ling 1952.) Rather, all or virtually all K^+ in living cells are in close-contact, one-on-one adsorption on the β -, and γ -carboxyl groups carried respectively on aspartic and glutamic residues of intracellular proteins. In a recent review (Ling 2005), I have shown that by the year 2005, this suggestion has been

Abbreviations: AI Hypothesis (association-induction hypothesis); EDC (electron-donating cardinal adsorbent); EWC (electron-withdrawing cardinal adsorbent); LFCH (Ling's Fixed Charge Hypothesis); PCS (pseudo-cardinal site); PM theory (polarized-oriented multilayer theory of cell water); POM theory (polarized-oriented multilayer theory of cell water).

fully verified by theoretical and experimental advances made in my own laboratory and by others including the earlier work of Kern (1948) and later definitive work of Edelman (1977, 1980, 1983, 1998.)

In 1965 I introduced another theory, called the polarized multilayer theory — later modified to polarized-oriented multilayer theory (POM or PM) theory of cell water (Ling 1965.) In this theory, all or virtually all water molecules in most living cells are adsorbed as polarized-oriented multilayers on the exposed NHCO groups on arrays of fully-extended cell proteins. In two recent reviews, I have shown that here too progress in both theory and experimental studies made in the preceding 39 years have fully verified the validity of the POM theory (Ling 2004, 2006.)

Considering at once these two conclusions, one reaches a third conclusion. That is, the three major components of the living cell — water, proteins and K^+ — are in direct or indirect contact with one another.

This is a landmark perception in the study of living phenomenon on its own merit. More important, this conclusion affirms the association arm of the much broader unifying theory of the living cell called the *association-induction (AI) hypothesis*, which I introduced in 1962. And, it is the one and only (surviving) unifying theory of cell physiology known then or now. The near-completion of the association aspect of the AI Hypothesis already achieved shifts attention to the less extensively studied induction-arm of the AI hypothesis, which actually also began in 1952 as part of the LFCH, when it addressed the question, why is the K^+ accumulated in living cells lost on cell death? What follows was the answer offered.

As an expression of an equilibrium phenomenon, this postulated (selective adsorption and hence) accumulation of one ion (K^+) over another (e.g., Na^+) does not demand a continual energy expenditure as in the now completely disproved membrane-pump hypothesis (Ling 1997.) Nonetheless, over the long run and in particular after work-performance, metabolic energy is required to recharge the system back to its high (negative) energy-low entropy *resting living state* (Ling 1962, p. xxii, 1992, p. 32, 2001, p. 154.) That energy is provided by the adsorption of the ultimate end-product of aerobic and anaerobic metabolism, ATP.

Figure 1, reproduced from my paper of 1952, shows diagrammatically how ATP adsorption on controlling sites — later named “cardinal sites” (Ling 1962 p. 118, p. 420) — *electronically* regulates and maintains the selective adsorption on β^- , and γ -carboxyl groups near and far — as part of the maintained resting living state.

The electronic mechanism suggested in that 1952 paper can be called the direct electrostatic effect or D-effect. In years following, this was modified to what is known as the F-effect, incorporating both the D-effect mediated through space and inductive, or I-effect, mediated through intervening atoms (Ling 1962, pp. 57–58.) As more time went by, however, it became clear that the inductive or I-effect plays the predominant role.

How such a short-range inductive effect could be marshaled and organized to bring about action at a distance and in a one-on-many manner became a central theme of the association-induction hypothesis.

With the introduction of the POM theory of cell water in 1965 (Ling 1965), it was suggested that ATP does not just control and maintain the selective adsorption of (cationic) partners of the β^- , and γ -carboxyl groups like K^+ , ATP adsorption on cardinal site also controls and maintains the polarization and orientation of all the bulk-phase water molecules.

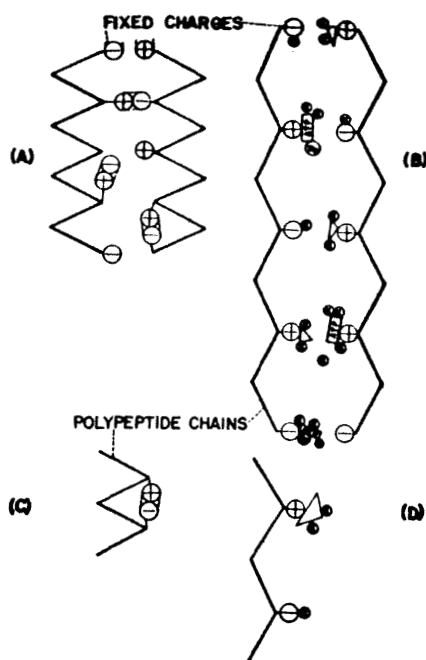


FIGURE 1. Diagrammatic illustration of the hypothetical unfolding of protein chains as a result of the adsorption of ATP. (from Ling 1952, by permission of the Johns Hopkins University Press)

