ANN Multiscale Model of Anti-HIV Drugs Activity vs AIDS Prevalence in the US at County Level Based on Information Indices of Molecular Graphs and Social Networks

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Ⓢ *Supporting Information*

ABSTRACT: This work is aimed at describing the workflow for a methodology that combines chemoinformatics and pharmacoepidemiology methods and at reporting the first predictive model developed with this methodology. The new model is able to predict complex networks of AIDS prevalence in the US counties, taking into consideration the social determinants and activity/structure of anti-HIV drugs in preclinical assays. We trained different Artificial Neural Networks (ANNs) using as input information indices of social networks and molecular graphs. We used a Shannon information index based on the Gini coefficient to quantify the effect of income inequality in the social network. We obtained the data on AIDS prevalence and the Gini coefficient from the AIDSVu database of Emory University. We also used the Balaban information indices to quantify changes in the chemical structure of anti-HIV drugs. We obtained the data on anti-HIV drug activity and structure (SMILE codes) from the ChEMBL database. Last, we used Box-Jenkins moving average operators to quantify information about the deviations of drugs with respect to data subsets of reference (targets, organisms, experimental parameters, protocols). The best model found was a Linear Neural Network (LNN) with values of Accuracy, Specificity, and Sensitivity above 0.76 and AUROC > 0.80 in training and external validation series. This model generates a complex network of AIDS prevalence in the US at county level with respect to the preclinical activity of anti-HIV drugs in preclinical assays. To train/validate the model and predict the complex network we needed to analyze 43,249 data points including values of AIDS prevalence in 2,310 counties in the US vs ChEMBL results for 21,582 unique drugs, 9 viral or human protein targets, 4,856 protocols, and 10 possible experimental measures.
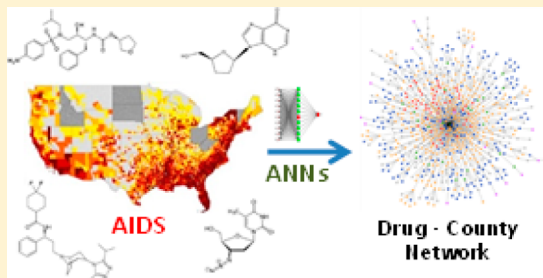
1. INTRODUCTION

The acquired immunodeficiency syndrome (AIDS)[1] caused by the human immunodeficiency virus (HIV) is still considered as one of the most life-threatening diseases, and the HIV[2,3] pandemic continues to spread. Since the beginning of the epidemic, more than 60 million people have been infected with HIV, and over 25 million have died from the disease. Since the first case of AIDS was reported by the US in 1981, tremendous progress has been made in the prevention and treatment of HIV/AIDS,[4] especially in the development of antiretroviral therapy[5] that has proven to be life-saving to millions of people. Therefore, the discovery and development of novel, highly potent anti-HIV drugs remain imperative, although the eradication is still a difficult goal to achieve due to a low level of viral persistence in treated subjects.[6]

In this context, different Computer-Aided Drug Design (CADD) techniques, useful to predict the behavior of anti-

HIV drugs, may play an important role in reducing the number of preclinical and clinical studies. For instance, we could use chemoinformatics models that link the chemical structure of drugs with their biological activity. In fact, there are many reports of chemoinformatics models, useful to predict anti-HIV activity in preclinical assays.[7] In principle, we could upgrade these models to predict the anti-HIV activity of drugs not only in preclinical screening but also in clinical and pharmacoepidemiology studies. Such a model may become a very useful tool not only for the Pharmaceutical Industry in order to reduce clinical assays. They should ideally be useful also for Public entities responsible for implementation of Health policies in the phase IV of drug development. However, there are no reports of models

useful to predict the performance of anti-HIV drugs in both preclinical and pharmacoepidemiology studies on large populations without carrying out clinical studies. We neither had at our disposal models able to extrapolate, at least, the performance of anti-HIV drugs from preclinical studies to epidemiology studies on large populations without carrying out clinical studies.

