A New Model of Intracellular Communication Based on Coherent, High-Frequency Vibrations in Biomolecules

L. Dent

Pepperdine University/NASC, 24255 Pacific Coast Highway, Malibu, CA 90263–4321, USA. laurieanne.dent@pepperdine.edu

Abstract

Chemistry has been the ruling paradigm for understanding the communication network that integrates a living cell. However, biochemistry alone is insufficient to explain how widely-separated biomolecules locate and move toward one another with accuracy and speed. We propose a new model wherein cytoplasmic motion is vibrationally-directed due to a community of oscillating biomolecules. DNA vibrations have been predicted in the 2-GHz range, thus we used high-frequency laser-Doppler vibrometry to test the hypothesis that resonance-driven molecular motion would be detectable as picometer surface displacements in live onion epidermal cells and fish eggs but would be absent in dead cells. Although, no surface vibrations were detected under these conditions, we discuss implications for the vibrational model of intracellular communication and suggest future experiments.

Key words: cellular communication networks, intracellular signaling, DNA vibrations, biomolecular resonance, biological oscillators

Introduction

Cells are constantly processing information from their external and internal environments in order to function properly. Information about the status of energy sources, cell-specific functions, and the condition of the genome must be communicated continuously. To give a few examples: a) the presence of a carbon source, lactose, in the environment induces expression of bacterial *lac* operon genes, efficiently optimizing the biochemistry of the cell for lactose utilization; b) reciprocal signaling between adjacent cells expressing *wingless* and *hedgehog* genes maintains precise segmental boundaries in the developing fruit fly; and c) the p53 DNA repair pathway is activated when chromosomal damage has been detected. These astonishingly complex cellular communication systems, constituted of biochemical pathways and signaling cascades and involving interactions between myriads of biomolecules, have been described only in small part by biochemists and molecular biologists.

So complicated are subcellular processes, that in recent years computer animators have been employed to help us visualize these sophisticated molecular machines and processes at work. When watching an animation of, say, gene expression, we see biomolecules "flying around", apparently guided to their targets; protein transcription factors glide to their specific DNA-binding sequences, mRNA transcripts seem to be directed through nuclear pores toward ribosomes for translation, tRNAs land on a ribosome and perfectly align with mRNA to make the anticodon-codon hybrid. What we cannot appreciate from these animations are the blinding speeds at which these processes occur. DNA replication occurs at a rate of 50 nucleotides per second in humans, and *Escherichia coli* bacteria can add 40 amino acids per second during protein synthesis. Animators have greatly reduced the speed of these systems so the motion can be apprehended by the human eye. How, then, do these biomolecules locate each other with such accuracy and rapidity?

Classically, Brownian motion has been invoked as the mechanism in cellular biochemistry wherein two biomolecules perform a "random walk" through the cell, and then by chance, collide at just the right orientation to allow a chemical reaction [reviewed in 1]. This may happen in cases where enzymes and substrates are at high density and close proximity — such as in a typical bacterium, where each soluble enzyme contacts every other enzyme and substrate once every second — ,but it is not sufficient to explain cases where large molecules must find each other, starting from relatively great distances. Illustrations of this problem would include the precise synapsis of homologous chromosomes during meiosis I, or the *trans*-acting factors (proteins that initiate transcription) which must locate a specific DNA sequence on a specific chromosome amid billions of base pairs during gene regulation. Brownian motion simply does not appear to be adequate to overcome the "crowded-cell problem" in terms of the need for vast numbers of macromolecules to find their distant targets quickly. These well-established biochemical models of cellular communication do not adequately consider the localization and transport information that is required for all the component parts to find each other and react in assembly line fashion. For example, forty years ago, it was shown that the targeting of the *lac* repressor to its DNA-binding site occurred up to 1,000 times faster than the predictions of diffusion and random collision [2]. This finding spawned what has become a very large research effort in structural and molecular biology focused on discovery of protein-nucleic acid target-search mechanisms. These studies have yielded hypothetical "one-dimensional diffusion" mechanisms of protein hopping, sliding, and intersegmental transfer. In their excellent review of experiments investigating these mechanisms, Gorman and Green [3] conclude,

> Importantly, none of the published studies where one-dimensional diffusion was visualized used DNA substrates that actually contained specific target sites for the

proteins being studied, so diffusion and target binding still remain to be seen in the same reaction trajectory

Thus, a chronic challenge in diffusion and macromolecular crowding research is the difficulty of interpreting data from experimental or theoretical studies that strain to approximate the complex intracellular environment [1, 4, 5].

