Artículo de Reflexión ▪

Uses of entropy in medical research

Usos de la entropía en la investigación médica

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SUMMARY

Entropy is a basic concept of physics, with analogues in communication theory and other fields. We review applications of entropy in medical research, under three headings of increasing scientific profundity. First, we consider the use of entropy as a summary statistic to measure the diversity of ecological and other systems. We emphasize the exponential of the Shannon entropy as a dispersion index, illustrated in sample size determination for pupal surveys of the dengue vector mosquito Aedes aegypti. Secondly, we review maximum entropy as a method of statistical modelling, illustrated by spatial analysis of the malaria vector mosquito Anopheles nuñeztovari. Finally, we review the postulate of Extreme Physical Information (EPI), which elegantly yields many key laws of physics, including general relativity. EPI has been applied to some biological problems, such as predicting rates of cancer growth, and we suggest that it may have fruitful applications in immunology.

KEY WORDS

Entropy
Information
Malaria

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Dengue
Biomedical research

RESUMEN

La entropía es un concepto básico en la física, con conceptos análogos en la teoría de las comunicaciones y en otros campos. Revisamos las aplicaciones de la entropía en la investigación médica, bajo tres lineamientos de creciente profundidad científica. Primero, consideramos el uso de la entropía como una herramienta estadística para medir la diversidad ecológica y de otros sistemas. Se enfatiza el carácter exponencial de la entropía de Shannon como un índice de dispersión, el cual es ilustrado por su uso en las encuestas de pupas del mosquito vector del dengue Aedes aegypti para la estimación de tamaños de muestra. Segundo, revisamos la entropía máxima como un método de modelación estadística. Se ilustra mediante el análisis espacial del mosquito vector de malaria Anopheles nuñeztovari. Finalmente, revisamos el postulado Información Física Extrema (EPI), el cual soporta varias leyes físicas, incluyendo la de la relatividad. EPI ha sido aplicado a algunos problemas biológicos, como por ejemplo para predecir tasas de crecimiento de cáncer. Sugerimos que puede tener aplicaciones útiles en inmunología.

PALABRAS CLAVE

Entropía
Información
Malaria
Dengue
Investigación médica

1. INTRODUCTION

The word entropy derives from the Greek *entropía*, meaning a turn inwards, a sense it retains in the ophthalmological term 'entropion'. In common use, entropy currently implies decay; a kind of inevitable ageing. Some philosophers and artists see it as a key concept for our current society, in which the control of information is vital, but inevitably imperfect (1,2). The art critic Robert Hughes said of Andy Warhol: "His ideal society has crystallized around him and learned to love his entropy" (3).

In science, the term 'entropy' was introduced by Clausius in 1865, meaning a ratio of heat to temperature, denoted S. According to the second law of thermodynamics, heat flows spontaneously from hot bodies to cold ones, and not the reverse, and this implies that S always increases. In 1877, Boltzmann used a molecular approach to derive an equivalent form, which depends on the number W of microscopic states consistent with the macroscopic state of a system: $S = k\log(W)$, where k is Boltzmann's constant. This can be interpreted as a measure of disorder in the system, or ignorance of it.

In the twentieth century the concept of entropy was used as a measure of information, which is currently applied in telecommunications and other information technologies (4). Recently a theory has been derived which encompasses these concepts as special cases of Fisher information (5).

In the current paper we describe uses of entropy in medical research. We start with its use as a simple summary statistic of disorder in a series of categories, and proceed to the postulate of Extreme Physical Information (EPI) as a basic scientific principle.

2. ENTROPY AS A MEASURE OF COMPLEXITY OF ECOLOGICAL SYSTEMS

In ecology, entropy is used under the name of Shannon-Wiener index to measure diversity, or niche breadth (6), and has the following form:

$$H' = -\Sigma\, p \log(p)$$

The symbol Σ means a sum of the various values of p. For example, to measure species diversity, each p is the proportion of individuals in each species. The alternative Brillouin index has a different form, but Stirling's formula can be used to show that it is numerically similar to H´, especially for large sample sizes(7). Here we have included a negative sign in the definition of H´. Without this, H´ becomes a measure of information, which can be defined as the negative of entropy 'negentropy'(8). Similar applications have been made to antigenic and genetic diversity (9-11).