A useful chemoinformatics-pharmacoepidemiology model should be multilevel by definition as it is expected to account for both molecular and population structure. It means that, in order to develop such computational models, we need to process different types of input data coming from many different levels of organization of matter. On the one hand, we need to introduce information about the anti-HIV drugs including at least the chemical structure of the drug (level i) and the preclinical assay information, such as biological targets (level ii), organisms (level iii), or assay protocols (level iv). On the other hand, we need to incorporate population structure descriptors (level v) that quantify the epidemiological and social and economic factors affecting the population selected for the study. Last, as populations in modern society are not close systems we should also quantify the effect of interaction of the population under study with other populations that may influence the pharmacoepidemiology study (level vi). The data for levels i--iv were obtained from public databases of biological activity of organic compounds. These databases accumulated immense data sets of experimental results of pharmacological trials for many compounds. For instance, ChEMBL (https://www.ebi.ac.uk/chembl/)[8,9] is one of the biggest with more than 11,420,000 activity data for >1,295,500 compounds and 9,844 targets. Specifically, ChEMBL contains >43,000 outcomes for assays of anti-HIV compounds.

In addition, we obtained the data for levels v and vi from public epidemiological databases. For instance, AIDSVu[10] (http://aidsvu.org/about-aidsvu/) is the most detailed publicly available view of HIV prevalence in the US. AIDSVu is a compilation of interactive online maps that displays the HIV prevalence data at the national, state, and local levels and by different demographics, including age, race, and sex. Researchers at the Rollins School of Public Health at Emory University compiled the county-level data displayed on AIDSVu from the CDC (U.S. Centers for Disease Control and Prevention). State, county, and city health departments, depending on the entity responsible for HIV surveillance provided data on the HIV prevalence at the ZIP code and census tract. An Advisory Committee and a Technical Advisory Group guide the project with representatives from federal agencies, state health departments, and nongovernmental organizations working in HIV prevention, care, and research.

The formulation of mathematical models of this large data set from ChEMBL is very complex per se[9,11] but becomes an even more complicated problem when AIDSVu data are added. This is not only a problem of analysis of a huge number of data points (Big Data),[12-17] it is also a problem of dealing with the mathematical representation/codification of such diverse information from many different levels of organization of matter and areas of scientific knowledge. We can talk about three features of the problem resulting from the combination of chemical, pharmacological, and epidemiological information: (1) multitargeting, (2) multiobjective, and/or (3) multiscaling features. The multitargeting nature of the problem[18-20] refers to the existence of multitarget compounds that can interact with more than one molecular or cellular target. The multiobjective optimization problem (MOOP)[21-25] refers to the necessity of prediction/optimization of results for different experimental measures obtained in different pharmacological assays. Last,

multiscaling refers to the different structural levels of the organization (i–vi) of matter that input variables. It means that we need to develop models able to link the changes in the AIDS prevalence in a given a^{th} population with the changes in the biological activity of the qth drug (d_q), due to variations in the chemical structure, detected in preclinical assays carried out under a set of jth conditions (c_j).

We can use numerical descriptors of the molecular graph of the drug. In particular, some of these parameters are useful to quantify information about the properties of molecular, biological, and/or social systems (information measures). For instance, Shannon's entropy measures are universal parameters used to codify biologically relevant information in many systems. In the 1970s Bonchev and Trinajstic et al. published some works about the use of Shannon's entropy to calculate a structural information parameter.[26-29] Kier published other seminar works on the use of Shannon's entropy to encode molecular structure in chemoinformatics studies in 1980.[29] In this context, a drug molecule is considered an information source. Many other authors used Shannon's entropy parameters to encode small molecule structure.[30-35] Graham et al.[36-40] used entropy measures to study in depth the information properties of organic molecules. These concepts were extended to describe protein,[41,42] DNA sequences,[43] or protein–protein interaction networks.[44] Mikoláš et al.[45] reviewed several studies about the use of entropy measures in functional magnetic resonance. In a recent work we have used Shannon entropy measures and the idea of Moving Average (MA) operators in a time series analysis with a similar purpose.[46] Additionally, information indices are graph-theoretical invariants that view the molecular graph as a source of different probability distributions to which information theory definitions can be applied. They can be considered a quantitative measure of the lack of structural homogeneity or the diversity of a graph, in this way being related to the symmetry associated with structure.[47-49] Ivanciuc and Balaban[50] defined the indices for simple and weighted molecular graphs and tested the information theory-indices for modeling alkane densities. Moreover, Ivanciuc et al.[51] also found that the information indices were extended for any symmetric molecular matrix derived from vertex-and edge-weighted molecular graphs. Dehmer et al.[52-55] mentioned the Balaban information indices[56] in their work about novel topological descriptors for biological networks.

