Functional and Malignant Cell Growth obey Extreme Information Pathways

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Abstract

Living systems use information and energy to maintain stable entropy in a system that is far from thermodynamic equilibrium. However, a quantitative relationship between information and the function and growth of a living system has not yet been developed. We propose a fundamental principle of living systems is that every process of life, including metabolism, signal transduction and protein synthesis, represents a flow of information which, when expressed as Fisher information in particular, is constrained to be either a maximum or minimum. Either extreme state is invariant to first-order perturbation and, hence, maintains stable entropy, as required. Such a state also optimizes intracellular information flow, by the suitable adjustment of the information source and the trajectories of information carriers. This principle has, so far, predicted the (i) observable function and growth characteristics of normal cells or multicellular organisms; the (ii) Lotka-Volterra equations and (iii) power laws of allometry for normal growth. Similarly, it has predicted the (iv) loss of normal function and growth in early cancers, by assuming that carcinogenesis is fundamentally an information "catastrophe" where information regarding cell age and location undergoes transition from a maximum to a minimum state. The minimum leads to a predicted (and confirmed) power-law governing in situ cancer growth in time. (v) It also predicts a program of chemotherapy (termed "adaptive therapy") that converts the process of cancer mass growth into one of monotonic mass reduction, indicating conversion to a chronic, but manageable, condition.

Introduction

Growth and function of a living system depends positively upon its information state [1]. This connection ultimately traces to the 2nd law of thermodynamics which, oddly enough, is a statement of *decreased* information. That is, the 2nd law requires the level of *dis*order of a system, i.e. its entropy H, to temporally approach a *maximum* value. Increased disorder implies reduced information. However, the 2nd law is of a specifically global nature. This permits *local* pockets of disorder that is less than that of the surrounding system..

Such local increases in order can occur randomly in, for example, crystal formation. These local alterations in entropy also require energy and typically move toward a stable, equilibrium state of low entropy and energy.

Living systems, in contrast, maintain a dynamic but stable state of lower entropy which is far from equilibirium. This is by using energy judiciously. The stability of this low entropy state requires the expenditure of energy in order to both maintain and use information that forms the entropy gradient between the living system and its surround. Thus, living systems achieve not the lowest possible entropy state but, rather, the lowest possible entropy gradient as constrained by available energy. This suggests that Fisher information, which is both a measure of entropy and order (see below) and an estimate of energy cost, can be used as the metric in a first principle of the thermodynamics of living systems. This leads, in turn, to the principle that the information state of a living system is at an extreme value. An extremum can be a maximum, minimum or point of inflection. The types of extema attained in living systems are as follows.

In single cell organisms, energy costs dominate and information is maintained at a *minimum*. This is the minimum level necessary to maintain a stable system, robust to environmental perturbations.

In larger, multicellular organisms, the information is maintained at a *maximum*, because the energetic cost of maintaining sufficient order and information storage is minimized by the state of *multicellularity.*

The particulars of these effects follow.

Maximum Fisher Information

We propose that normal evolutionary dynamics favor living systems that approach a state of maximum information which allows such systems to remain robust in the face of random environmental perturbations. In effect, evolution favors organisms that are maximally different from the disordered environment. Many growth and development laws of natural science have, in fact, *been derived* on the basis of this principle of maximum Fisher information [2]. One example is the famous Lotka-Volterra equations which describes the interactions of competing populations [2,3]. Another is the quarter-power laws of biological allometry [4,5]

$$y = m^{n/4}, \qquad (1)$$

where y is a biological observable such as heart rate, n is a corresponding integer (e.g. $n = -1$ for observation y of heart rate), and m is the mass of the organism. Most recently, a requirement of maximum Fisher information [6] was used to derive Fisher's fundamental theorem of natural selection.

Minimum Fisher Information

Cancer cells, by contrast, grow in an uncontrolled, visibly disordered fashion. Hence, an intuitive corollary of the preceding is that *cancer* cells are in states of *minimum information*. This is the low level of information necessary to maintain the ability to proliferate in the absence of the differentiated function of normal mammalian cells [1,2,7,8]. The latter is consistent with clinical observations that cancer cells lose normal functionality so that malignant cells are invariably less differentiated than are their normal counterparts. For example, lung cancer cells no longer participate in gas exchange which is a major differentiated function of normal lung epithelial cells from which the originate. Similarly, malignant cells, as a result of damaged or *missing telomeres*, effectively lose function about their age so that they are typically immortal unlike normal cells that undergo apoptosis after approximately 100 doublings (the Hayflick limit). Thus, somatic evolution in carcinogenesis favors organisms with a minimum information state – opposite from the process usually observed in nature.

A hallmark of cancer cells is continuous, inappropriate proliferation which results from disordered flow of information between the cell and its tissue environment. That is, cancer cells are both unresponsive to normal growth inhibitory signals from the environment and constantly receive pro-proliferation signals due to upregulation of oncogenes. Central to control of cell growth are messenger proteins that carry information from receptors on the cell membrane to the nucleus, which then controls cellular response. For example a common mutation in cancer alters one or more components of the epidermal growth factor receptor (EGFR) signaling pathway so that it is continuously activated. Since the EGFR pathway promotes (among other things) proliferation, the cell is essentially sending itself artifactual signals to proliferate. Thus,

even in the absence of actual ligand binding to the EGFR, the nucleus receives signals as though a high concentration of the ligand (i.e. epidermal growth factor) were present in the environment. Interestingly, as a result of these mutations, a large amount of information in the form of messenger proteins passes between the CM and the NM, but virtually all of it is false. Thus, cancer cells suffer a progressive loss of accurate information regarding the proliferation instructions from the surrounding normal tissue We propose that a cell, in fact, becomes cancerous when accumulated mutations result in a maximal state of inaccuracy. That is, the information content of the cell regarding, for example, its age and growth instruction from surrounding tissue, is minimal. We will show that this state of minimum information actually gives rise to the known temporal power-law $\propto t^{1.62}$ governing the in situ growth [1,2,7,8] of such cells.

Extreme Fisher Information

In summary, we propose that *biological growth in general follows principles of extreme Fisher information. This is either maximum information for normal growth or minimum information for cancer growth.* Interestingly, the difference appears to depend on the fundamental unit of growth (i.e whether it is a single cell or a multicellular organism) and the information state of the environment. Evolution favors individual cancer cell with an information minimum; while functioning muticellular organism in a heterogeneous environment must approach an information maximum. Extremizing the Fisher information also benefits cell function in other ways, as discussed in the next two subsections.

Stable Entropy

An extreme state is, by definition, stable to first-order perturbation, e.g. due to exterior factors such as random temperature shift. Hence a living system that is in a state of extreme Fisher information, whether the extremum is a maximum or a minimum, *gains an advantage of stability*. This tends to keep it in a stable entropic state, as is required of living cells. This stability property is easily shown, e.g., for the wide range of probability laws that are members of *the exponential family* (see below). There the entropy H and Fisher information I are connected by the relation

$$I = (2\pi e)\exp(-2H), \text{ so that } \delta I / I = -2\delta H \qquad (2)$$

after taking a differential. Since $\delta I \approx 0$ at extremum solutions then likewise $\delta H \approx 0$. That is, *extremizing the Fisher information stabilizes the entropy*.

Another manner by which Fisher information controls the stability of the entropy is as follows.