And, it does so, according to the AI Hypothesis, by its action as an *electron-withdrawing cardinal adsorbent* or EWC (for definition, see Ling 1992, pp. 144–145, Ling 2001, pp. 167–168.) A mechanism was introduced and steadily improved to show how such an EWC can produce a uniform, across-the-board electron reduction at a large number of β -, and γ -carboxyl groups, near and far (Ling 2001, pp. 171–175. For earlier versions see Ling 1964 p. 254, Ling 1969, p. 45, Ling 1992 pp. 147–149.) In addition, it can at the same time, produce an electron density reduction of the oxygen atom of a vast number of backbone *carbonyl* groups (CO) of the CONH links near and far. The important consequence of this change will be made clear below.

Somewhere along the way, the need to build a broader quantitative theory became apparent. To that end, I began by introducing a parameter called the *c*-value (Ling 1958, 1961 p. 156, 1962 p. 58.) Measured in Ångstrom units, the *c*-value is roughly speaking a measure of the effective density of electrons of the singly charged oxygen atom of an oxy-acid group such as a β -, or γ -carboxyl group.

(By analogy, a *c'*-value was introduced for the cationic charge of fixed cations including the ϵ -amino groups of lysine residue and guanidyl groups of arginine residues. A further extension was in the introduction of the *c*-value analogue for the oxygen atom of the CONH peptide group and the *c'* value analogue of the positively charge H atom of the CONH peptide link (Ling 1962 p. 60.) Unlike the carboxyl and amino groups, these CO and NH groups do not carry net electric charges and are bipolar. This means that the negative charges of the oxygen atom of CONH groups are due to the lone pairs of electrons and thus seen only at short range. The same holds for the positive charge due to the H atom of the NH component of the NHCO group.)

With the c -value defined, we went on to construct the so-called Linear Model and proceeded from there to compute the adsorption energies of the five alkali-metal ions (Li^+ , Na^+ , K^+ , Rb^+ and Cs^+) in addition to H^+ and NH_4^+ on β -, or γ -carboxyl groups at different c -values. (NH_4^+ is also seen as a prototype of the fixed cationic ϵ -amino groups carried on lysine side chains and guanidyl groups carried on arginine side chains.) The details of this theoretical model was presented in the fourth chapter of my first book, *A Physical Theory of the Living State: the Association-Induction Hypothesis* (Ling 1962.) This book has long since been out of print. Since I own its copyright, I have reproduced this entire chapter as an Appendix (Appendix 1) at the end of this article.

Figure 2 — which is a copy of Figure 4-11 in Appendix 1 — indicates that for any pair of any two monovalent cations, the relative preference indicated by a higher (negative) adsorption (association) energy shown on the ordinate of the figure reverses itself sooner or later as the c -value increases. However, for the simple objectives on hand, all we need to remember here is that at low c -value, K^+ is preferred over Na^+ ; at higher c -value, Na^+ may be preferred over K^+ .

A similar relation exists also between K^+ and a fixed cation (i.e., ϵ -amino group and guanidyl group) but here the fixation of these fixed cations adds a favorable entropy element in the bargain, making a fixed cation more preferred even when their respective $-\Delta E$'s are equal. However, this entropy contribution due to salt-linkage formation between a fixed anion and a fixed cation is constant and does not change with c -value change.

In 1981, another basic concept of the AI Hypothesis was made more quantitative (Ling 1981.) It shows that the electron density of the carbonyl oxygen of the polypeptide chain — characterized by the c -value analogue mentioned above with the c -value — plays a similar role as the c -value (of the β -, and γ -carboxyl groups) in deciding which one of the alternative partners of adsorption is energetically favored.

More specifically, the c -value analogue decides the preference of the backbone peptide linkage for one or the other of the two alternative partners. These partners are respectively, (i) the NHCO groups on the third amino acid residue up or down the same protein chain (thus forming an α -helical fold) or (ii) multiple layers of water molecules. At high c -value analogue the polypeptide chain prefers to form α -helical folds; at low c -value analogue, the polypeptide chain prefers to adsorb multilayers of water molecules.