The index H´ is mathematically identical to the Shannon entropy (12). In communication theory, each p represents the relative frequency of a symbol, for example a letter of the alphabet. Whether in ecology or communication theory, the entropy is greater if the distribution is more uniform. The base of logarithms determines the units of H´. For base 2, the units are bits (abbreviation of 'binary digit'). For base 10, the units are decits, and for base e they are nats (13).

2.1 Application to sampling of Aedes breeding sites

Dengue is a viral illness with 50-100 million cases each year, of whom 0,25-0,5 million have the severe form, dengue haemorrhagic fever (14). Given the current lack of a vaccine, the only preventive method is control of the vectors, which are mosquitoes of the genus A*edes*, principally A*edes aegypti*. As breeding sites, these mosquitoes use a wide variety of water-holding containers. To make control more efficient, it is possible to think in terms of 'key' container types, which contain a majority of immature forms (larvae and pupae) (15). These key types would be the priorities for control efforts.

As part of an international project to develop methods for A*edes* control (16), there arose a need for a method for determining sample size to confidently identify key container types. In statistical terms, this task was more complicated than most sample size calculations. It deals not with a single parameter (such as a mean or proportion) but, rather, a distribution over an indefinite number of container types. Moreover, the method had to be sufficiently simple for use by control personnel, who do not necessarily have mathematical or statistical training.

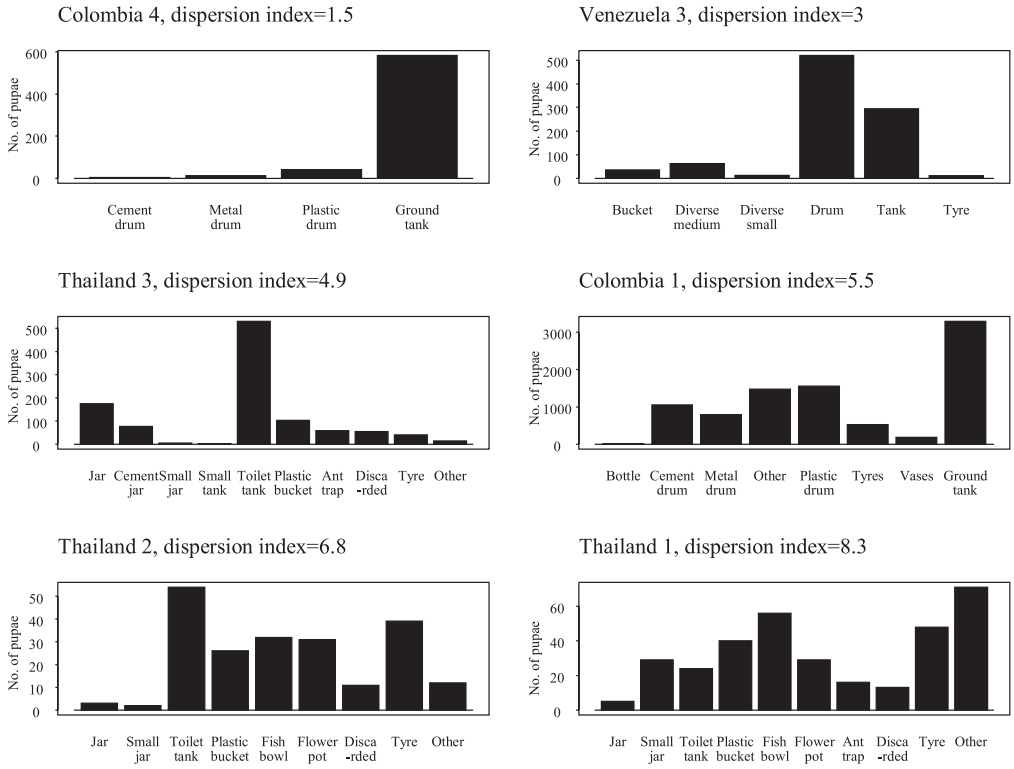
It was expected that, where pupae were more concentrated in fewer container types, the sample size would be smaller. The use of entropy (the Shannon-Wiener index, H) was investigated for measuring the concentration of pupae, and for predicting sample size. More specifically, the exponential of H´ was used; conventionally denoted N_1. The use of the exponential removes the dependency on the base of logarithms, and yields a dispersion index with the following simple characteristics:

- The dispersion index N_1 is larger when the pupae are distributed more uniformly between the container types.
- The maximum value of N_1 equals the number of container types, and is reached when the same proportion of pupae are found in each type. For example, with four container types, an even distribution would have four proportions of 0,25, and N_1 would be $10^{-4 \times \log_{10}(4)/4} = 4$. Any other distribution gives a lower value. For example, 20 % in each of three types, and 40 % in the fourth, gives $N_1 = 10^{-(3 \times 0.2 \log_{10}(0.2) + 0.4 \log_{10}(0.4))} \approx 3.8$.
- A uniform distribution between a smaller number of container types yields a smaller value of N_1 than does a uniform distribution between a larger number of types. For example, we already saw that four container types, each with a quarter of pupae, would have $N_1 = 4$. Similarly, five container types each with a fifth of the pupae would have $N_1 = 5$.
- A container type with very few pupae does not substantially affect N_1.

Figure 1 shows examples of the dispersion index N_1 with data from studies done in Colombia (Barran-

quilla) (17), Venezuela (Trujillo) (18) and Thailand (Chiang Mai and Khon Kaen) (19). Each study did multiple surveys. In the Colombian survey number 4, almost all the pupae were found in ground tanks (*albercas* or *tanques bajos*), and this survey has the smallest dispersion index among the six shown. At the other extreme, the highest dispersion index is N_1=8,3 found in the Thai survey number 1. In this survey, four container types had more than 10 % of pupae, although none had more than 22 %. It was expected that, in such situations of high dispersion index, it would be more difficult to define the key container types, i.e. that a larger sample size would be needed.

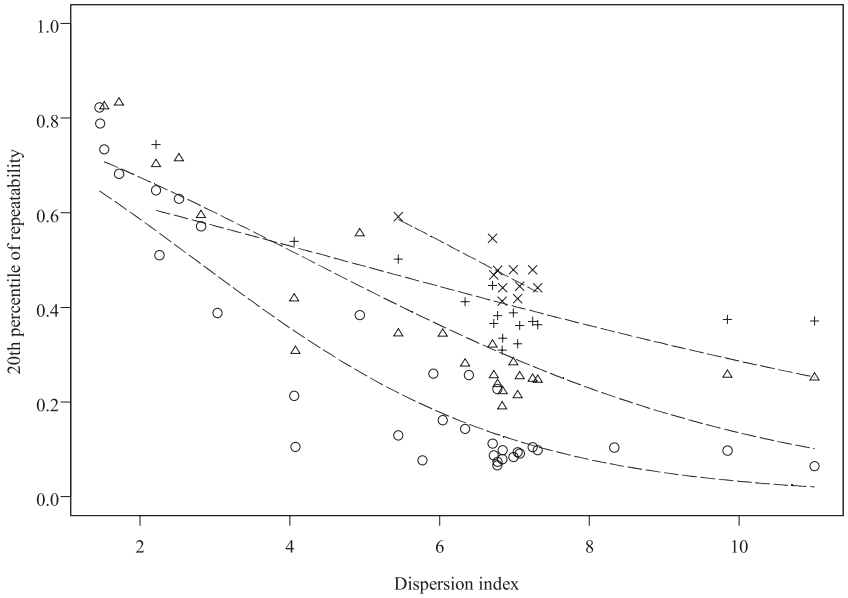
Figure 1. THE DISTRIBUTIONS OF A*edes aegypti* PUPAE OVER CONTAINER TYPES IN SIX SURVEYS. THE EXPONENTIAL OF SHANNON ENTROPY IS SHOWN AS A DISPERSION INDEX (N1).