However, the codification of the molecular structure of the drug is only the first step here. We have information about a high number of assays carried out in very different conditions (c_j) for the same or different targets, which may be molecular or not. The nonstructural information herein refers to different assay conditions (c_j) like time, concentrations, temperature, cellular targets, tissues, organisms, etc. A possible solution may rely upon the use of the idea of MA operators used in a time series analysis with a similar purpose.[46] MA models became popular after the initial works conducted by Box and Jenkins.[57] In a time series analysis, MA models may combine other operators I = Integrated, AR = Autoregressive, N = Nonlinear operators, or X = Exogenous effects. In this sense, we can develop models like ARMA, ARIMA, VARIMA, ARIMAX, NARMA, etc., combining different operators. The MA operators used in time series are the average value of a characteristic of the system for different intervals of time or seasons. In multiobjective modeling, we calculate the MA operators as the average of the property of the system (molecular descriptors or others) for all drugs or targets with a specific response in an assay carried out at under a subset of conditions (c_j). Consequently, our MA operator does not act over a time domain but over a subset of conditions of the pharmacological assays. The idea of application of

MA operators to other domains different from time is gaining adepts due to its advantages. For instance, Botella-Rocamora et al.[58] developed a model map of diseases called SMARS: Spatial Moving Average Risk Smoothing. They applied the MA of time series theory to the spatial domain, making use of a spatial MA to define dependence on the risk of a disease occurring.

Certainly, we can see this entire problem as the prediction of a complex network represented by the Boolean matrix **L** with elements L_{aq}. That is, we have to seek a model able to assess the formation ($L_{aq} = 1$) or not ($L_{aq} = 0$) of links between nodes in a complex network of AIDS pharmacoepidemiology in the US. Two different classes of nodes make up this network, the first representing the US counties (a) and the other class of nodes representing drugs (d_q). In the present context, we can use MA of properties of network nodes (drugs, proteins, organisms, counties, etc.) that form links (L_{aq}) in a specific subset of conditions (c_j). For this reason, we decided to call this strategy ALMA (Assessing of Links with Moving Averages) models. Speck-Planche and Cordeiro[59−61] have reported different multitarget models using the same type of ALMA approach.

Last, we can use these information descriptors and MA operators as inputs for a Machine Learning (ML) algorithm. This ML has to seek the coefficients of the ALMA model able predict the correct links in **L**. The neural network approximates the operation of the human brain,[62,63] and this initially "trained" or fed large amounts of data and rules about data relationships. ANNs are in general nonlinear algorithms with a high number of processors (called neurons) which, in a classic picture, are distributed in layers and act in parallel (neurons in the same layer) or in series (pairs of neurons connected in different layers). In recent years, ANNs[64,65] have turned out to be a powerful method for various practical applications in a great variety of disciplines, and they can be used to find complex relationships between inputs and outputs or to find models in data. Another

aspect of ANNs[66,67] is that there are different architectures, which require different types of algorithms for training; the trained ANN do not need to be reprogrammed.

2. MATERIALS AND METHODS

Linear and Nonlinear ALMA Models. The ALMA models are useful to assess the formation of links in different complex networks that are representations of complex systems. They are adaptable to all types of molecular descriptors and/or graphs invariants or descriptors for complex networks. In this work, we tried to seek a classification model. The overall output of this model is $L_{aq}(c_j)_{pred}$. This variable is a prediction of the observed variable $L_{aq}(c_j)_{obs}$. Both the observed and predicted variables are discrete Boolean variables (1, 0). The observed variable takes the value $L_{aq}(c_j)_{obs} = 1$ if the observed score $S_{aq}(c_j)_{obs}$ > input cutoff or $L_{aq}(c_j)_{obs} = 0$ otherwise. In analogy, the predicted variable $L_{aq}(c_j)_{pred} = 1$ if the predicted score $S_{aq}(c_j)_{pred}$ > output cutoff or $L_{aq}(c_j)_{pred} = 0$ otherwise.