Fisher I as a bound to entropic change

Although the 2nd law states that $dH/dt \geq 0$ at all times t it does not prescribe any *upper* bound to the change dH in entropy. In fact systems of mass m kept at a temperature T obey a well defined upper bound [2] to dH according to the level $I(t)$ of Fisher information present. The relation is

$$\frac{dH}{dt} \leq C\sqrt{I(t)}, \text{ with } C = \sqrt{\frac{2kT}{m}}, \qquad (3)$$

T the temperature and k the Boltzmann constant. Thus, if I is at an extreme value so is the allowed change dH in entropy. Also, the increase of C with T shows that the higher the temperature is the more the system disorder can increase relative to the present level

of information (or 'order,' as discussed next) I. This makes intuitive sense, and gives rise to the following speculations.

Eq. (3) predicts that if a system is perturbed by some external effect, the I of the system will constrain the effect of that perturbation . Doesn't this then imply that a robust living system will want to have a minimal I to effectively damp the effects? But perhaps this does not apply to multicellular organisms because the organism itself dampens the environmental perturbation dH so that the individual cells are protected. This may be part of a "deal" by which individual cells give up their independence to become a component of the multicellular organism. It also tends to explain the earlier statement that single cells tend to seek minimum I while multicellular organisms seek a maximum I .

Are information and 'order' synonymous?

We use the words 'order' and 'information' interchangeably. As recently found [9]: (a) A system's level of order *varies linearly* with its level of Fisher information, i.e. order

$$R = \left(8^{-1} KL^2\right) I., \qquad (4)$$

Here K is the number of system dimensions, L is its one dimensional extension; and (b) both the order and the information are entropies, i.e. measures of system order that change monotonically with the time. Hence, information I is an intrinsic *property of the system*, as well as a property of its data.

Result (4) indicates that a linear polymer protein, with $K = 1$, represents intrinsically less order than a cell membrane, with $K = 2$, and this has less order than the composite cell, of dimension $K = 3$. Thus, the energy requirements for maintaining these levels of

order likewise increase in this manner. Maintaining systems of high complexity intrinsically require higher levels of energy.

Result (4) is also in agreement with the observation that, unlike crystals – which have relatively uniform order throughout -- living systems are dynamic. These require *variations in order* (as discussed below), e.g. in transition from the ordered cell membrane to the relatively disordered cytoplasm, in order to maintain a stable state far from equilibrium. The relation (4) predicts the requisite variation, or flow dI, of information that gives rise to the required change dR so as to maintain that state. The connection is $dR = (8^{-1}KL^2)dI$.

Overall extremum condition

Maximum and minimum values are of course extreme values. Thus, *in general, cells grow on the basis of extreme Fisher information I*. If they are cancerous the extreme value is a minimum; or if functional, the extreme value is a maximum. The purpose of this paper is to summarize and further develop this hypothesis. Its central tool, Fisher information, is introduced and discussed next.

Fisher information

Consider a system with a characteristic parameter whose value is sought by analysis of its data. The data are used to form a mathematical estimate of the parameter. The information I defined by R.A. Fisher [10] measures the *level of information in the data about the parameter*. It is a local measure (see below).

Shift invariance property

Let a required parameter x_0 be measured, as a data value $y = x_0 + x$, with x a random error obeying some probability law $p(x)$. The system is assumed to obey shift

invariance, i.e. $p_Y(y \mid x_0) = p(y - x_0) = p(x)$. The data are processed arbitrarily to form an estimate of x_0. Denote the mean-squared (ms) error over many such estimates of x_0 as e^2.

Cramer-Rao inequality

Its *minimum* possible error ${e_{\min}}^2$ obeys [11], [12]

$${e_{\min}}^2 = 1/I \text{, where } y = x_0 + x \text{ ,} \tag{5}$$

where I is the level of Fisher information about the parameter that is present in the data. Thus, a system with a high level of information gives rise to a low ms error, and vice-versa. Relation (5) is called the Cramer-Rao inequality.

The information may be expressed alternatively as

$$I \equiv \int dx p'^2(x) / p(x) = 4 \int dx q'^2(x), \quad q(x) \equiv \sqrt{p(x)}, \tag{6}$$

with $q(x)$ defined as the probability *amplitude* of the system. Primes denote derivatives d/dx. The amplitude (second) - form of I is often used to compute I because of its lack of a quotient in the integrand. Information I has the following distinctive property that makes it well suited for predicting living systems.

Local nature of I

Central to our thesis is *that life is a local phenomenon* (see Introduction). Note in this regard that either expression (6) for I is a *local measure*. This agrees with the view that a cell is not a a single unit but, rather, consists of two or more local units, each with its own value of I (examples are the membrane and a DNA molecule). This makes sense since the building blocks of each region are different: DNA is made up of nucleotides while the cell membrane is made up of lipids which are long carbon chains. The point is that the

cell will have several internal, local probability amplitudes, including ones for nucleotides, lipids, and amino acids and ones for the intracellular space and its environment .

Note also that, mathematically, a "local measure" is one whose value can change drastically under local rearrangement of its points x. Any such rearrangements of points x excite discontinuities in the curves of $p(x), q(x)$, giving local points of infinite slope $p'(x)$ or $q'(x)$, and contributing infinities to the integrals (6) for I. By comparison, a *global measure*, such as the entropy

$$H = -\int dx p(x) \log p(x) \qquad (7)$$

or its corresponding summation form, does not depend upon local derivatives of $p(x)$ or $q(x)$ and, hence, *does not change* its value if the points x are rearranged. As discussed above, life is an expression of high local order. On this basis, the use of a local measure such as I seems optimum, and a global measure such as H suboptimal, for purposes of mathematically modeling its structure, i.e. complexity of order. By comparison, the use of H is essential in evaluating the inputs and outputs of heat and other forms of energy from the ordered, living system. This is through the well-known equivalence $E = kHT$ equation of heat energy E and entropy H with T the temperature.

Exponential family

The exponential family [12] of probability laws $p(x)$ will be of particular interest to us. It includes many of the most common laws, including the normal, exponential, gamma, chi-square, beta, Dirichlet, Bernoulli, binomial, multinomial, Poisson, Rayleigh and many others. Each of these has a well-defined variance value σ^2 in the random

variable x. Remarkably, substitution of any of these laws $p(x)$ into (2) gives the same result

$$I = 1/\sigma^2 . \qquad (8)$$

for the Fisher information about the parameter. Note that this formula in particular will be shown to describe the spatial growth of functional cells. Also of use is that any member function of the exponential family actually *achieves* the minimum possible error $e_{\min}$ value $1/I$ expressed in Eq. (5).

Intuitively, a high variance, or uncertainty, in its data defines a system that provides low order or information I about the unknown parameter. This is quantified in (8). It states that a haphazardly growing cell, with a resultingly high spread σ^2 in values of a parameter defining its stage of growth, contains *minimum Fisher information* about that stage of growth. Or, conversely, cell growth obeying small spread σ^2 in the parameter displays maximum Fisher information about the growth.

Cancer cell growth obeys minimum temporal information

A cancer cell characteristically exhibits diminished function, and structural order (dedifferentiation and dysplasia) while multiplying and expanding its population with little if any constraint (with a rate likely to vary with cell type). Thus, a given cancer typically displays a high level of genotypic and phenotypic heterogeneity among its cells. The "tissue" formed by the malignant cells is both morphologically and functionally disordered compared to the tissue of origin This amounts to a degree of structural disorder compared to that of the normal tissue of origin. Typical levels of disorder range from well-differentiated to anaplastic. Furthermore, cancers ofen become progressively less differentiated as they progress [1,2,7,8]. A fundamentally related characteristic of

cancer cells is that they become immortal, so that their proliferation is inappropriate, within both the context of tissue formation and of their age. We discuss this latter phenomenon next.