While the role of cytoskeletal trafficking of biomolecules within the cytoplasmic [*Drosophila* axis patterning: 6, 7, 8; signal transduction pathways in yeast: 9; hyphal polarity in fungi:10; review: 11] and nucleoplasmic [plant chromatin remodeling: 12; interphase chromosome repositioning: 13, 14; Cajal bodies and U2 snRNA gene:15; nuclear rearrangement and transcription enhancement: 16, 17] compartments is an integral principle, cytoskeletal mechanisms cannot account for all instances of biomolecular transport. Curiously, filamentous actin (the cytoplasmic type) is not found in the nucleus whereas many actin-binding proteins (ABPs) are. The ABPs of the nucleus accomplish chromatin remodeling via nucleosome and histone interactions. When actin is translocated to the nucleus, it appears to be facilitated by cofilin [18]. These beg the question of how actin and non-filamentous actin-related proteins themselves find their specific nuclear targets. An as yet undiscovered mechanism must be at work in marshaling distant biomolecules involved in coordinated cellular functions.

To address the problem of how biomolecules might find each other apart from simple Brownian motion, we have developed the following hypothetical model. We propose that the molecular motion in the cytoplasm is not truly random, but is vibrationally-directed and coherent due to a community of oscillator structures within chromosomes and proteins, within a narrow distribution of resonant frequencies. We predict that specific nucleotide sequences will vibrate at characteristic resonances, and that these are closely matched to the inherent oscillation frequencies of the α-helices in functionally-linked proteins (e.g., transcription factors). Such harmonic interaction might facilitate the mutual identification and attraction of protein-DNA binding. These vibrationally-coupled "communication channels" may then synchronize the resonant motifs within other biomolecules, perhaps establishing oscillations across a family of harmonic frequencies, with the DNA molecule vibrating at the fundamental frequency; and in so doing, attract biomolecules to one another with great specificity while providing an essential cell "lubricant" to free cellular molecules from the "stickiness" associated with the cytoskeleton and crowded cytoplasm so that molecules can find each other with greater rapidity. This novel hypothesis may help us to understand how molecules might interact from a distance, and if correct, would reveal an entirely new level of biological information.

Vibrations in DNA molecules and proteins have been known for more than twenty years. Vibrational modes in DNA and proteins have been predicted theoretically [19–23] and measured experimentally using Raman spectroscopy

techniques [24–28]. One of the principal investigators, studying theoretical models of DNA vibrations in the microwave range, was K. C. Chou who predicted an ultra-high frequency vibrational mode in DNA, around 2 GHz [23].

In this light, we felt our model was potential useful and should be tested. Since DNA vibrations in the gigahertz range have been predicted [23] and eukaryotic nuclei have a high DNA content, it seemed reasonable to begin looking for ultra-high frequency vibrations in the vicinity of a cell nucleus. These collective vibrations may be transmitted to the cell surface and detectable as ultra-high frequency displacements. In this paper, we present preliminary experiments aimed at detecting such coherent molecular motion within living cells, which should be absent from dead cells, in onion cells and fish eggs using ultra-high frequency laser-Doppler vibrometry.

Materials and Methods

Cellular material

We prepared plant and animal cell specimens in order to investigate the possible presence of high frequency vibrations at the cell surface. Onion epidermal cells were selected as representative plant cells because of the following attractive features: size, proximity of nucleus to cell surface, and ease of preparation. Cells are large (approximate length = 100 μm) and form a flat monolayer which can be teased easily from an onion scale by use of fine forceps. Also, the nucleus is relatively large (approximately 10-μm diameter), larger than some eukaryotic cell types. Owing to the size of the nucleus, it easily visible under low magnification and lies near the cell surface which consists of a plasma membrane covered by a cell wall. Live cells were obtained from freshly-harvested green onions. We determined whether cells were living by observing cytoplasmic streaming under light microscopy.

Animal cells were obtained from freshly killed female jacksmelt fish which had been caught the same day by fishermen at Newport Beach, California. We manually expelled roe from two gravid females, and hundreds of unfertilized fish eggs were available for immediate analysis. Eggs were spread into a single layer in a plastic petri dish and assumed to be viable based on the rapid collection protocol.