More specifically, we can say that the value is $L_{aq}(c_j)_{obs} = 1$ when the $S_{aq}(c_j)_{obs}$ = Drug-Disease Ratio = $DDR_{aq}(c_j)$ > cutoff and $L_{aq}(c_j)_{obs} = 0$ otherwise. We defined the ratio as follows: $S_{aq}(c_j)_{obs} = DDR_{aq}(c_j) = [D_q(c_j)/D_a]$. We calculated the numerator term as $D_q(c_j) = \delta_j \cdot z_q(c_j) = \delta_j \cdot [v_q(c_j) - AVG(v(c_j))]/SD(v(c_j))$. In this operator, $v_q(c_j)$ is the value of biological activity (EC_{50}, IC_{50}, K_i, ..., etc.) reported in the ChEMBL database for the qth drug assayed under the set of conditions $c_j = (c_1, c_2, c_3, c_4)$. The parameter δ_j is similar to a Kronecker delta function. The parameter $\delta_j = 1$ when the biological activity parameter $v_q(c_j)$ is directly proportional to the biological effect (e.g., K_i values, Activity (%) values, etc.). Conversely, $\delta_j = -1$ when the biological activity parameter $v_q(c_j)$ is in inverse proportion to the biological effect (e.g., EC_{50} values, IC_{50} values, etc.). The parameter $z_q(c_j)$ is the z-score of the biological activity that depends on the functions AVG and SD. These functions are the average and standard deviation of $v_q(c_j)$

Table 1. Examples about How To Calculate the Moving Average Operators for Some Compounds

Cmpd ID	Name	SMILE	Target	I^q_1	$<I^q_1>$	$\Delta I^q_1(c_2)$
57	Nevirapine	Cc1ccnc2N(C3CC3)c4ncccc4C(=O)Nc12	HIV-1	25.731		-5.2763
129	Zidovudine	CC1=CN([C@H]2C[C@H](N=[N+]=[N-])[C@@H](CO)O2)C(=O)NC1=O	HIV-1	33.488	31.007	2.48066
483	Tenofovir	C[C@H](Cn1cnc2c(N)ncnc12)OCP(=O)(O)O	HIV-1	33.803		2.79566
964	Disulfiram	CCN(CC)C(=S)SSC(=S)N(CC)CC	CC-CKR-5	60.801		15.9376
39879	Dipyridyl	c1ccc(nc1)c2ccccn2	CC-CKR-5	17.119	44.863	-27.7443
1201187	Maraviroc	CC(C)c1nnc(C)n1[C@@H]2C[C@H]3CC[C@@H](C2)N3CC[C@H](NC(=O)C4CCC(F)(F)CC4)c5ccccc5	CC-CKR-5	56.67		11.8066
31574	Fisetin	OC1=C(Oc2cc(O)ccc2C1=O)c3ccc(O)c(O)c3	HIV-1 IN	32.01		-1.4976
28626	Morin	OC1=C(Oc2cc(O)cc(O)c2C1=O)c3ccc(O)cc3O	HIV-1 IN	34.236	33.507	0.72833
50	Quercetin	OC1=C(Oc2cc(O)cc(O)c2C1=O)c3ccc(O)c(O)c3	HIV-1 IN	34.277		0.76933