Lack of a telomere-based 'internal clock'

Telomeres are small sections of DNA at the end of each chromosome that shorten each time the cell undergoes mitosis. In this way the cell can "know" its age and after reaching senescence (ie. undergoing a specific number of proliferation events) the cell undergoes programmed death. However, cancers typically lack this measure of aging. .Thus, a cancer cell's growth is no longer limited by spatial constraints (generated by the environment) or temporal constraints such as age. Thus, a cancer cell possesses minimal temporal information,

$$I = \min . \qquad (9)$$

(We will see below that the situation is exactly the opposite for a functioning cell.)

Scenario of periodic screening for cancer

We next apply these results to an important scenario. We now know that cancers typically evolve through a series of premalignant lesions over many years or even several decades. Cancer can be detected clinically only when it achieves a volume that is either palpable, visible on an x-ray, or causes symptoms such as pain. While this can obviously vary, 1 cc of tumor is usually the minimum detectable mass – but this tumor will contain on the order of 1 billion cells.

An important question is the value of screening in reducing mortality. The clinical outcome of most cancers is dependent not on the size of the primary tumor mass but on the presence of metastases. That is, about 90% of cancer deaths are due to metastases

with the primary tumor having been controlled or eradicated. While the size of the tumor is generally predictive of metastases (i.e. the bigger the tumor the more likely metastases are or will occur), this is by no means a flawless relationship so that small tumors can disseminate and large tumors may not seed tumors in other organs. Here we examine this relationship by assuming that the dissemination of metastases from a primary tumor is directly related to its stage in the carcinogenesis process which we will designate as its "age." However, detection of tumor is based on its size. We ask the question: What is the limitation of screening because of the difference between size and age? This has clinical relevance because it places a lower boundary on the efficacy of current cancer screening strategies.

To approach this problem we assume a patient acquires the first stage of carcinogenesis at age t_0. This defines the theoretical onset time of the cancer. However, the initial observation of a cancer requires it to be greater than some minimal size. It results that any screening method that attempts to measure t_0 must always suffer some random *delay*, giving a generally greater value $t_0 + t$ for the assessed onset time, where t is a random variable. Let this obey some probability law $p(t)$, where $0 \le t \le T$, the latter the fixed total time between routine screenings of the patient for cancer.

A guiding principle underlying the choice of course of such treatment is the general assumption that the older a tumor is the more likely it is for metastases to have developed. growth Hence, the ultimate question to be addressed here is accuracy of the tumor size (which determines its detectability in screening) and its age (which determines probability of metastases) As it turns out, these can be known once we determine the cancer.mass growth law $m(t)$, with m the mass.

The growth law

Using principle (9) results in the prediction [1,2,7,8] that the relative mass $p(t) \equiv m(t)$ of an *in situ* breast cancer (its mass relative to the total breast mass) grows with time t as simply

$$m(t) \equiv p(t) = \left(\frac{\phi + 1}{T}\right)\left(\frac{t}{T}\right)^{\phi}, \tag{10}$$

where T is the time between clinical screenings for cancer, and the exponent $\phi = 1.618...$, the Fibonacci golden mean. This law shows a price paid for having a long time T between screenings: a more spread out law $p(t)$ governing uncertainty in knowledge of the onset time. This, in turn, gives lower information I about t_0 as shown below. The law (10) was clinically confirmed as well. See Fig. 1.

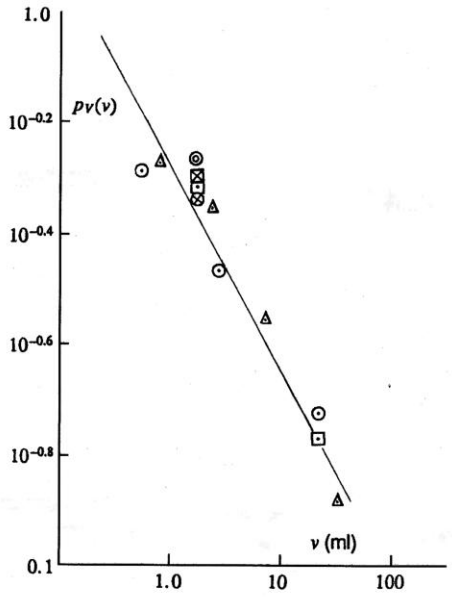

Fig. 1 Comparison of theoretical growth curve (straight line) with clinically observed values (details in [10])

The theoretical (straightline) curve of (10) (on the log-log basis) shows good agreement with clinically observed values of the cancer mass.

Minimized information level

Also, using result (10) in either of Eqs. (6) (with $x = t$ here) gives the information level

$$I = \frac{1}{T^2}\left(\frac{\phi+1}{\phi-1}\right)\phi^2 \qquad (11)$$

about the growth time t_0. Thus, the information level (11) falls off rapidly (quadratically) with the time T between screenings.

At this point the value of ϕ *is unknown*. However, by hypothesis (9) $I =$ *a minimum* value. Hence, with a given screening period T, (11) can only be a minimum through choice of ϕ. Then we merely differentiate (11) with respect to ϕ and set the result equal to zero. This is handily done, giving a quadratic equation in ϕ whose only positive root is $\phi = \frac{1}{2}(1+\sqrt{5}) = 1.618034...$ Interestingly, this is the Fibonacci golden mean, a parameter well known to describe biological growth (although for functional-, rather than the malignant, growth assumed here).

Resulting error in estimated age of cancer

Substituting this number ϕ into (11) and using the resulting I in (5) gives

$$e_{\min} = 0.3003T\,. \qquad (12)$$

Thus, there is a 30% error in the best estimate of the age of a cancer! With yearly examinations ($T = 12$ mo) *this is an error of about 4 months*, rather substantial. Thus, cancer screening is intrinsically limited by the inherent discordance between tumor size

and age. This is consistent with even rigorous screening for breast cancer and lung cancers by yearly mammograms and CAT scans respectively cannot totally eliminate deaths caused by the disease.

This, and the experimentally confirmed result in Fig. 1 further support the information minimization approach (9) for malignant cells. The extensive data on telomere shortening in malignant populations [13] further supports these results.

Programs of therapy

The ultimate aim of therapeutic programs for cancer is to induce catastrophic collapse in the cancer growth. In fact the *power-law* form of the growth Eq. (10) conveniently lends itself to such collapse [14]. One merely replaces the real exponent ϕ with a generally complex one, with the imaginary part linear in a time-dependent therapeutic activity program $a(t)$. Effectively, the imaginary part acts as a phase effect capable of canceling the basic power law growth. Consequently the growth law takes the form $p(t) = A(t/t_0)^{\phi}\cos^2(a(t)\ln(t/t_0))$, where quantity $(a(t)\ln(t/t_0))$ is the phase angle mentioned previously.

The activity program may be clinically imposed, e.g. as chemotherapy of dose $a(t)$, or may occur naturally as a time-dependent immune response $a(t)$. Then, with *constant therapy* $a(t)$ = const. the cancer mass $p(t)$ grows with time t as the power law (10) but modulated in time as a cosine wave. This wave describes the typical relapses and remissions of cancer growth that occur during chemotherapy.