Laser-Doppler vibrometry

A 0.5-cm^2 section of live, green onion epidermis was excised, and then flattened onto a dry microscope slide with the waxy surface facing up. The specimen was

positioned on the stage of the vibration-isolated workstation of a Micro System Analyzer (MSA-500-TPM2–20-D, Polytec, Inc., Irvine, California, USA) which combined microscopy with scanning laser-Doppler vibrometry for detection of surface vibrational signals across a large bandwidth of frequencies.

First, a living onion cell was located under 50X magnification via the live video stream capabilities of the MSA Optical Unit, and then a 1-μm laser spot was focused over the nucleus. We acquired cell surface displacement data over two frequency ranges, 0–20 kHz and 30 kHz–24 MHz. For the first range, the surface velocity was measured and then converted to displacement using the Polytec vibrometer software. For the latter frequency range, the surface displacement was measured directly. Data acquisition as well as conversion of the raw data into the frequency domain, using a Fast Fourier Transform (FFT), was performed within the Polytec vibrometer software. We utilized an extremely broadband approach because we hypothesized that the supercoiling of DNA molecules may lower the functional frequencies, although the work of Chou and his colleagues predicted DNA vibrations in the ultra-high frequency range. In probing the cell surface for the presence of vibratory signals, both single-point measurement and scanning routines were used. In the latter, the optical unit was programmed to analyze several points across a two-dimensional array of the cell surface above the nucleus, and then the beam collected velocity/displacement measurements at each point according to this pre-programmed routine. Off-line data analyses were performed in MATLAB (v. 7.10.0.499, R2010a, The MathWorks, Inc.).

For comparison with live cells, we continued to collect measurements from cells that showed no cytoplasmic streaming after having been probed for several minutes with the beam; these were presumed to be dead due to damage from the laser, although no defects could be seen in the vicinity of the laser spot. Also, we took measurements on other varieties of onions, red and white, that did not show cytoplasmic streaming; however, we could not ascertain whether the cells were dormant or dead.

On the basis of Chou's theoretical modeling of DNA vibrational modes in the gigahertz range, onion cells were also examined for the presence of ultra-high frequency surface vibratory signals, up to 1.2 GHz, using the UHF-120 Ultra High Frequency Vibrometer (Polytec, Inc., Irvine, CA, USA). As in the case of the MSA-500 for the frequency range of 30 kHz to 24 MHz, the UHF-120 also measures surface displacement directly. Experimental protocols and data analysis similar to those used with the MSA-500 system were carried out for ultra-high frequencies.

We repeated these tests on fish eggs, employing the same measurement protocols described above. Here, the chief difficulty was determining the health of the cells; we did not have an assay for live versus dead animal cells.

Both the MSA-500 and the UHF-120 are laser Doppler vibrometers, which are precision non-contact optical transducers used for detecting vibration velocity and displacement at a fixed location. The technology is based on the Doppler Effect, sensing the frequency shift of the back scattered laser light. The surface velocity is determined using the following relationship:

$$v = \frac{f_D * \lambda}{2}$$

v is the surface velocity of the object at the location of the laser spot, f_D is the Doppler shift in frequency and λ is the wavelength of the laser light.

Results

We tested the prediction that ultra-high frequency vibrations emanating from the nucleus of live onion epidermal cells and fish eggs would be detectable at the cell surface, whereas in dead cells, no surface vibrations would be present.

Cell surface vibrations are not detectable in onion cells

Highly-sensitive laser-Doppler vibrometry capable of detecting frequencies up to 1.2 GHz with picometer displacement resolution did not reveal a passive vibratory signal at the surface of an onion epidermal cell (Fig. 1a-c). The only peaks present in the lower frequency bandwidth, 0–40 kHz (Fig. 1a), were noise components from the electronic circuitry. For example, peaks below 2.5 kHz included 60 Hz plus harmonics associated with the power grid; also, the two peaks around 24 and 25 kHz (arrow) were characteristic laser resonances from its power supply. We are confident that any nucleus-originating vibratory signal propagated to the cell surface would have been detectable with this instrumentation. It is generally accepted that plasma membranes are 7–10 nm-thick, so with a broadband noise floor in the order of a few picometers, any peaks of biological origin would have been apparent. Similarly, Figure 1b shows no cell surface vibrations across a frequency bandwidth of 30 kHz to 20 MHz. Here, the noise floor encompasses about 350 pm. The tailing off of signal magnitude observed at the upper ends of the frequency spectra is a function of filter roll-off (Fig. 1a and b, asterisks). Finally, no ultra-high frequency vibrations up to 1.2 GHz were present at the cell surface (Fig. 1c); the noise floor was about 20 pm. Resonances of biological origin characteristically produce broad peaks or “humps” in a magnitude-frequency plot.