In order to evaluate the use of the dispersion index (N_1) for determining sample size, the index was related to the repeatability of surveys. For this purpose, repeatability was defined in terms of two surveys which were simulated by drawing from the original data of each study. In the first simulated survey, the key container types were identified as those in which 70 % of pupae were found. The value of 70 % was a consensus value agreed by the investigators of the A*edes* control project. Then, the percentage of pupae in those same types was evaluated in the second simulated survey. This percentage was defined as the repeatability. The simulation process was repeated 1 000 times, in order to examine the distribution of repeatability. Ideally, the repeatability would almost always be close to 70 %: this would indicate the key contai-

ner types can be identified consistently between surveys. Figure 2 shows that the repeatability is greater a) If the sample size is greater, and b) if the dispersion index (entropy) is less.

Figure 2. INVERSE RELATION BETWEEN REPEATABILITY OF A*edes* PUPAL SURVEYS (VERTICAL AXIS) AND THE DISPERSION INDEX (N1, HORIZONTAL AXIS). FOR THE VERTICAL AXIS, A LOW VALUE PERCENTILE OF THE DISTRIBUTION WAS USED (ARBITRARILY CHOSEN AS THE 20TH), SO THAT THE REPEATABILITY HAS A HIGH PROBABILITY (80%) OF BEING AT LEAST AS HIGH AS THE VALUE PLOTTED. SAMPLES SIZES WERE 10 (O), 25 (D), 50 (+) OR 100 (×) HOUSES POSITIVE FOR PUPAE. THE DASHED LINES SHOW FITS FROM REGRESSING THE LOGISTIC TRANSFORMATION OF THE REPEATABILITY ON THE DISPERSION INDEX. SEE THE TEXT OF SECTION 2.1 FOR MORE DETAILS.



This analysis was used to construct a flow diagram for determination of sample size (20). It requires a minimum of 10 houses positive for pupae (i.e., with at least one pupa). If the pupae in these ten houses have a dispersion index (N_1) less than 2, the survey can be halted and the key container types identified. Otherwise, the survey should continue until a point defined by the values of N_1 at the following steps of the flow diagram (after 25, 50 and 100 positive houses). The method also permits the investigators to join categories. For example, in the Thai survey number 2, 'small jar' could be joined with 'jar'.

3. STATISTICAL ANALYSIS BY MAXIMUM ENTROPY

Likelihood is a fundamental concept in statistics (21), and means the probability of the data, under the assumption of a particular probability distribution. Analysis by maximum likelihood involves finding the parameters which maximize the likelihood of the data, for the assumed type of distribution. Analysis by maximum entropy is complementary. Rather than starting with a distribution and estimating

parameters, it treats the parameters as constraints, and finds the distribution with the maximum entropy. For example, we may specify values of the mean and standard deviation (e.g. the sample mean and standard deviation of a particular dataset). Then, the normal (Gaussian) distribution has higher entropy than any other. More formally, certain types of problems yield equivalent solutions by maximum likelihood or maximum entropy (22), although one method or the other may be more convenient. Until recently, maximum entropy analysis has been used mostly in certain fields such as physics (23), linguistics (24) and bioinformatics (25).

Recently, Phillips et al (26,27) presented a method for spatial analysis by maximum entropy, for prediction of species' geographic distributions. The method requires a set of locations in which the species has been found. This type of data is called 'presence only', because it does not contain locations in which the species was sought but not found. Prediction is done on the basis of environmental or other geo-referenced variables, which are available in the region for which the predictions are to be made. The results are usually reported in terms of relative probability, so that the most likely predicted location for the species has a value of 100 %. One limitation of the method is possible sampling bias, i.e. the locations sampled tending to have certain environmental characteristics, perhaps associated with being more accessible. The authors state that their approach could, in the future, be extended to presence/absence data, although this is not done in their publications.