These have a biological basis in the known existence of multiple alleles during cancer growth, which take turns dominating as their more dominant rivals are suppressed by the

therapy. The curve also agrees fairly well with clinical data on breast cancer recurrences following mastectomy. Evidently a constant dose rate is not the answer.

Fortunately, since the theory allows use of a time-varying dose $a(t)$, an optimum such program may be imposed. The aim is to achieve a non-oscillatory, gradual approach to full remission over time. This would effectively convert cancer into a chronic, and manageable, disease. Such a mathematical solution was found. Both activity $a(t)$ and cancer mass $m(t)$ monotonically decrease with time, the dose $a(t)$ as $1/(\ln t)$ and mass remission as $t^{-0.382}$. The latter curve is shown in Fig. 2, for different initial values a_0 of the dose. The theory was partially confirmed in laboratory experimentation with mice bearing a human ovarian cancer xenograft and treated with a platinum-based chemotherapy[15].

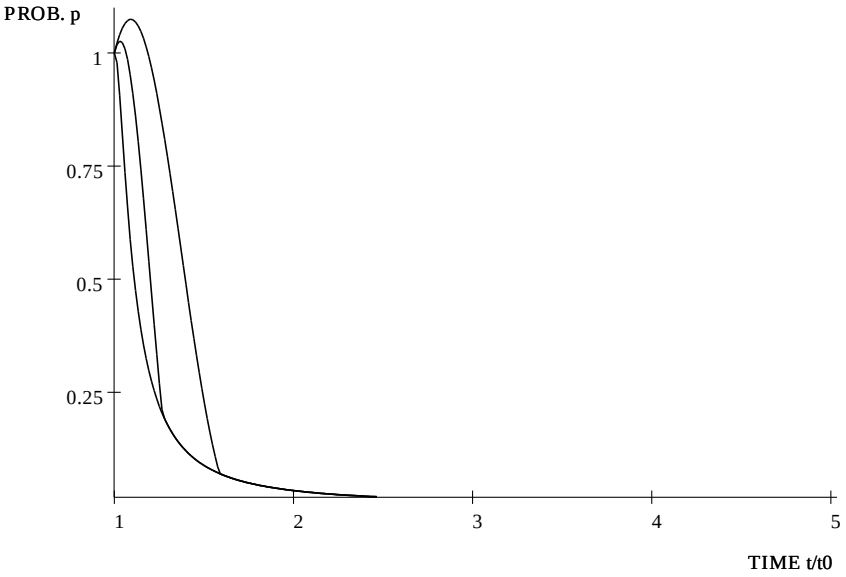

Fig. 2. Cancer mass *p* vs relative time t/t_0 in induced catastrophe. The therapy is turned on at $t = t_0$. Growth histories at different initial therapy levels a_0: the top curve is for a_0 = 3; the middle is for a_0 = 5; and the bottom is for a_0 = 10 or higher, effectively defining the remission curve.

Functional cell growth obeys maximum spatial information

Normal tissue development and organization requires an exchange of information among cells. Much of this information is carried by excreted proteins (such as growth factors) that diffuse through the tissue and bind to specific receptors on the cell surface. The information is then carried (transduced) from the cell membrane to the nucleus via messenger protein. There are three components of information that are potentially available when a growth factor binds a membrane receptor; the

1. presence of the ligand in the environment; the
2. time at which the ligand bound to the receptor; and the
3. location on the cell membrane at which the ligand arrived

Clearly the messenger protein, by its mere presence, carries information that a ligand bound to a receptor on the CM. We propose that these also carry both timely and spatially accurate environmental information.

The information transfer is initiated when a ligand binds to a CM receptor. This, in turn, results in the addition of phosphates to specific amino acids on a messenger protein. (This can also be a sequence of messenger proteins, as in the case of the EGFR signal which is carried by 3 different pathways, with one consisting of sequential phosphorylation of RAS-RAF-MEK-ERK). Here we focus on information that is specifically spatio-temporal, i.e. about the initial time and position at which this cascade of phosphorylation began in response to ligand binding of EGFR.

Thus, in contrast to cancerous cells, we postulate that *functioning cells* have a *maximum level* of structural order, enabling them to develop and function as differentiated cells. Then, intuitively, if (as above) dysfunctional cancer cells operate out

of a state of minimum Fisher information, the opposite scenario of highly ordered, functioning cells should be in states of *maximum information*,

$$I = \max . \qquad (13)$$

We first concentration attention upon the information about the lateral *position* x_0 of a typical messenger protein as it strikes the nuclear membrane (the temporal information is considered later). Here the random variable x and the size of the protein define the uncertainty in knowledge of x_0. Once this is calculated, the corresponding temporal information will follow readily.

An interesting question we address is, why are there 4 proteins in the EGFR sequence? Why not 6 or 8? Also, why does the cell go to the trouble of passing on information from one constituent EGFR protein to the other when it seems it would be easier and more efficient to just have one protein messenger carrier?

Information capacity requirement of functional growth

We propose that the hypothesis of maximum information requires optimal transfer of information from CM to NM via messenger proteins. That is, the channel of information achieves its full capacity in transmitting the information. (Note: this is not the usual Shannon information channel capacity [12] since we are using Fisher information instead.) The information is calculated on the basis of a recent paper [16], summarized next.

Directed protein motion

The CM-NM information transfer will be maximal only if the proteins obey *directed motion* toward the nucleus. The alternative - motion purely by *diffusion* - would instead randomly disperse the proteins and the information they carry throughout the cytoplasm.

Consider a cohort of proteins that simultaneously leave the CM. Since the distance each protein travels through the cytoplasm is the order of 1000 times its diameter, if each traveled purely by diffusion the resulting motion would be extremely slow, and with highly variable transit times at the NM. Furthermore, since the phosphorylated messenger proteins are subject to inactivation by phosphorylases within the cytoplasm, their dispersal throughout the cytosol would result in significant information loss. Thus, movement of messenger proteins by random walk would result in slow and unreliable information flow to the NM, which is contrary to our hypothesis (13). In fact we propose that messenger protein movement is not purely diffusive but, rather, dominated by an intra-cytoplasmic electric field $E(r)$ originating at the positively charged nuclear membrane. This type of motion turns out to obey hypothesis (13).

Critical role of phosphorylation

Typically, information is passed from one messenger to another through sequential phosphorylation of specific amino acids in the protein. Extensive research on this information transfer has entirely focused on the changes in protein structure that result from phosphorylation. However, we propose that a critical additional result of phosphorylation is that it adds net negative charges to the protein. Hence the latter is attracted toward the positively charged nucleus, obeying directed motion rather than undirected, random diffusion.

We frame the information hypothesis as a mathematical principle of cell development, asking: Under the charge-directed motion that is proposed, *what protein pathway accomplishes a maximum information transfer rate from CM to NM? And what is the value of this information?*

Here the information is that contained in the arrival position y on the NM of a typical messenger protein, where the ideal position is x_0. The ideal position is defined purely by the shielded Coulomb law previously considered. The position x_0 is 'ideal' in that it follows some program of optimum cell growth with time. Thus the total excursion of the protein is

$$y = x_0 + x, \tag{14}$$

with x random according to some law with standard deviation $\sigma(x)$.