Here, only "lines" are present, spikes of energy at a single frequency, typical of laser resonances (coherent light) and electronic artifacts.

Measurements collected from epidermal cells in other varieties of onions, red and white, showed a similar lack of cell surface vibrations (data not shown).

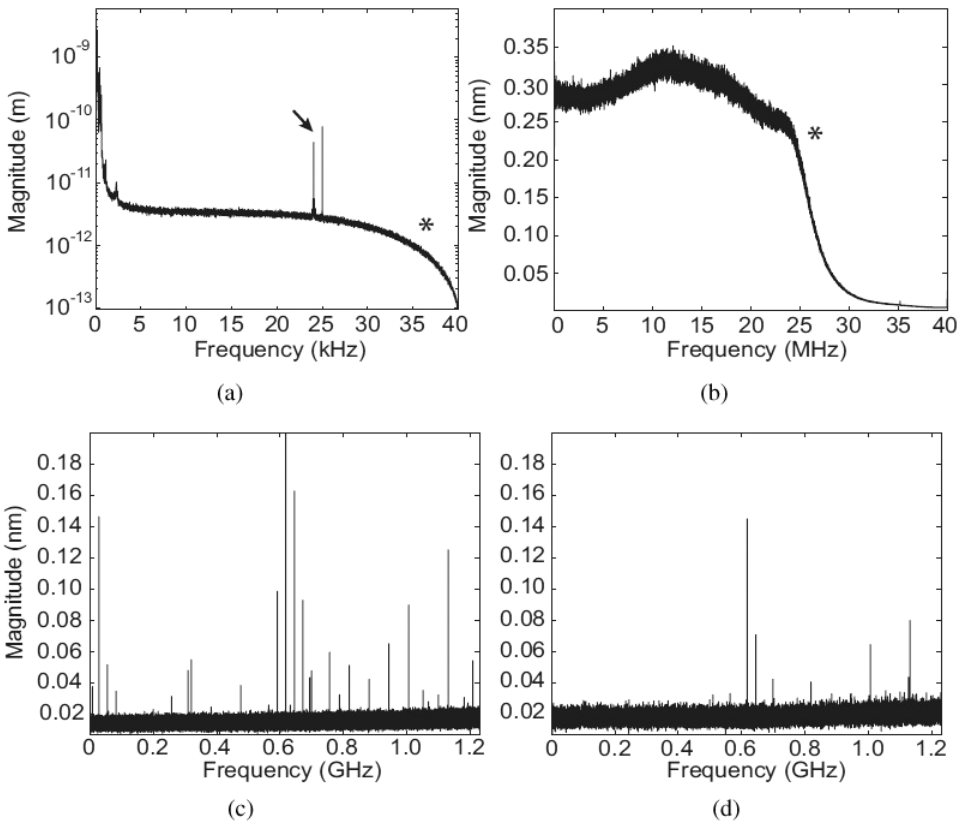

Fig. 1. Broadband frequency analyses performed by laser-Doppler vibrometry show no cell surface vibrations in onion epidermal cells or fish eggs. (a) Surface displacement magnitude as a function of lower frequencies, 0–40 kHz, is shown for a region over the nucleus of a live green onion. Low-frequency peaks, <2.5 kHz, are non-biological and represent electronic noise (e.g., fundamental and harmonics of 60 Hz contribution from electrical power grid). The log-transformed y-axis reveals two prominent peaks around 24–25 kHz (arrow) known to represent the laser power supply. The upper bandwidth limit of the decoder is evident in the filter roll-off response at higher frequencies (asterisk). (b) The same specimen in 'a', analyzed for higher frequency vibrations across a range of 30 kHz–20 MHz, produces no signal above the noise; and then, again, (c) for ultra-high frequencies, up to 1.2 GHz, where peaks present are not of biological origin. (d) Also, no peaks of biological origin are present in a fish egg analyzed for ultra-high frequency surface vibrations. It is important to keep in mind that all the vibration signals represented in the plots (a) through (d) are well below 1 nm, which is very small.