Phillips et al. illustrated their approach using data from South America on the sloth B*radypus variegatus* and the rodent M*icroryzomys minutus*. They compared the maximum entropy method to the Genetic Algorithm for Rule-Set Prediction (GARP), which can also use presence-only data, and which has been used to predict the distributions of several species, including those of insect vectors of leishmaniasis and Chagas' disease in South America (28,29). Phillips et al. found that, in their example, the maximum entropy method was generally superior to GARP in terms of a) the proportion of known localities which were successfully predicted, and b) the area under the curve (AUC) of the receiver operating characteristic (ROC), which is a summary measure of sensitivity and specificity. In the following section we will apply the same maximum entropy method to a mosquito vector of malaria.

3.1 *Prediction of the presence of* A*nopheles* (N*yssorhynchus*) *nuñeztovari* Gabaldon, 1940.

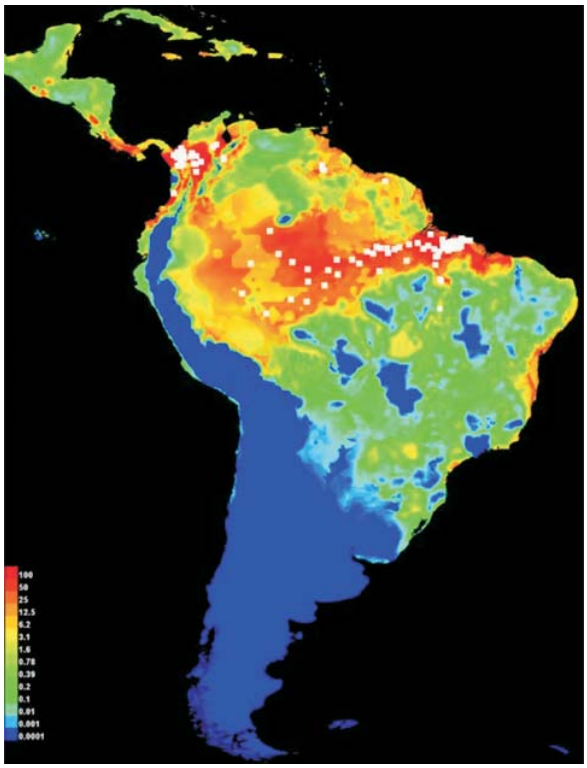
A*nopheles nuñeztovari* is the principal malaria vector in western Venezuela and northern Colombia, and has been incriminated as a vector in Peru, Brazil and Surinam (30). Twenty-three georeferenced locations of A*nopheles nuñeztovari* in Colombia were obtained directly in the field using a GPS (Garmin III) in the departments of Antioquia and Cordoba. The adult mosquitoes were collected directly in houses resting on walls. Seventy-seven other locations were extracted from published reports (30,34).

The analysis used the software made available by Phillips et al.(27), and with the same 14 predictor variables. Twelve of these were obtained from the Intergovernmental Panel on Climate Change and relate to temperature, precipitation, cloud cover, frost frequency, and vapour pressure. The remaining two variables were elevation, and a classification of 'major habitat type', which was intended to reflect vegetation. The map of predictions is shown in Figure 3.

The predictions of the distribution of A*n*. N*uñeztovari* show generally good agreement with the known distribution. In particular the predictions of presence in the east of Panama, northern Colombia, western Venezuela, the Guyanas and the Brazilian Amazonian basin coincided with almost all the known niches of the species. However, there are

some exceptions. For the north of Peru and Bolivia the prediction is weak, possibly due to those areas' environmental conditions (mainly dry with xerophytic vegetation), which are totally different to those of other areas (tropical rain forests with high levels of precipitation). The actual presence of *An. nuñetovari* in those areas could be explained as a species complex with cryptic forms and different cytotypes. Finally, predictions in Central America and some Caribbean islands should be tested: those areas could be part of the species' fundamental niche.

Figure 3. PREDICTION BY MAXIMUM ENTROPY OF THE DISTRIBUTION OF THE MALARIA VECTOR *Anopheles nuñeztovari*. WHITE SQUARES INDICATE LOCATIONS WHERE THIS SPECIES WAS FOUND. WARMER COLOURS INDICATE A HIGHER PREDICTED LIKELIHOOD OF PRESENCE, NORMALIZED TO HAVE A MAXIMUM VALUE OF 100.