It is shown in Appendix A that the information I about achieving the ideal messenger position x_0 on the NM obeys Eq. (A10) of the Appendix,

$$I \equiv I(x_0) = \left(\frac{A}{2D}\right)F, where\ D = \sigma^2(x)/2t_a = 5\times 10^{-11} m^2/s \tag{15}$$

is the diffusion constant in cytoplasm, $A \approx \pi a^2$ is the cross sectional area of the nucleus, and F is the arrival flux rate. Notation $I(x_0)$ signifies specifically the information about the ideal position x_0 on the NM. The information $I(t_0)$ about the ideal transit time t_0 will be found later. The spatial information (15) thereby decreases with increasing diffusion D, which makes sense, and increases with both the nuclear area A and flux rate F. These are also intuitively correct trends. Eq. (15) also shows that, for given values of A and D, if F is maximized so is I. We first observe how F varies with values of the Debye-Huckle parameter k_0;, and then compute I from this.

Particle flux F curve

Using the constants in Table 1 of Appendix A and Eqs. (14), (17), in Fig. 3 the flux F by is plotted vs. values of k_0.

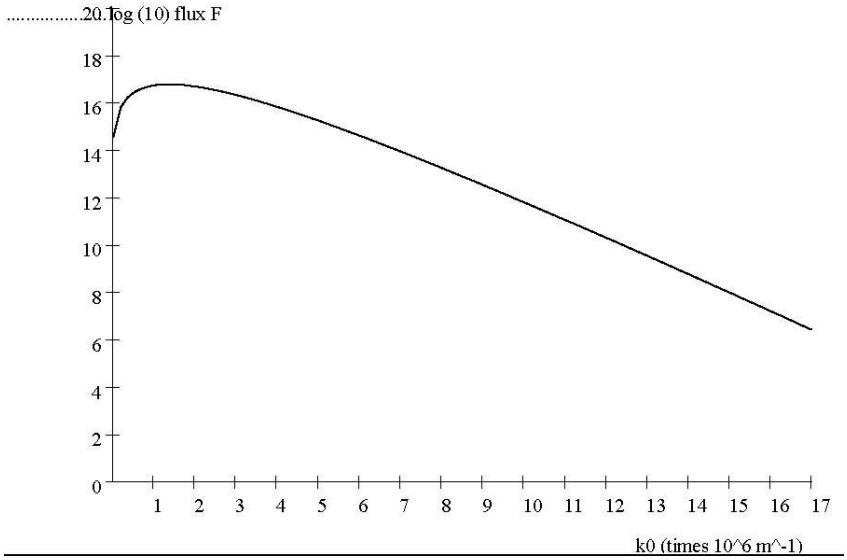

Fig. 3. Flux *F* (proteins/area/ time) at the NM as a function of k_0

The curve for *F* shows a strong decrease (by orders of magnitude) once k_0 is greater than roughly $5.0\times10^{6}\,\mathrm{m}^{-1}$.

Of key importance in Fig. 3 is that *F* goes smoothly to zero at both small k_0 and large k_0 . This implies a definite *in-between value* $k_0 \equiv k_{\max}$ for which *F* = max.$\equiv F_{\max}$. From the figure this

$$F_{\max} \approx 10^{17},\ for\ k_0 = (1.0, 1.4, 1.7\ or\ 2.0)\times10^{6}\,m^{-1},\ with\ k_0 = k_{\max} \approx 1.7\times10^{6}\,m^{-1} \quad (16)$$

central to the range. These represent the presence of either 1,2,3 or 4 types of protein (see Appendix S2 of [16] and Conclusions section).

Resulting information $I(x_0)$

Our overall criterion of cell development is that information $I(x_0) = \max$. Using $F_{\max}$ from (16), D from Eqs. (15), and by $A \approx \pi a^2 = 28.3\mu m^2$ from Table 1, Eqs. (15) gives

$$I(x_0) \equiv I_{\max} = \left(\frac{2.83\times10^{-11} m^2}{10^{-10} m^2/s}\right) 10^{17} m^{-2} s^{-1} = 2.83\times10^{4}\,\mu m^{-2}. \quad (17)$$

Then from Eq. (5) the corresponding rms error in position is

$$e_{\min} = \frac{1}{\sqrt{I_{\max}}} = 5.94 \times 10^{-3}\,\mu m\,. \qquad (18)$$

Relative to the NM size $2a = 6\mu m$, this is an error of 0.1%, quite small. Even more remarkably, this small error is attained every 0.01 sec by a protein cloud (or 'scaffold,' see below).

Predicted size of messenger protein

The figure (18) of $e_{\min} = 5.94nm$ represents the total uncertainty in protein position x_0 at the NM on the basis of maximum information. The calculation took into account protein density and, hence, *protein size*. Of course, at present it is not known how the nucleus estimates the ideal position x_0 of a protein. However, it must depend upon (at least) both (a) observed positions y_n [see Eqs. (14)] and (b) size values d_m of the protein. These may be regarded as random samples from two probability laws: (a) on the uncertainty x of the center of gravity of the protein; and (b) the uncertainty d in the size of the protein, arising out of random protein foldings en route. Let both random variables x and d be Gaussian distributed, the latter with an rms uncertainty of value d_p. This also represents the effective size of the protein. Since the processes governing x and d are statistically independent, the total information $I_{\max}$ is then the sum [10,11,12] of the two.

It results that the total information acquired by the NM from each protein detection event has a two-fold contribution

$$I(x_0) = \frac{1}{{\sigma_X}^2} + \frac{1}{{d_P}^2} = \max. \equiv I_{\max} = 2.83 \times 10^4\,\mu m^{-2}, \qquad (19)$$

the latter from (17).

But to find the protein size d_p we need another relation: There are two independent and additive contributions, x and d, to the positional error. Then by (18) its variance ${e_{\min}}^2$ obeys

$$ {e_{\min}}^2 = {\sigma_X}^2 + {d_P}^2 = 5.94 \times 10^{-3} \mu m^2 . \qquad (20) $$

We may regard this as a Lagrange constraint on the extremum condition (19). The two together give a unique solution for the unknowns d_P and σ_X,

$$ d_P = \sigma_X \approx 4nm. \qquad (21) $$

As a check on this solution, the extension of an EGFR protein is about $3nm$, close to this value. It follows that, on the basis of maximum information and conservation of resource, *the largest permitted messenger protein is about the size of the EGFR.*

Required processing task

The nucleus can process detected protein positions no more rapidly than the traversal time $t_a = 0.01s$ for all proteins . The quality of each such output estimate x_0 then grows with the net number N_a of detected proteins per traversal time t_a. How large is N_a?

The arrival flux of proteins about the position x_0 on the NM was found at (16) to be $F_{\max} \approx 10^{17}\ proteins/m^2 s = 10^5\ proteins/\mu m^2 s$. Multiplying this by the NM area of about $\pi a^2 = 28 \mu m^2$ gives the total arrival rate, of about 2,800,000 $proteins/s$. Or, the nucleus processes $N_a = 28{,}000$ arrival locations every traversal time $t_a = 0.01s$. This is a challenging problem of data reduction. In summary, evolution has developed a very accurate ($e_{\min} = 5.94nm$), fast (28,000 locations processed per 0.01 s) system for accomplishing the spatial aspect of the overall problem of cell development. There are also temporal uncertainties, as next.