Ultra-high frequency cell surface vibrations are not detectable in fish eggs

We used ultra-high frequency laser-Doppler vibrometry to probe for cell plasma membrane vibrations on unfertilized fish eggs for comparison with onion cells which have a cell wall. No resonance peaks of biological origin were present in frequency analyses up to 1.2 GHz (Fig. 1d; similar to experimental parameters of Fig. 1c); only artifactual resonance lines appeared above the approximately 15-pm noise floor. We conservatively suggest that these data were collected from viable oocytes, since only two hours had lapsed between collection of fish at the pier and analysis in the laboratory.

Discussion

In this study, we are seeking to test one hypothesis that arises from a new model of a communication network that may integrate a living cell. Our model proposes that nuclear-originating, broadband vibrational frequencies elicit sympathetic vibrations in functionally-related biomolecules and order the molecular motion of the cytoplasm. To our knowledge, this study is the first test of the vibrational model of intracellular communication. We tested the specific prediction that cell surface vibrations will be present as ultra-high frequencies due to the propagation of coherent molecular motion, especially emanating from the nucleus; furthermore, we predicted that vibrations would be present in live cells but absent in dead cells. Although we were unable to detect vibrations on the surface of living cells across a broad frequency range using the highest-precision, most-sensitive instrumentation available, we propose the following causes may have prevented signal detection, including (i) constraints of cell architecture, (ii) heat damage during laser measurements, and (iii) the limitation of detecting frequencies above 1.2 GHz.

Plant cells are surrounded by a rigid cell wall. This thick, inflexible structure may have damped any high frequency vibrations that may have propagated to the perimeter of the cell. However, animal cells do not have a cell wall, and we were not able to detect any surface vibrations on the fish eggs. It is possible that nucleus-originating vibrations are not reaching the cell's plasma membrane. The filtering properties of the nuclear envelope in response to compressional waves are not known. Its double-thick phospholipid bilayer, separated by a space of 20–40 nm, may be sufficient to restrict intranuclear vibrations to the nuclear compartment. Even if some vibratory energy were transmitted to the cytoplasm, the filtered signal may attenuate rapidly, especially as frequency increases. One might imagine

that the intranuclear environment — a relatively small space packed with nucleic acids and other biomolecules — requires a communication system which utilizes ultra-high frequency carrier signals for high-energy, short-range signaling. If, therefore, DNA is oscillating at frequencies in the gigahertz range, it may not be possible, due to the short reach of the vibrational energy, to detect the signal at the cell surface, whether plant or animal.

We also considered that the cells may have sustained heat damage from the laser beam during scans, denaturing DNA and proteins and, thus, disrupting normal cell functions. For this reason, we were careful to check for cytoplasmic streaming after each point scan of onion epidermis to confirm the health of the cell. However, following one extended multi-point scanning routine, no cytoplasmic streaming was observed, and we inferred the cell had sustained heat damage from the laser measurement. The fish eggs, without the additional protection of a cell wall, may be even more liable to laser damage. In both laser-Doppler vibrometry systems, the MSA-500 and the UHF-120, mechanisms are in place to minimize exposure of the specimen to the laser; the laser power can be attenuated manually (MSA-500), or a built-in gating function dims the laser when measurements are not being taken (UHF-120).

Detecting out-of-plane vibrations of 1.2 GHz is at the limit of cutting-edge laser-Doppler vibrometry, however, it is unlikely to be "good enough." On the basis of the predictions of Zhang and Chou [23], though, 2-GHz vibrational modes in DNA would, indeed, be beyond the detection capabilities of the instruments used in these experiments.

Of these possible explanations for the absence of cell surface vibrations in our experiments, I believe the most likely is the compartmental organization of the cell. Suppose the mechanism of intracellular communication includes an intranuclear communication network consisting of ultra-high frequencies generated by DNA. One might expect the vibratory frequency to be predictably related to DNA nucleotide sequence; possibly, prominent resonances could develop most easily across sequences of tandem DNA repeats. It is interesting that more than 50% of the human genome consists of repetitive DNA. Much of this repetitive DNA is located in the centromeres of chromosomes (which facilitate proper segregation of replicated chromosomes during mitosis). Centromeric DNA is characterized by repetitive, simple, non-coding sequences called "satellite" DNA; one type in particular, α-satellite DNA, consists of a 171 bp-long repeating unit, and thousands of tandem arrays may stretch over one million bases of a chromosome. The higher-order molecular structure of centromeric DNA has been difficult to study, however it may be similar to non-centromeric DNA structure which has been compared to a "solenoid" — 160 bp of DNA wrapped twice around a histone octamer core (nucleosome) which is further coiled into a superhelix that contains

six nucleosomes per turn [29]. (The assumption of higher-order supercoiling in centromeric DNA motivated our search for cell surface vibrations in the megahertz frequency range — larger coils should affect downward frequency modulations.) It may be that the three-dimensional architecture of a centromere fundamentally based on tandem repeats of DNA generates a standing oscillation which could act as a vibratory signal, possibly ultra-high frequency, to other biomolecules within the nuclear compartment.