4. EXTREME PHYSICAL INFORMATION

So far we have seen the use of entropy in statistical methods. Now we will consider the application to medical research of a physical principle which is based on a concept closely linked to that of entropy.

4.1 Fisher Information

Named after the statistician and geneticist Ronald Fisher, Fisher information is best known as a measure of statistical uncertainty in the estimation of parameters. For example, in the case of a single parameter, the Fisher information is the reciprocal of the square of its standard error.

Frieden (5) shows that Fisher information is a generalization of the thermodynamic and Shannon entropies and therefore calls it a 'mother' information measure. He postulates the principle of Extreme Physical Information (EPI), which states that any measurement extracts a quantity of Fisher information from the observed object, and that this quantity is an *extremum* (a minimum or maximum), given the constraints of the problem. In physical applications, these constraints could be conservation principles. For example, from the principles of EPI and conservation of momentum, Frieden derives general relativity. Another example is the derivation of the Cramér-Rao lower bound (i.e. the lowest possible statistical variance of an unbiased parameter estimate) as an instance of the Heisenberg uncertainty principle (i.e. the quantum mechanical observation that, for example, the position and velocity of a particle cannot be simultaneously known with exact precision). That EPI can elegantly yield such important results suggests that it has an important role in physics.

Furthermore, Frieden and his colleagues have applied EPI to some examples in other fields, including biomedicine. Gatenby & Frieden (35) applied EPI to tumour growth. The 'information'

in this case is signalled between malignant and healthy cells, and 'protons appear to be the dominant messengers because increased glucose uptake and excessive secretion of acid into the extracellular spaces are observed in the vast majority of clinical cancers.' The authors predicted that *in vivo* growth rate would follow a power law. This is less than the maximum possible rate, which would be exponential. The authors extrapolate their predictions to the distribution of tumour size, and show a close fit to published data. Their interpretation is that the malignant cells forego maximum growth in order to minimize the information available to their benign neighbours on the time at which they became malignant. This work suggests that EPI could have other physiological applications.

4.2. The immune system as an information processor

'Antigens bear Shannon-type information intrinsically, as a consequence of their particular molecular organization', according to Atlan and Cohen(36). Such statements seem to promise, for the immunological network, the same kind of informatic theory that Shannon developed for telecommunication networks. Unfortunately, however, much of this literature is rather verbose and does not attempt to quantify immunological phenomena. However, it may be possible to use the principle of EPI to make predictions and indicate new experimental directions.

Gatenby & Frieden's interpretation of their tumour growth analysis was that malign cells minimize the information they provide to their benign neighbours on the time of origin of the tumour. This may provide a clue to some aspects of parasite immunology. For example, parasite development and growth may be optimized to balance speed against stealth in evading the immune system. Immune evasion is ubiquitous in parasites (37), with its mode depending on the particular immune cells and molecules available to the host. These, together with the substances which the parasite exposes to the host, would constitute the signalling mechanism corresponding to the much simpler lactic acid molecules in the cancer growth example.

In order to investigate this, a useful model parasite would be one which occurs in different locations of the body in which different immune responses may be available. For example, metacercariae of the digenean helminth P*aragonimus westermani* usually develop into adults in the lungs of the host, but may do so in several other locations including muscle, subcutaneous tissues, spleen, liver, peritoneum, urinary tract, and central nervous system (38). Comparative data on the rates of development, and the signalling molecules present in different locations, could enable an analysis similar to that done for cancer growth, although most of the information-bearing molecules would be more complex. Finally, another possible application of EPI would be migration rates of parasites through tissue, and this is currently the subject of further investigation.