Temporal information level $I(t_0)$

The information $I(x_0)$ about the ideal transverse position x_0 on the NM was found at (17). It is also important to know the information $I(t_0)$ about the ideal *time* $t_0 \approx t_a$ of arrival at the NM. This can be defined by the use of (8) for a known rms fluctuation in time $\sigma(t_a)$. This gives rise to a fluctuation $\Delta x \equiv v\sigma(t_a)$ in path length at apparent arrival at the NM, for a mean protein velocity over the trajectory of $v = (r_0 - a)/t_a$. On the other hand, by geometry the rms angular displacement to the side obeys both $\Delta x/\sigma(x)$ and $\sigma(x)/(r_0 - a)$. Setting these equal, and by the definition of D in (15)

$$\sigma(t_a) = \frac{2Dt_a^{\,2}}{(r_0 - a)^2} = 2.5\times 10^{-3} s. \qquad (22)$$

Compared with the mean traversal time $t_a = 0.01s$ this is a relative error of 0.25 or 25%.

Finally, the information level (8) in each such traversal time is

$$I(t_0) = 1/\sigma^2(t_a) = 0.16\times 10^6 s^{-2}. \qquad (23)$$

A corroborating scaffolding effect

The prediction (16) that either 1 (say RAS), or 2 (say RAS and RAF), or 3 (RAS, RAF and MEK), or 4 (RAS, RAF, MEK and ERK) types of protein travel together is verified by a known 'scaffolding' effect. Thus, although the MAPK pathway is typically portrayed as a sequence of interactions among well mixed proteins, it appears that efficient phosphorylation of one protein by the kinase that precedes it in the sequence is achieved by scaffolding proteins that bind RAF, MEK and ERK together into a large molecular complex. Thus, during much of the transit from the CM to the NM, these

proteins appear to travel together. This can be in a cloud-like or, perhaps, mutually scaffolded association.

Protein Correlations

Our picture of a pulsed cloud of like proteins traveling together toward the nucleus is substantiated by studies of *protein correlation* in organelles of the cell. Thus [27] "Proteins in eukaryotic cells are organized according to their functions within a dynamic network of membranes. Localization is therefore paramount in ... processes occurring in subcellular compartments." A correlation in time accompanies such spatial localization, as shown by elution time ion sequencing [28]. MEK and ERK2 proteins, in particular, were experimentally found to correlate [29].

Such correlation also permits a necessary cross-talk to occur between the different limbs of a protein pathway. A major contributor to cross-talk is the phosphorylation of a protein in one pathway by a protein from another pathway. This causes the activity in the 1st pathway to increase the activity of the 2^{nd}.

Narrow Mean Width of Messenger Protein Pulse

Finally, the very brief transit time $t_a \approx 0.01$s does not permit a substantial random component to the spatial motion. The diffusion formula (15) gives a root-mean square diffusion distance σ=1 micron. Hence, were the motion undirected, in our *directed* transit time $t_a \approx 0.01$s the protein scaffold would move but 1 micron. This is in any direction, e.g. toward the nucleus (also see next subsection) but also sideways. The latter defines a minimum width of the protein scaffold emanating from one CM receptor. This is $\approx 2\times(1 micron) = 2 micron$; i.e about 20% of the width $2r_0 = 2\times 5 = 10\, micron$ of the cell. With multiple adjacent protein sources the pulse would be wider yet, so the 20%

value represents a minimum scaffolding width.

Indicators of whether a cell obeys maximum, or minimum, information

Cells have been postulated to be in states of extreme information during their growth and regulation. The information extremum is a maximum (13) in functioning cells; or a minimum (9) in cancer cells. One indicator of which respective alternative will hold appears to be whether the fundamental unit of growth is a multicellular organism or a single cell. Another indicator is that, in *cancer*, the EGFR pathway is commonly upregulated. That is, at least one component of the pathway is upregulated in 60 to 80% of cancers. This is reasonable since this pathway controls proliferation and survival. But the specific protein to be upregulated is something that has not been addressed: Mutations in EGFR, RAS, and RAF are commonly observed in cancer and they are regarded as "oncogenes". However, mutations in MEK and ERK are *never* seen in cancer. Thus, the presence or absence of MEK and ERK seems to have importance as to whether the cell is attaining maximum, or minimum, information. The nature and degree of the importance currently unknown.

Summary

It was shown that mathematically requiring cell growth to obey a principle of *extreme information* gives rise to long-known laws of biological growth, such as the Lotka-Volterra equations [2],[3] and the quarter-integer power laws of allometry [4],[5]. It also gives rise to clinically confirmed predictions of *in situ* cancer growth (10), and of messenger protein pathway flux values (16) and trajectories (A6) (in Appendix A) in normal cells. For example, the time t-dependent growth law (10) for *in situ cancer mass* $m(t)$ results from a requirement of *minimum temporal* information. This is a simple

power law $m(t) = (\phi + 1)T^{-1}(t/T)^{\phi}$, where T is the time between routine screenings for the existence of cancer in the patient, and $\phi = 1.618...,$ the Fibonacci golden mean. The minimized level of information level so obtained is given by (11) as $I \approx 11.0902T^{-2}$. This, in turn, determines the minimum possible root mean-square error in estimated onset time of the cancer at (12) as $e_{\min} \approx 0.3003T$.

Alternatively, assuming *maximum spatial information* transmittance to the NM defines the protein trajectories in normal cells. The proteins are modeled as traveling from effectively a point x_0 on a CM receptor toward a corresponding ideal position x_0 the NM. The proteins travel as a scaffold whose minimum width is $\approx 2 \times (1 micron) = 2 micron;$ i.e about 20% of the width $2r_0 = 2 \times 5 = 10\, micron$ of the cell. The motion is mainly directed, rather than diffusive, and arises out of a shielded Coulomb force field exerted by positive charge on the NM. Using classical mechanics, the resulting levels of protein particle flux F at the NM are found for various values of the Debye-Huckel parameter k_0. This is plotted in Fig. 3 (after being derived at Eqs. (A6)-(A9) in Appendix A). Also, the spatial information $I(x_0)$ is found to be proportional to this flux F at Eq. (15). In conformity with our thesis of maximized information, the maximum value of $I \equiv I(x_0)$ is computed at Eq. (17) as $2.83 \times 10^4\, \mu m^{-2}$. In turn, this predicts the rms error in the estimated initial position of the messenger on the CM to be value (18) of $e_{\min} = 5.94 \times 10^{-3}\, \mu m$. Relative to the NM size of $2a = 3 \mu m$ (Table 1), this is about a 0.1% error, very small.

This figure also predicts a net protein pathway consisting of not more than 3-4 constituents, which is obeyed by the EFGR pathway. In agreement, the latter protein is also of a size found following Eq. (21).

Also, *arrival time*s at the NM are found to occur with a level of accuracy (22) given by $e_{\min} = 2.5 \times 10^{-3} s$. This is comparable to the accuracy (18) of $5.94 \times 10^{-3} \mu m$ for positions. The implication of such low errors in space and time is that these aspects of cell development are highly developed, lending themselves to effective processing by a sophisticated program of processing by the nucleus. This program has the task of processing $N_a = 28{,}000$ arrival locations every traversal time $t_a = 0.01 s$ (see material between Eqs. (21) and (22)). However, such a high flux rate has the benefit of allowing very effective processing of information, e.g. highly accurate averaging, and is consistent with an efficiently operating system.