It would seem, then, that the operation of the vibrational model may be limited to the intranuclear compartment. How might other biomolecules in the nucleus receive this signal? The first three-dimensional structure of a biomacromolecule to be solved was the α-helix in proteins in 1948 by Linus Pauling who later won a Nobel Prize for his discovery. These α-helices may function as resonance structures within proteins, something like an antenna. Notably, many proteins that interact with specific DNA sequences have multiple α-helix domains; for example, the α-helices of the p53 tetramer (modulates the cell cycle by controlling expression of DNA repair proteins) are closely associated with the DNA helix in predicted three-dimentional models of the complex. It may be that the α-helices of DNA-binding proteins have characteristic resonances that are related fundamentally or by harmonics to the resonance of its specific DNA sequence. These functionally-related biomolecules may oscillate within a narrow bandwidth such that spontaneous sympathetic vibration occurs, generating directed, rapid movement between protein and target DNA sequence. In the relatively small, "noisy" nuclear compartment, densely populated with nucleic acids and proteins, an ultra-high frequency, high-intensity, but short-range signaling network, shielded from the rest of the cell by a double-thick phospholipid bilayer nuclear envelope, may constitute ideal conditions for rapid, high-precision intranuclear communication.

Molecular vibration as a mechanism for carrying information via biomolecules is not entirely without precedent. Recently, behavioral studies in fruit flies (*Drosophila melanogaster*) showed that the animals could discriminate between isotopes of the same odorant [30]. The researchers were interested in testing the mechanism of odorant-receptor recognition, which is not understood. Traditionally, odor recognition has been attributed to a biochemical mechanism where binding affinity depends on a "lock-and-key" fit between odorant and receptor. In this study, flies were trained to choose between deuterated and nondeuterated odorants that would have had the same molecular shape but would have differed in vibrational modes due to differences in mass numbers of the atomic nuclei. Although this study of odorant recognition strongly suggests that vibrational differences in molecules carry different information detectable by the animal's nervous system, it does not go as far as our hypothesis which suggests that different vibrational modes in biomolecules give rise to directed motion in a medium.

The theoretical grounds for resonant mechanical vibrations giving rise to directed motion may be found in the asymmetry of biomolecules. Asymmetrical objects that are enveloped by moving fluids experience differential pressures at different points on the object, resulting in motion of the object down the pressure gradient. A classic example is an airfoil that experiences lift due to lower fluid pressure on the more-curved upper surface where fluid is flowing faster relative to the flat lower surface. Asymmetrical biomolecules like DNA and proteins vibrating in resonance may create regions of low pressure by displacing more fluid on one side, between them where the molecules can "fall together", sliding down a steep pressure gradient, perhaps something like the nodal patterns of Chladni plates that change as a function of resonant frequency. An interesting study by Baldwin and colleagues [31] showed that DNA molecules aggregate *in vitro* in a sequence-specific fashion. They constituted a mixture of two types of double-helical DNA molecules with similar nucleotide composition and length but differing in nucleotide sequence, labeled with green or red fluorescent dye, and then used confocal imaging to quantify the fluorescence to indirectly measure the segregation of DNA. They observed that in a protein-free, electrolytic environment, DNA molecules with similar sequences aggregated, while DNA molecules with dissimilar sequences segregated as evidenced by significant color separation. The mechanism they proposed was based on the ability of double helices to remain in register because of the sequence-dependent pitch of juxtaposed DNA molecules. In an important DNA–DNA interaction like homologous chromosome synapsis, the result of this study is powerfully suggestive because it rules out mechanisms of Brownian motion and cytoskeletal transport.