In consequence of the c -value decrease and c -value analogue decrease brought on by an electron-withdrawing cardinal adsorbent (EWC) like ATP, the β -, and γ -carboxyl groups would enhance its propensity toward adsorbing K^+ (over Na^+ or fixed cation) and the backbone NHCO groups would prefer to stay fully-extended and adsorb multilayers of water molecules. Figure 3 is the latest version of a series of more or less similar illustrations published between 1952 and 2001 (Ling 2001, p. 153.)

Thus far, experimental testing of this model during the past forty years has been performed mostly on intact living cells — where the physiological attribute involved determines what part of the cell and hence what kind of protoplasm is involved. The overall results are highly encouraging and reviewed in a sister article soon to be published. The title of that article is: *Reinstating the (redefined) protoplasm as the physical basis of life* (Ling 2007.)

However, to help gain a more and deeper understanding of the complex phenomenon, it would be ideal if we could deal with a model system that is much simpler than a living

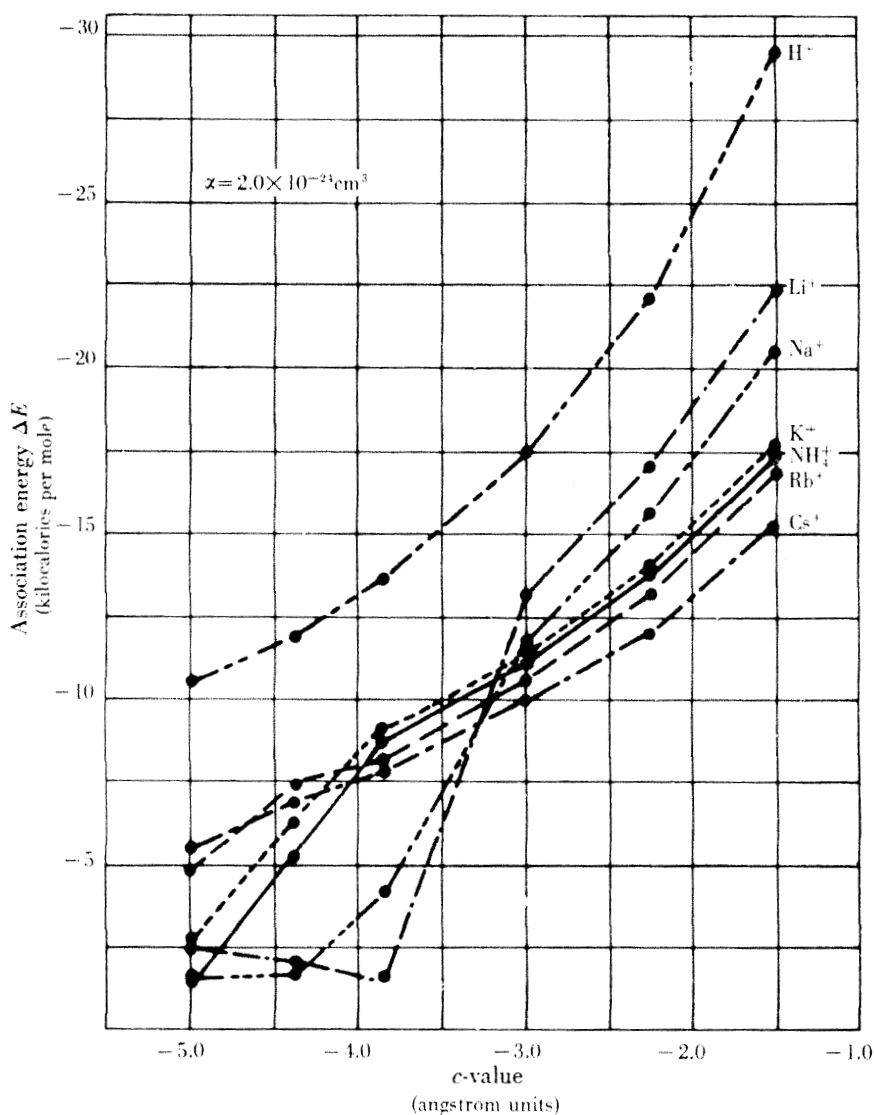


FIGURE 2. The theoretically computed adsorption (association) energies in kilogram calories per mole of H^+ , Li^+ , Na^+ , K^+ , Rb^+ , Cs^+ and NH_4^+ respectively on a singly charged oxyacid group with a polarizability of $2.0 \times 10^{-24} \text{ cm}^3$ and c-value as shown on the abscissa. An ion, say K^+ , which shows a higher negative energy of adsorption of 8.3 kcal/mole on the fixed oxyacid anion at a c-value of -4.0 \AA is preferentially adsorbed over Na^+ , which at the same c-value, shows a lower negative adsorption (association) energy of 3.3 kcal/mole. However, at a higher c-value of -2.5 \AA , the preference is reversed since at this c-value, the negative adsorption energy of Na^+ at 14.3 kcal/mole is higher than that of K^+ at 13 kcal/mole. (from Ling 1962, the relevant chapter 4 is attached to the end of the article as Appendix 1)