As we saw, there is overall good agreement between theory and experiment in the preceding work. This lends plausibility to the working hypothesis that living cells, whether functional or cancerous, obey a principle of extreme Fisher information.

As was discussed, the presence or absence of MEK and ERK pathways seems to have strong bearing on whether the information state of the cell is at a maximum or a minimum.

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Discussion

The idea of seeking a cross-disciplinary variational principle that could predict both physical *and biological* effects was proposed some 40 years ago by the population biologists Crow and Kimura [30] and, even before them, by Delbruck [32]. More

recently, the physicist E.T. Jaynes [31] proposed the use of a principle of maximum entropy for deriving all statistical laws of nature. As indicated here, this goal is now met by the use of Fisher information and the Fisher-based EPI principle [2-5,7]. Other possible *information-based* candidates [33] have been proposed, but not yet shown to meet the broad requirement. Apparently the laws of nature are laws of *order* [9]; and therefore, by the correspondence (4) between information I and order R, are defined by extreme levels of Fisher information.

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Appendix A

Newtonian model for protein trajectories

The following model is defined and analyzed in depth in [12]. Here we only need define its main features.:

(1) The messenger proteins are free to diffuse [17] in the cytoplasm between the CM and NM. Also, the major time expenditure of the trajectory of a messenger protein is *while in the cell cytoplasm*, as compared with much briefer times in microtubules and vesicles. The assumption of free diffusion is consistent with published observations and is in distinction to movement of recently synthesized proteins via microtubules and vesicles.

(2) Although the nucleus can be located eccentrically within the cell, we assume the NM and CM to be concentric spheres, of respective radii $r = a$, $r = r_0$, as in Fig. 4.

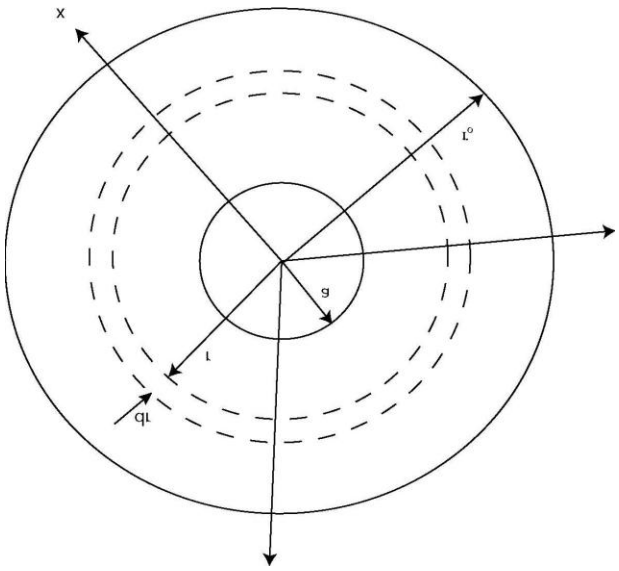

Fig. 4: Spherical model of cell

(3) The cell is that of a typical human organ, with the parameters[2] in Table 1.

(4) The valence z (or number of free electrons) of each protein is allowed to be some function $z(t)$ of the time, for example

$$z(t)=z_0+6p_0t, \text{ with } z_0=2, \text{ where } p_0=1/sec = 3600/hr \qquad \text{(A1)}$$

is an average phosphorylation rate [18]. The factor 6 arises since phosphorylations tend to occur sporadically in time, each adding about 3 phosphates, or $3z_0 = 6$ negative charges,

CM radius r_0	5 micron
NM radius a	3 micron (Note: $a/r_0 \approx 60\%$ for mammals)
Cytoplasm dielectric const.	$\varepsilon = 60\varepsilon_0 = 7.1\times10^{-10}$ F/m

Thermal energy k_BT	4.14×10^{-21} J
Positive charge on nucleus Q_{NM}	$\approx +0.3\times10^{-11}C$ (Coulomb)
Viscosity η of cytoplasm	$\approx 10^{-3}$ (water)
Reynolds number R_0	$462\times(0.4\,\text{nm})$

Table 1. Parameters of the cell

to the messenger protein. We assume that *initially*, at/near the CM, the protein (e.g., mammalian thioredoxin) uptakes $z_0 = 2$ electron charges [19].

(5) Friction with the cytoplasm exerts a drag effect on each protein, where the drag coefficient *K* is a function [17]

$$K = 6\pi\eta R_0 z^{1/3} \approx 4\times10^{-9} z^{1/3} \equiv \alpha z^{1/3}. \qquad \text{(A2)}$$

This assumes each protein to consist of a chain of 462 amino acids, typical of a human protein. The resulting drag force is

$$F_D = -K\frac{dr}{dt}, \qquad \text{(A3)}$$

with *dr/dt* the velocity.

Theoretical field strength values within cytoplasm

A major component of the model is the presence of an intracytoplasmic electric field. The field is due to *negatively charged* proteins in the cytoplasm and the *positive charge* Q_{NM} on the NM. The field causes each protein, of negative charge *z(t)q*, to be attracted toward the nucleus and shielded by other proteins (see below). Typically, environmental information is passed through the cell wall to messenger proteins through phosphorylation. A messenger protein is "activated" by addition of a phosphate to a specific amino acid by a kinase that is typically a messenger protein more proximal in the

information pathway. Each phosphorylation of the protein typically converts it to a specific kinase acting on the next protein in the sequence. Interestingly, phosphorylation also adds *negative charge* to the protein. In turn, such negative charge allows the protein to interact with, and be accelerated by, the intracytoplasmic electric field (found next).

Realistically [20] a messenger protein's force of attraction toward the NM is partially screened by the other proteins and ions that travel with it. With ρ the total number/volume of these charged particles in the cytoplasm, the result is a *screened Coulomb law* of attraction to the nucleus. This obeys

$$E(r) = \left(\frac{Q_{NM}}{4\pi\varepsilon r^2} \right) \times \left[\left(\frac{1+k_0 r}{1+k_0 a} \right) e^{-k_0 (r-a)} \right], \; k_0 = \sqrt{\rho q^2 (\varepsilon k_B T)^{-1}}, \qquad \text{(A4)}$$

$$\leftarrow \text{Coul.} \rightarrow \; \leftarrow \text{Screening term} \rightarrow$$

where *E(r)* is the force/charge or field strength at position *r*.

Debye-Huckel screening parameter

By (12), the net force is the product of a Coulomb $1/r^2$ law with a screening term whose strength is governed by k_0, the Debye-Huckel screening parameter. Its reciprocal is the screening length l_0.

Eq. (12) shows that k_0 depends upon the total density ρ of proteins within the cell. In turn, the latter increases with the number of protein types that are within the cell. Typical messenger proteins are RAS, RAF, MEK and ERK. The value of k_0 then depends upon the number of protein types that are within the cell. Values of k_0 are found on this basis (in Appendix S2 of [16]) for the simultaneous presence of either: 1 (say RAS), or 2 (say RAS and RAF), or 3 (RAS, RAF and MEK), 4 (RAS, RAF, MEK and ERK), or 9, 16, 36, 100, 400, or all possible protein classes within the cell. These are the respective

values

$$k_0 = 1.0, 1.4, 1.7, 2.0, 3.0, 4.0, 6.0, 10, 20, \text{ and } 141.0\times 10^6 \text{m}^{-1}. \quad \text{(A5)}$$

Resulting theoretical field strength curves $E(r)$

The corresponding *E(r)* curves were calculated in [16], showing the degree to which the unscreened field is forced down by the screening term in (A4) through the Debye parameter k_0 . As k_0 increases there is an increase in the number of protein classes, and hence number of proteins, that simultaneously move through the cytoplasm. These proteins move as a distinct cloud or scaffold through the cytoplasm.