for all drugs assayed under the same conditions. In this sense, $c_1 =$ is the experimental measure of activity, $c_2 =$ is the protein target, $c_3 =$ is the organism that expresses the target, and $c_4 =$ is the assay protocol per se. In the denominator, we used the term D_a that is the AIDS prevalence rate for the ath county. We can conclude that $L_{aq}(c_j)_{obs}$ and consequently $L_{aq}(c_j)_{pred}$ depend on both the prevalence of the disease and the effectiveness of the drug due to the definition of $DDR_{aq}(c_j)$. In Table 1, a simple example of calculation of MA operators is shown. In this example, we only use the condition (c_2), i.e., Balaban information index $\mathbf{U} = I^q{}_1$ and the target of the drug, to illustrate the method. First, we have the SMILE codes of the compounds obtained from ChEMBL. Next, using the DRAGON Software[68] we calculated the Balaban Information Indices (in this case only $\mathbf{U} = I^q{}_1$). Afterward, we calculated $\langle I^q{}_1 \rangle$ the average of the information index $I^q{}_1$ for the compounds with the same targets. Last, we calculated the MA operators with the formula $\Delta I^q{}_1(c_2) = (I^q{}_1 - \langle I^q{}_1 \rangle_{c_2}$. In our work, this method was applied to the 43,249 molecules characterized by different Balaban Information indices $(\mathbf{U} = I^q{}_1, \mathbf{V} = I^q{}_2, \mathbf{X} = I^q{}_3, \mathbf{Y} = I^q{}_4)$ and assay conditions $c_j = (c_1, c_2, c_3, c_4)$. In addition, $\langle D_q(c_j) \rangle$ is the average value of the biological activity for all the drugs assayed under the same conditions. Consequently, $\Delta D_q(c_j)$ is an MA operator that accounts for the deviation of the biological activity of the drug $D_q(c_j)$ in a preclinical assay with respect to the average value $\langle D_q(c_j) \rangle$ of this activity for all drugs assayed under the same conditions c_j.

In order to seek a model able to predict $L_{aq}(c_j)_{pred}$, we used as input different information descriptors for drugs and populations. In general, we refer to an information index $I^q{}_k$ of type k^{th} for the system (drug or county in this case) represented by a matrix **L**. The aim of this model is to predict scores $S_{aq}(c_j)$ of the formation of links L_{aq} using as input the structural information quantified by the indices $I^a{}_0(t)$ for the population (county) and $I^q{}_k$ of a given compound d_q. The simplest model may be based on the additive hypothesis H_0. The hypothesis H_0 states that $S_{aq}(c_j) = {}^qS_k + {}^{qj}S_k + {}^{as}S_k + e_0$. It means that it can be calculated as a summation of different scores or measures of factors plus a model error e_0. We have three types of scores or factors divided into two subtypes. The first subtype includes the scores for drugs and the second subtype the scores for counties. The first scores ${}^qS_k \approx e_k \cdot p(c_1) \cdot I^q{}_k$ account for information on both the contributions of the kth molecular descriptor and for the quality of raw data $p(c_1)$ to the final activity score $S_{aq}(c_j)$. In fact, we used the probability $p(c_1) = 1.0$; 0.75; or 0.5 for data curated in CHEMBL database at expert, intermediate, or autocuration levels, respectively. The second scores ${}^{qj}S_k \approx e_{kj} \cdot \Delta I^q{}_k(c_j)$ account for the contributions of deviations $\Delta I^q{}_k(c_j) = (I^q{}_k - \langle I^q{}_k \rangle_j)$ in the structure of the drug from the average of all those molecules assayed under the conditions c_j. In order to test this hypothesis we used the information indices and their MA operators $\Delta I^q{}_k(c_j) = I^q{}_k - \langle I^q{}_k(c_j) \rangle$ to express the different assay conditions for the drugs. We also used a simple information index $I^a{}_0(t)$ for income inequality in the different counties. The linear model ALMA has the following general form:

$$S_{aq}(c_j) = {}^qS_k + {}^{qj}S_k + {}^{as}S_k + e_0$$

$$= \sum_{k=1}^{k=4} e_k \cdot I^q{}_k + \sum_{k=1}^{k=4} \sum_{j=1}^{j=4} e_{kj} \cdot \Delta I^q{}_k(c_j) + e_{ak} \cdot I^a{}_k(t) + e_0$$

$$= \sum_{k=1}^{k=4} e_k \cdot I^q{}_k + \sum_{k=1}^{k=4} \sum_{j=1}^{j=4} e_{kj} \cdot (I^q{}_k - \langle I^q{}_k \rangle_j) + e_{ak} \cdot I^a{}_k(t) + e_0$$

(1)