5. DISCUSSION

We have seen three uses of entropy in medical research, in order of increasing profundity. The first is the use of Shannon entropy as a summary statistic of dispersion across a number of categories (section 2). The second use of entropy is a principle of statistical analysis, known as maximum entropy (section 3). This approach seeks the distribution which has the maximum entropy, subject to the conditions of the problem. This is, in a strict sense, complementary to that of the more well known method of maximum likelihood. Although currently little known outside a few specialties, such as bioinformatics, we saw an application to spatial analysis in ecology (27). This powerful technique has several advantages over alternatives such as GARP, and is easily available via the software made freely available by the authors. Nevertheless, an obstacle to the wider use of the method is the complexity of identifying the distribution which has the maximum possible entropy. Algebraic solution

requires mathematical techniques such as calculus of variations, and is more difficult than the typical maximum likelihood problem of estimating a small number of scalar parameters. On the other hand, in practice, solutions can be derived by numerical iteration.

A strong rationale for maximum entropy analysis is its correspondence to a principle which elegantly yields many basic components of physics, namely Extreme Physical Information (EPI). This states that any physical measurement extracts a quantity of Fisher information from the observed object, and that this quantity is an *extremum* (a minimum or maximum). This principle was postulated by Frieden (5), who has shown that Fisher information — a quantity better known in statistics — is a kind of 'mother' information which can be used to derive many physical laws, such as general relativity, and the Klein-Gordon equation. In biology, EPI has also had some successful applications, in particular in explaining rates of tumour growth, and we can look forward to its continued fruitful use in medical research.

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REFERENCES

1. Deleuze G. Postscript on the societies of control. October 1992: 3-7.
2. Ballard S. Entropy and digital installation. Fibreculture Journal 2005;7.
3. Bockris V. The life and death of Andy Warhol. London: Fourth Estate; 1998.
4. Von Baeyer HC. Information: The New Language of Science. London: Weidenfeld & Nicolson; 2003.
5. Frieden BR. Science from Fisher information: A unification. Cambridge: Cambridge University Press; 2004.
6. Krebs CJ. Ecological methodology. Menlo Park: Benjamin/Cummings; 1999.
7. Wilhm JL. Use of biomass units in Shannon's formula. Ecology 1968;49(1):153-156.
8. Bullock A, Stallybrass O, Trombley S (eds.) The Fontana dictionary of modern thought. London: Fontana Press; 1988.
9. Stewart JJ, Lee CY, Ibrahim S, Watts P, Shlomchik M, Weigert M et al. A Shannon entropy analysis of immunoglobulin and T cell receptor. Mol Immunol 1997; 34(15):1067-1082.
10. Wang X, Rikihisa Y, Lai TH, Kumagai Y, Zhi N, Reed SM. Rapid sequential changeover of expressed p44 genes during the acute phase of Anaplasma phagocytophilum infection in horses. Infect Immun 2004;72(12):6852-6859.
11. Schouls LM, van der Heide HGJ, Vauterin L, Vauterin P, Mooi FR. Multiple-locus variable-number tandem repeat analysis of Dutch B*ordetella pertussis* strains reveals rapid genetic changes with clonal expansion during the late 1990s. J Bacteriol 2004;186(16):5496–5505.
12. Jaynes ET. Probability theory: The logic of science. Cambridge: Cambridge University Press; 2003.
13. Pielou EC. Ecological diversity. New York: John Wiley & Sons; 1975.
14. Rigau-Pérez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV. Dengue and dengue haemorrhagic fever. Lancet 1998;352(9132):971-977.
15. Focks DA. A review of entomologial sampling methods and indicators for dengue vectors

(TDR/IDE/Den/03.1). Geneva: UNICEF/UNDP/ World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR); 2003.

16. Nathan MB, Focks DA, Kroeger A. Pupal/ demographic surveys to inform dengue-vector control. Ann Trop Med Parasitol. 2006;100 Suppl 1:S1-S3.

17. Romero-Vivas CME, Arango-Padilla P, Falconar AKI. Pupal-productivity surveys to identify the key container habitats of A*edes aegypti* (L.) in Barranquilla, the principal seaport of Colombia. Ann Trop Med Parasitol. 2006;100 Suppl 1:S87-S95.

18. Lenhart AE, Castillo CE, Oviedo M, Villegas E. Use of the pupal/demographic-survey technique to identify the epidemiologically important types of containers producing A*edes aegypti* (L.) in a dengue-endemic area of Venezuela. Ann Trop Med Parasitol. 2006;100 Suppl 1:S53-S59.