Agreement of theory with experiment

The curve of $E(r)$ for the value of $k_0 = 1.7 \times 10^6$ gives $E(r)$ values that agree fairly well with measured field values [21]. By (A5), this holds for a scenario where but *three types of protein* are moving together within the cytoplasm. With more protein types present, and therefore higher , by the 2nd Eq. (A4) parameter k_0 increases, and these give progressively lower curves $E(r)$. The lowest, for $k_0 = 141.0\times 10^6 \text{ m}^{-1}$, holds when *all possible* protein types are moving together toward the nucleus. The resulting $E(r)$ values show negligible attraction, and very low information transfer, to the nucleus.

Negligible charge screening by inorganic ions

A novel and major assumption of the preceding model is that the Coulomb shielding of the NM is principally due to organic ions, in particular a cloud of proteins. This assumes the absence of possible contributions due to mobile *inorganic* ions in the cytoplasm, such as K^+ and Cl_2. Indeed, including these in the Debye-Huckel effect would give an $E(r)$ field extending only distances l_0 = 1 to 2 nm from the membrane. These l_0 correspond to values $k_0 \approx 10^9 \text{ m}^{-1}$, giving effectively negligible field values. The proteins

would experience virtually zero force of attraction to the NM, negating our thesis that their motion there is principally due to Coulomb attraction.

We propose that, in fact, these inorganic ions do not effectively attenuate the E field. Instead the ions freely pass through the pores of the NM, and with a motion fast enough to not effectively shield the NM charge. This relies on the following effects. For an ion to speedily get through an NM pore, it should be narrower in diameter than the pore diameter. A Cl^- ion has a diameter of 181 pm (picometer), K^+ ion of 138 pm [22]. By comparison, average pore diameter in NM= 90 nm [23]. This is about 500 times that of the Cl^- ion, allowing multiple ions to simultaneously pass through the pore. Finally, the relaxation time to thermal equilibrium in liver cells measured experimentally ranges from about 0.1 to 1 microseconds [24]. By comparison, RNA molecules, which are much larger than the ions but do possess charge, pass through 1.5 nm wide pores of carbon nanotube membranes in 10 ns (nanosecond) [25]. This is one thousandth, or less, of the above equilibrium time for liver cells. The result is effectively no Coulomb shielding by the ions.

Analysis of protein trajectories

Using Newton's 2nd law, the screened Coulomb force law (A4), a drag force linear in the particle velocity and the usual 'terminal velocity' approximation for high-drag media, the trajectory of a typical protein obeys [16]

$$t \equiv t(r) = Cz_0^{-2/3}\left[e^{1+k_0 r_0}(k_0 r_0 - 2) - e^{1+k_0 r}(k_0 r - 2) + Ei(1+k_0 r_0) - Ei(1+k_0 r)\right], \quad \text{(A6)}$$

$$\text{with} \quad C = \frac{4\pi\alpha\varepsilon}{eqk_0^{\,3}Q_{NM}}\left(\frac{1+k_0 a}{\exp(k_0 a)}\right). \quad \text{(A7)}$$

Also, *Ei* is the exponential integral function.

Solution (A6) indicates that the point $k_0 = 1.7\times10^6$ corresponds to a transit time $t_a \approx 0.01$s. This will be found to describe as well the optimum scenario from the standpoint of information transmission to the NM. First, a preliminary quantity is needed.

Particle flux F

A basic quantity defining particle transport is the particle flux F. This is the number N of protein particles traversing from CM to NM per unit area A of the NM per unit time t,

$$F = \frac{dN/dt}{A} \approx \frac{N}{t_a A} = \frac{N}{t_a \pi a^2} \tag{A8}$$

This assumes dN/dt is approximately constant over a time interval $(0, t_a)$. Also, A is the cross sectional area of the spherical NM, approximately value πa^2. For later use, the flux may also be expressed in terms of the particle density ρ as

$$F \equiv \rho v = \rho(r_0 - a)/t_a . \tag{A9}$$

This is handy since it allows the flux to be computed from quantities that have previously been quantified using Table 1, the value $t \equiv t(a) \equiv t_a$ in Eq. (A6), and Appendix S2 of [16]. It is plotted as Fig.2 in the text of this paper.

Linear relation between information I and protein flux F at NM

The overall hypothesis is that, for this functional cell, the information is to be a maximum. But, information about what parameter?

Let N proteins leave essentially one point on the CM and move to the NM during the transit time t_a. Denote as x_0 the ideal position on the NM of the nth such protein. The ideal position is defined purely by the shielded Coulomb law previously considered. The

position x_0 is 'ideal' in that it follows some program of optimum cell growth with time. However, realistically, the protein's position on the NM suffers from an added random perturbation due to *undirected diffusion* by the cytoplasmic medium through which it travels. This degrades its motion, causing it to suffer a random sideways excursion x_n, $n=1,\ldots,N$. Therefore the total excursion of the protein is

$$y_n = x_0 + x_n, \qquad \text{(A10)}$$

with x random according to some law $p(x)$. This probability law then, defines a level of Fisher information [Eq. (6) of text] about the ideal position x_0 of the nth protein. *Our hypothesis is that this information level is to be a maximum value.*

How may it be computed? Assume that the probability law on the random x_n at least approximates any member of the family of *exponential distributions*, (defined above Eq. (8) of the text) with variance σ^2. As was discussed, the family has widespread application. Conveniently, these all give information $I = 1/\sigma^2$ as the value in any one experimental position y_n on the NM. Does I relate to F?

Let the N positions x_n be processed, in some presently unknown way, by the NM so as to estimate the ideal position x_0. By likelihood theory [10-12], the maximum likelihood estimate of x_0 is the arithmetic mean of the total excursions y_n, and the resulting error in a reading obeys $e^2 = \sigma^2 / N$. Also, by the additivity of the information, the N independent readings give a total information

$$I = N / \sigma^2. \qquad \text{(A11)}$$

The well-known diffusion formula for random walk [26] expresses

$$\sigma^2 = 2Dt_a, \text{ with constant } D = 5\times10^{-11} m^2/s \qquad \text{(A12)}$$

in cytoplasm. Thus, σ is the standard deviation, or rms fluctuation, due to the diffusion of any *one protein* during the transit time t_a through the cytoplasm.

Note: It is important to distinguish between the preceding rms fluctuation σ of one protein and the mean fluctuation of the *estimated value* of the *ideal* protein position on the NM. These are not the same. The latter estimate results from optimally processing *all detected protein positions* for their theoretical mean. The resulting rms error $e_{\min}$ is therefore much smaller than σ. It is computed below.

From (A12),

$$2D\frac{I}{A} = \frac{\sigma^2}{t_a}\frac{I}{A} = \frac{\sigma^2}{t_a}\left(\frac{N}{\sigma^2}\right)\frac{1}{A} = \frac{N}{t_a A} = F\,. \qquad \text{(A13)}$$

The second equality is by (A11), and the last is by definition (A8). Thus, from the outer equality,

$$I = \left(\frac{A}{2D}\right)F. \qquad \text{(A14)}$$

This relation is discussed and used in the main text.

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