The reader should note that the predicted, output, or dependent variable $S_{aq}(c_j)$ is not a discrete variable but a real-valued numerical score. However, the variable $S_{aq}(c_j)$ is directly proportional to the observed variable (L_{aq}). Please, note that all the parameters $S_{aq}(c_j) => L_{aq}(c_j) => DDR_{aq}(c_j) => D_q(c_j)$ form a series that in the last instance depends on ($=>$) the conditions of the initial preclinical assay used to measure the activity of the drug $c_j = (c_1, c_2, c_3, c_4)$. In general, c_j refers to different boundary conditions for the assay, e.g., targets, assays, cellular lines, organisms, organs, etc. In this sense, $c_1 =$ is the experimental measure of activity, $c_2 =$ is the protein target, $c_3 =$ is the organism that expresses the target, and $c_4 =$ is the assay protocol per se. Some inputs of the models depend on parameters of the type of deviations $\Delta I^q{}_k(c_j)$, which are similar to the MA operators used in the time series analysis for ARIMA models and others.[57] This means that, first, we add up for instance the values of $I^q{}_k$ for all the n_j drugs under the assay conditions c_j. Next, we divide this sum by the number of compounds n_j under this condition.

$$\langle I^q{}_k \rangle_j = \frac{1}{n_j} \sum_{i=1}^{i=n_j} I^q{}_k(c_j)$$

(2)

In order to seek the coefficients of the model, we can use a linear classification technique like ANN implemented in the STASTITICA 6.0 software package.[69] The statistical parameters used to corroborate the model were as follows: Number of cases in training (N), and overall values of Specificity (Sp), Sensitivity (Sn), and Accuracy (Ac).[70]

CHEMBL Data Set of Drugs. We downloaded from the public database CHEMBL a general data set composed of >8,000 multiplexing assay end points (results of multiple assays).[8,9] The data set used to perform the model included $N = 43,249$ statistical cases made up of $N_d = 21,582$ unique drugs. These drugs have been assayed one by one in at least one out of 10 possible standard type measures determined in at least one out of 4,856 different assays (experimental protocols reported as different in ChEMBL). Each assay involved, in turn, at least one out of 9 nonmolecular or protein targets expressed in tissues, cells, or viral particles of at least one out of 5 different organisms (including human cells lines).

Balaban Information Indices of Molecular Graphs of Drugs. The Balaban information indices[56] U, V, X, and Y are very useful to quantify information about the chemical structure of drugs.[71] These indices use some the following parameters: $\sigma_x =$ vertex distance degree of xth atom (i.e., sum of topological distances from the considered atom to any other atom), d_{xy} is the topological distance between atoms x^{th} and y^{th} atoms; n is the number of non-H atoms. Other parameters used are ${}^gf_x =$ the number of distances from the xth vertex equal to g and $\eta_x =$ the eccentricity of the xth atom (i.e., the maximum topological distance from the considered atom). We denoted these indices in the present work as $I^q{}_k$. In this notation, the letter I stands for the information index, q indicates the number of order (label) of the drug in the data set, and k indicates the type of index. The mathematical formulas for calculation of these indices are

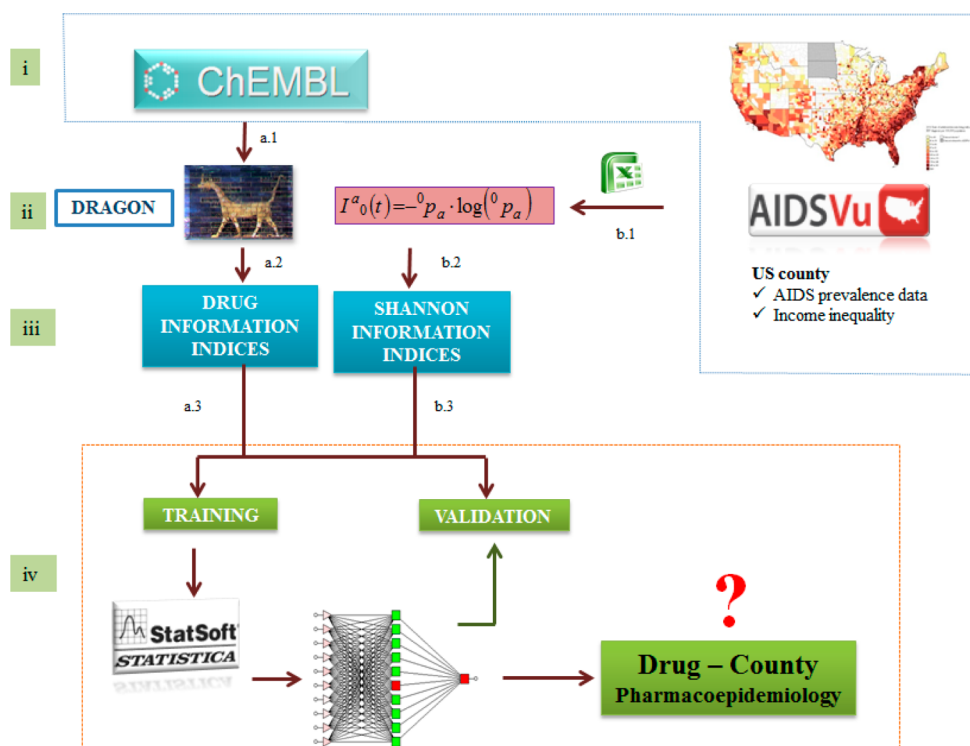$$I^q{}_1 = U_q = -\sum_{j=1}^{n} \frac{d_{xy}}{\sigma_x} \cdot \log_2 \frac{d_{xy}}{\sigma_x}$$