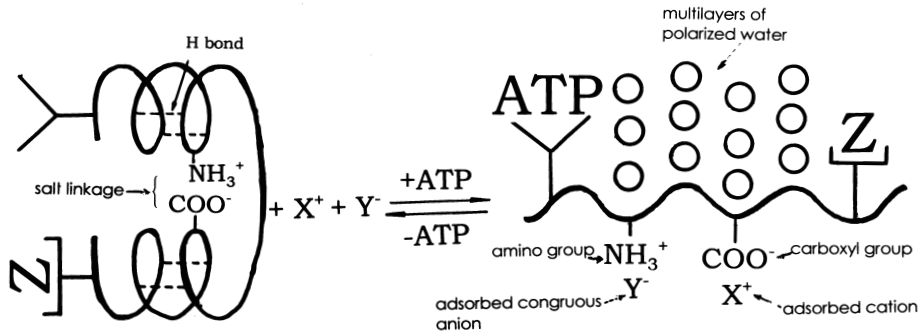


FIGURE 3. Diagrammatic illustration of how adsorption of the cardinal adsorbent ATP on the ATP-binding cardinal site and “helpers” including the *congruous anions* (shown here as “adsorbed congruous anions”) and *Protein-X* (shown here as Z) unravels the introverted (folded) secondary structure shown on the left-hand side of the figure. As a result, selective K^+ adsorption can now take place on the liberated β -, and γ -carboxyl groups (shown on the right hand side figure as “carboxyl groups”) and multilayer water polarization and orientation can now occur on the exposed backbone NHCO groups and the resting living state is thus achieved and maintained. (from Ling 2001)

cell. In theory, the ideal model would contain all the key elements of the protoplasm according to the AI Hypothesis. They include the polypeptide chain and functional groups on short side chains, in particular, the β -, and γ -carboxyl groups, their alternative partners (K^+ , Na^+ , fixed cations) and the alternative partners for the backbone NHCO groups, i.e., other CONH groups, three amino acid residues up or down the chain and bulk-phase water molecules.

It may produce a moment of disbelief to realize that all these requirements are present in an aqueous solution of a protein plus KCl or NaCl. All with the exception of one missing player, the cardinal site. So we will have to invent one. It is our next task to describe how.

1.0 Inventing a cardinal site

Inventing the cardinal site — which includes what are widely known as receptor sites (for drugs and hormones) — begins with a postulation. It says that all real-life cardinal sites are made of the same ingredients that make up proteins. In other words, each cardinal site is a gathering of different or similar amino acid side chains and stretches of the polypeptide chain posed in a geometric configuration.

On the basis of this postulation, we would suggest that many pure proteins may contain within their normal primary structure segments of the protein chain that have the potential of acting fully or in part like real-life cardinal sites of one kind or another seen in living protoplasm. As a result of this fortuitous event and the fundamental attributes and activities of living protoplasm seen in the light of the association-induction hypothesis, reaction of these proteins with real-life cardinal adsorbents might produce long-range, one-on-many impact on distant sites of the protein. For convenience of discussion, I shall call these sites, *pseudo-cardinal sites* (PCS). Having said that, I must add that only future study can determine if a pseudo-cardinal site demonstrated is truly pseudo.

With the only missing component of the *ad minimum* protoplasm model made up in theory by the invented *pseudo-cardinal sites*, our next task is to lay out outlines of how

to test the theory of protoplasmic coherence and connectedness and all its basic postulations in experiments simple enough to be done by the real vanguard of future cell physiologists worldwide rich or poor as they may be.

2.0 Testing for the existence of “pseudo-cardinal sites” (PCS) and (if they do) how they can interact with one or more specific real-life cardinal adsorbents and bring about the predicted one-to-many, from-here-to-there response in the simplest model of protoplasm suggested

In theory, the successful binding of a cardinal adsorbent onto a “pseudo-cardinal site” on a protein molecule could create an across-the-board change of the electron density and hence the preferred partners of the backbone peptide groups and of all functional groups on short side chains. This then provides the basis for the new kind of experimental testing outlined below.