If our vibration-based model is limited by the nuclear envelope to intranuclear communication, what form of energy might carry the information that integrates the *entire* cell? For example, how might a specific transcription factor manufactured by ribosomes in the cytoplasm get "called up" for translocation to the nuclear compartment? It is known that many cellular processes are affected by electromagnetic fields [32–35]. Thus, another component of our model, not addressed by the preliminary experiments of this paper, proposes there is a cellular ("global") positioning system based on electromagnetism that establishes a three-dimensional coordinate system across the cell. In addition to providing spatial coordinates, it may be that DNA or another nucleus-associated biomolecule, generates timing information, a kind of "clock frequency" (as in a computer), that provides the fundamental frequency and harmonizes cellular components and biomolecules via families of harmonic frequencies. More locally, functionally-related biomolecules may have intrinsically-oscillating electromagnetic resonances that vibrate sympathetically and generate a local field within which directed motion may occur. We have begun to explore the theoretical basis for resonance between biomolecules

that must locate a specific target within a broad search area — transcription factors and their specific DNA-binding sequences. Specifically, we are in the process of planning computer simulation-based investigations of the model's prediction that molecules with similar vibrational signatures may attract at a distance, allowing directed molecular motion in the cell.

While this study provided no evidence for our hypothesis that living, nucleated cells have a vibration that may originate in the nucleus and cause coherent cytoplasmic motion, we hope to find a suitable cell model and the right experimental and computational approaches to continue testing the vibrational model of intracellular communication. Developing an *in vitro* system where resonance correlations between DNA-binding proteins and DNA can be studied may be the next logical step. Raman spectroscopy techniques may reveal frequency patterns in functional families of biomolecules. I strongly believe the attraction-at-a-distance mechanism is based on a resonance principle, but whether the resonance may be mechanical or electromagnetic or a combination of both—will have to wait for future experiments.

Addendum

Other researchers are also seeking evidence for a resonance principle at work in directing important cellular events. They have predicted from theoretical models that electrical fields arising from synchronized oscillations within centrosomes, microtubules, and chromatin drive centrosome movements and homologous chromosome synapsis during mitosis and meiosis (Zhao and Zhan, 2012a); and that "chromatin oscillation cluster" formation may coordinate the efficient transcription of genes across the genome (Zhao and Zhan, 2012b). See references Zhao Y, Zhan Q (2012a) Electrical fields generated by synchronized oscillations of microtubules, centrosomes and chromosomes regulate the dynamics of mitosis and meiosis. Theor Biol Med Model 9:26.; Zhao Y, Zhan Q (2012b) Electrical oscillation and coupling of chromatin regulate chromosome packaging and transcription in eukaryotic cells. Theor Biol Med Model 9:27.

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References

1. Dix JA, Verkman AS (2008) Crowding effects on diffusion in solutions and cells. Annu Rev Biophys 37:247–263.
2. Riggs AD, Bourgeois S, Cohn M (1970) The *lac* repressor-operator interaction. 3. Kinetic studies. J Mol Biol 53:401–417.
3. Gorman J, Greene EC (2008) Visualizing one-dimensional diffusion of proteins along DNA. Nat Struct Mol Biol 15:768–774.
4. Ellis J, Minton AP (2003) Join the crowd. Nature 425:27–28.
5. Hall D, Hoshino M (2010) Effects of macromolecular crowding on intracellular diffusion from a single particle perspective. Biophys Rev 2:39–53.
6. Theurkauf WE, Hazelrigg TI (1998) In vivo analyses of cytoplasmic transport and cytoskeletal organization during *Drosophila* oogenesis: characterization of a multi-step anterior localization pathway. Development 125:3655–3666.
7. Byeong-Jik C, Koppetsch BS, Theurkauf WE (2001) In vivo analysis of *Drosophila* bicoid mRNA localization reveals a novel microtubule-dependent axis specification pathway. Cell 106:35–46.
8. Kugler JM, Lasko P (2009) Localization, anchoring and translational control of oskar, gurken, bicoid and nanos mRNA during *Drosophila* oogenesis. Fly 3:15–28.
9. Forgacs G, Yook SH, Janmey PA, Jeong H, Burd CG (2004) Role of cytoskeleton in signaling networks. J Cell Sci 117:2769–2775.
10. Zarnack K, Feldbrügge M (2010) Microtubule-dependent mRNA transport in fungi. Eukaryot Cell 9:982–990.
11. Mammoto T, Ingber DE (2010) Mechanical control of tissue and organ development. Development 137:1407–1420.
12. Meagher RB, Deal RB, Kandasamy MK, McKinney EC (2005) Nuclear actin-related proteins as epigenetic regulators of development. Plant Physiol 139:1576–1585.
13. Chuang CH, Carpenter AE, Fuchsova B, Johnson T, Lanerolle P, Belmont AS (2006) Long-range directional movement of an interphase chromosome site. Curr Biol 16:825–831.
14. Kumaran RI, Rajika T, Spector DL (2008) Chromatin dynamics and gene positioning. Cell 132:929–934.