(3)

Figure 1. Flowchart of all steps given to construct the ANNs for the Drug-County Pharmacoepidemiology model in the United States.

$$I^{q}{}_{2} = V_{q}$$

$$= \sigma_{x} \cdot \log_{2}(\sigma_{x}) - u_{q} = \sigma_{x} \cdot \log_{2}(\sigma_{x}) + \sum_{j=1}^{n} \frac{d_{xy}}{\sigma_{x}} \cdot \log_{2} \frac{d_{xy}}{\sigma_{x}} \qquad (4)$$

$$I^{q}{}_{3} = Y_{q} = \sum_{g=1}^{\eta_{i}} {}^{g}f_{q} \cdot g \cdot \log_{2}(g) \qquad (5)$$

$$I^{q}{}_{4} = X_{q} = \sigma_{q} \cdot \log_{2}(\sigma_{q}) - \sum_{g=1}^{\eta_{i}} {}^{g}f_{q} \cdot g \cdot \log_{2}(g) \qquad (6)$$

AIDSvu Data Set of AIDS Prevalence in the US at County Level. Data were drawn from the AIDSVu database of the Rollins School of Public Health at Emory University (www.aidsvu.org). We downloaded the values of epidemiological variables for AIDS in the US at county level from the public database. The values used in this study included the percentage of adults/adolescents living with an HIV diagnosis in 2010 per 100,000 populations. The county-level HIV surveillance data displayed on AIDSVu are estimated data for persons aged 13 and older living with an HIV infection diagnosis. All race groups are non-Hispanic, and the Hispanic/Latino ethnicity is inclusive of all races. Sex is defined as "sex at birth". Data are not displayed at the county level for Asians, Native Hawaiians/Other Pacific Islanders, and American Indians/Alaska Natives because these data do not meet CDC's criteria for statistical reliability, data quality, or confidentiality due to small population denominators and HIV case counts. The total number of counties is $n_{a} = 2{,}310$.

Shannon Information Indices of Income Inequality. We can calculate an information index to quantify the possibility of AIDS spreading/prevalence in different counties (a) of the US. Let be an initial situation in which each county has a value of AIDS prevalence rate D_{a} at the initial time ($t_{0} = 2010$). We used

here a simple information index $I^{a}{}_{0}(t)$ for income inequality in the different counties that year. This index depends on the probability ${}^{0}p_{a}$ with which the county presents certain income inequality. We set here this probability ${}^{0}p_{a} = G_{a}$. In this definition, G_{a} is the Gini measure of income inequality in the ath county of (a) given state(s) in the US.[72] The class of information indices selected by us was the Shannon entropy indices.[73]

$$I^{a}{}_{0}(t) = -{}^{0}p_{a} \cdot \log({}^{0}p_{a}) \qquad (7)$$

3. RESULTS AND DISCUSSION

Definition of the Algorithm. In this work, we report for the first time a model based on information indices of chemical structure, biological assay, and county level income inequality. The model is able to link the deviations in the AIDS prevalence in the ath county with the changes in the biological activity of the qth drug (d_{q}). In so doing, the model considers the biological activity of anti-HIV compounds detected in preclinical assays carried out under a set of jth conditions (c_{j}). Using this type of model, we can predict the pharmacoepidemiology complex network for AIDS in the United States at county level.