2.1 Functional groups on short side chains

The most prominent among these functional groups on short side chains are the β -, and γ -carboxyl groups because they are most numerous in many isolated proteins, usually making up about 10% of all the amino acid residues of the protein (see Table 0-2 on page xxvii in Ling 1962 and also Ling 2007.) One advantage offered by its high concentration lies in greater ease in detecting small changes. For this reason, we will begin with the study of the β -, and γ -carboxyl groups. Once we have gained some experience in following this new approach, we can then look into other functional groups on short side chains. They may include SH groups on cysteine side chains, phenol on tyrosine side chains, tryptophane on phenylalanine side chains and even prosthetic groups like heme anchored onto imidazole groups on histidine side chains. But all that is on a future menu.

Let us begin with the mono-valent cation that is most strongly adsorbed on the β -, and γ -carboxyl groups, H^+ . Figure 2 shows how the binding energy of this ion increases or decreases sharply with changing c -value. If both the fundamental theory of molecular connectedness of protoplasm and the postulation that many isolated pure proteins contain PCS that react with real life cardinal adsorbents, then one would expect that the exposure for a suitable duration of time of say 10.0 ml of a 0.5% solution of protein X would lead to a change of the association constant, K_H , of the β -, and γ -carboxyl groups of the protein. What that could tell is that that PCS acts as a EWC or EDC. The basic method used in determining the acid binding constants is by the titration method used, for example, by Foster and Sterman (1956) in their study of the effect of urea upon the pK_a values of bovine serum albumin. The employment of a truly good pH electrode is vital.

Since the total amount of the drug or cardinal adsorbent added to the solution is known, comparison with the number of the β -, and γ -carboxyl groups that have altered their K_H could yield information of the extent of the one-on-many factor demonstrated. Additional insight can be obtained by including in the protein solution either KCl or NaCl as follows.

As pointed out above, with c -value rise or fall, the preference of the β -, and γ -carboxyl groups for either K^+ or Na^+ could reverse itself as shown in Figure 2. One can experimentally investigate the impact of a drug or cardinal adsorbent on a protein X by monitoring the acid binding constant K_H as described in the preceding section, only the solution beside the protein will also contain say 25 mM of either KCl or NaCl. Since K^+

and Na^+ compete against H^+ for the same β - and γ -carboxyl groups, the apparent K_H determined would be affected. From the observed changes, one can calculate the relative adsorption constants of both K^+ and Na^+ . And from their relative magnitude, one can easily determine whether that drug (or cardinal adsorbent) behaves as an *electron donating cardinal adsorbent* (EDC) or an EWC and how effective they are in either capacity.

2.2 Bulk-phase water molecules

According to the polarized-oriented multilayer (POM or PM) subsidiary theory of the AI Hypothesis, the exposed NHCO groups of fully extended protein chains could polarize and orient the bulk phase water molecules to varying degree. Thus, if a drug or other cardinal adsorbent brings about a change in the c-value of the β - and γ -carboxyl groups of a protein X, it is expected that the surrounding bulk-phase water molecules would also undergo extensive changes. The following outline shows one experimental approach to investigate these predicted changes, including the validity of the postulation of pseudo-cardinal sites

The basic method planned is the equilibrium dialysis method such as that employed in many similar studies made in our laboratory in the past (Ling and Ochsenfeld 1989, Ling *et al* 1993.) In general a much higher concentration of protein X is needed for dialysis studies than for the β - and γ -carboxyl group studies described in the preceding section. And, for the same reason, the choice of the protein would have to be limited to very inexpensive varieties available. For probe molecules, two most useful ones would be Na^+ (Cl^-), sucrose (or trehalose, which is more stable than sucrose.) In order to determine the true equilibrium distribution coefficient or q-value (rather than the apparent equilibrium distribution coefficient or ρ -value), a plot of the final equilibrium concentration of the probe inside the dialysis sac against the final equilibrium concentration in the external solution is required. If a straight line is obtained, the slope of the line equals the q-value of that probe in the protein solution inside the sac (for example, see Ling *et al* 1993.) The lower the q-value obtained, the clearer it shows a cogent connectedness between the PCS and the farthest water molecule in the sac. Insight gained in recent times from our extensive studies on solute distribution in living cells as well as model systems would provide valuable guideline in interpreting the data obtained (Ling *et al* 1993, Ling and Hu 2004, Ling and Fu 2005.)

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