15. Dundr M, Ospina JK, Sung MH, John S, Upender M, Ried T, Hager GL, Matera AG (2007) Actin-dependent intranuclear repositioning of an active gene locus in vivo. J Cell Biol 179:1095–1103.
16. Hu Q, Kwon YS, Nunez E, Cardamone MD, Hutt KR, Ohgi KA, Garcia-Bassets I, Rose DW, Glass CK, Rosenfeld MG, Fu XD (2008) Enhancing nuclear receptor-induced transcription requires nuclear motor and LSD1-dependent gene networking in interchromatin granules. Proc Natl Acad Sci USA 105:10199–19204.
17. Castano E, Philimonenko VV, Kahle M, Fukalova J, Kalendova A, Yildirim S, Dzijak R, Dingova-Krasna H, Hozak P (2010) Actin complexes in the cell nucleus: new stones in an old field. Histochem and Cell Biol 133:607–626.
18. McDonald D, Carrero G, Andrin C, de Vries G, Hendzel MJ (2006) Nucleoplasmic beta-actin exists in a dynamic equilibrium between low-mobility polymeric species and rapidly diffusing populations. J Cell Biol 172:541–552.
19. Chou KC (1983) Identification of low-frequency modes in protein molecules. Biochem J 215:465–469.
20. Chou KC (1984) Low-frequency vibrations of DNA molecules. Biochem J 221: 27–31.
21. Chou KC (1988) Low-frequency collective motion in biomacromolecules and its biological functions. Biophys Chem 30:3–48.
22. Chou KC, Maggiora GM, Mao B (1989) Quasi-continuum models of twist-like and accordion-like low-frequency motions in DNA. Biophys J 56:295–305.
23. Zhang CT, Chou KC (1996) Beat motion in DNA double helix and a mechanism of energy exchange its two strands with microwave frequency. Chem Phys 206: 271–277.
24. Painter PC, Mosher LE, Rhoads C (1981) Low-frequency modes in the Raman spectrum of DNA. Biopolymers 20:243–247.
25. Urabe H, Tominaga Y (1982) Low-lying collective modes of DNA double helix by Raman spectroscopy. Biopolymers 21:2477–2481.
26. Urabe H, Tominaga Y, Kubota K (1983) Experimental evidence of collective vibrations in DNA double helix Raman spectroscopy. J Chem Phys 78:5937–5939.
27. Lindsay SM, Powell JW, Rupprecht A (1984) Observation of low-lying Raman bands in DNA by tandem interferometry. Phys Rev Lett 53:1853–1855.
28. Lamba OP, Wang AHJ, Thomas Jr GJ (1989) Low-frequency dynamics and Raman scattering of crystals, of B-, A-, and Z-DNA, and fibers of C-DNA. Biopolymers 28:667–678.
29. Hartwell LH, Hood L, Goldberg ML, Reynolds AE, Silver LM, Veres RC (2008) Genetics: From Genes to Genomes, 3rd edn. McGraw-Hill Companies, Inc., New York.
30. Franco MI, Turin L, Mershin A, Skoulakis EMC (2011) Molecular vibration-sensing component in Drosophila melanogaster olfaction. Proc Natl Acad Sci USA 108: 3797–3802.

31. Baldwin GS, Brooks NJ, Robson RE, Wynveen A, Goldar A, Leikin S, Seddon JM, Kornyshev AA (2008) DNA double helices recognize mutual sequence homology in a protein free environment. J Phys Chem B 112–1060–1064.
32. Shi R, Borgens RB (1995) Three-dimensional gradients of voltage during development of the nervous system as invisible coordinates for the establishment of embryonic pattern. Dev Dynam 202:101–114.
33. Song B, Zhao M, Forrester JV, McCaig CD (2002) Electrical cues regulate the orientation and frequency of cell division and the rate of wound healing in vivo. Proc Natl Acad Sci USA 99:13577–13582.
34. Blank M, Goodman R (2004) Initial interactions in electromagnetic field-induced biosynthesis. J Cell Physiol 199:359–363.
35. Cifra M, Fields JZ, Farhadi A (2011) Electromagnetic cellular interactions. Prog Biophys Mol Biol 105:223–246.