19. Alexander N, Lenhart A, Romero-Vivas C, Barbazan P, Morrison A, Barrera R, et al. Sample sizes for identifying the key types of container occupied by dengue-vector pupae: the use of entropy in analyses of compositional data. Ann Trop Med Parasitol. 2006;100 Suppl 1:S5-S16.

20. Focks DA, Alexander N. Multicountry Study of A*edes aegypti* Pupal Productivity Survey Methodology: Findings and Recommendations (TDR/IRM/Den /06.1). Geneva: World Health Organization; 2006.

21. Lindgren BW. Statistical Theory. New York: Collier Macmillan; 1976.

22. Grendár M, Grendár M. in Bayesian inference and maximum entropy methods in science and engineering: 20th International Workshop 49-60 (Gif-sur-Yvette, France, 8-13 July 2000).

23. Skilling J (ed.) Maximum entropy and bayesian methods. Dordrecht: Kluwer Academic Publishers; 1989.

24. Rosenfeld R. A Maximum entropy approach to adaptive statistical language modeling. Computer, Speech and Language 1996; 10:187-228.

25. Cosmi C, Cuomo V, Ragosta M, Macchiato MF. Characterization of nucleotidic sequences using maximum entropy techniques. J Theor Biol 1990;147(3):423-432.

26. Phillips SJ, Dudík M, Schapire RE. In Proceedings of the Twenty-First International Conference on Machine Learning 655-662 (Banff, Canada, 2004).

27. Phillips SJ, Anderson RP, Schapire RE. Maximum entropy modeling of species geographic distributions. Ecological Modelling 2006;190:231–259.

28. Costa J, Peterson AT, Beard CB. Ecologic niche modeling and differentiation of populations of T*riatoma brasiliensis* Neiva, 1911, the most important Chagas' disease vector in northeastern Brazil (Hemiptera, Reduviidae, Triatominae). Am J Trop Med Hyg 2002; 67(5):516-520.

29. Peterson AT, Martinez-Campos C, Nakazawa Y, Martinez-Meyer E. Time-specific ecological niche modeling predicts spatial dynamics of vector insects and human dengue cases. Trans R Soc Trop Med Hyg 2005;99(9):647-655.

30. Moreno J, Rubio-Palis Y, Sánchez V, Mariany D. Primer registro de A*nopheles* (N*yssorhynchus*) *nuneztovari* Gabaldón,1940 (Diptera: Culicidae) en el estado Bolívar, Venezuela y sus implicaciones eco-epidemiológicas. Entomotropica 2004;19(1):55-58.

31. Xavier SH, Mattos SdS. Geographical distribution of Culicinae in Brazil III, State of Pará (Diptera, Culicidae). Mosquito Systematics 1975;7(3):234-268.

32. Xavier SH, Mattos SdS. Geographical distribution of Culicinae in Brazil - IV. State of Amazonas (Diptera, Culicidae). Mosquito Systematics 1976;8(4):386-412.

33. Hribar LJ. Geographic variation of male genitalia of A*nopheles nuneztovari* (Diptera: Culicidae). Mosquito Systematics 1994;26(3):132-144.

34. Posso CE, González R, Cárdenas H, Gallego G, Duque MC, Suarez MF. Random amplified polymorphic DNA analysis of A*nopheles nuneztovari* (Diptera: Culicidae) from Western and Northeastern Colombia. Mem Inst Oswaldo Cruz 2003;98(4):469-476.

35. Gatenby RA, Frieden BR. Application of information theory and extreme physical information to carcinogenesis. Cancer Res. 2002;62(13):3675-3684.

36. Atlan H, Cohen IR. Immune information, self-organization and meaning. Int Immunol 1998;10(6):711-717.

37. Damian RT. Parasite immune evasion and exploitation: reflections and projections. Parasitology 1997;115:S169-175.

38. Choi DW. P*aragonimus* and paragonimiasis in Korea. Korean J Parasitol 1990; 28 Suppl:79-102.