First, we propose a new algorithm to construct this type of models. The algorithm/model used as input both drug structures and preclinical information as well as county income inequality data. We understand here as algorithm the series of all steps given in different stages in order to seek and use the model. We illustrate the different steps of this algorithm in Figure 1. The stages of the algorithm proposed are the following: (i) data compilation, (ii) data preprocessing, (iii) calculation of inputs, (iv) development, and use of the model. These stages are similar and divided into two parallel branches (A and B). Both branches have different steps, one for the chemical and biological information of drugs and the other for the information about county pharmacoepidemiology. Next, after the preprocessing

stage (ii), the two branches are joined into a single branch (C) that enters a cycle of training vs validation of the different ANN models and ends with the selection and use of the best model found. In this context, we understand as model the ANN trained and validated in the final step of the algorithm. The most important steps for the branches A and B are the following (the software/databased used are between round brackets):

a.1. Gathering of the chemical structure and biological activity information from public sources (ChEMBL).

a.2. Processing of the information about molecular structure (SMILE codes) and biological activity (EXCEL).

a.3. Calculation of I^q_k values and MA operators for the molecules (DRAGON,[68] EXCEL).

b.1. Downloading the US AIDS prevalence and income inequality data (AIDSVu).

b.2. Calculation of the simple information index $I^a_0(t)$ for income inequality in the different counties.

c.5. Training and validation of ANN predictive models (STATISTICA).[69]

Model Training and Validation. In the first step, we calculated the values drug-disease ratio $DDR_{aq}(c_j)_{obs}$ for the 43,249 drug-county pairs. After that, we carried out a cutoff scanning and found that we can split the data set into 11,089 cases with $L_{aq}(c_j)_{obs} = 1$ and 32,160 cases with $L_{aq}(c_j)_{obs} = 0$ using a cutoff = 500. This is 25.6% of the positive cases that ensure a ratio of above 1/4 of positive vs control cases. The data set used to train the model includes $N = 32,437$ statistical cases. The data set used to validate the model includes $N = 10,812$ statistical cases. The cases used in the validation set (external validation set) were never used to train the model. Overall, training + validation sets include $N = 43,249$ statistical cases. Next, we calculated the values of the Balaban information indices I^q_k for all the drugs/organic compounds present in our ChEMBL subset (step a.2). Table 2 shows some examples of these values I^q_k for known drugs. In addition, in Table SM1 of the Supporting Information content we list the values of I^q_k for all the drugs studied. We can see that the information indices I^q_k have different numerical values for different molecular structures of drugs. After that, we calculated the average values of these indices $\langle I^q_k \rangle$ for the different boundary conditions (c_j). In Table 3, you can see some examples of these average values for different boundary conditions like targets, organisms, etc. After a visual inspection, one can note that the $\langle I^q_1 \rangle$ values seem to distinguish more clearly between the different boundary conditions. For instance, they have differences in the range of 10−100 units for 9 different protein targets (4 HIV vs five human proteins) present in the data set. However, the other averages $<I^q_k>$ with $k > 1$ seem to be worse at differentiating the proteins. In Table SM2 of the Supporting Information, we list the values of $<I^q_k>$ for all the organisms, assay protocols, protein targets, and experimental measures studied.

Next, we calculated the values of the information indices $I^a_0(t)$ for different US counties. Consequently, we used only the $I^a_0(t)$ as inputs for the model. After that, we obtained the ANN models using as input 19 descriptors: 4 Balaban information indices of the molecules (I^q_k), 14 MA operators $(\Delta I^q_k(c_j))$ for the different assay conditions for drugs (c_1,c_2,c_3,c_4), and the $I^a_0(t)$ of the US counties. In Table 4, we illustrate the values of $I^a_0(t)$ for some counties of different states. In Table SM3 of the Supporting Information, we list the values of $I^a_0(t)$ for the 2,310 US counties studied here.

The results obtained using the STATISTICA software show that the Multilayer Perceptron (MLP)[74] method fails to generate

Table 2. Values of Balaban Information Indices for Some Anti-HIV Compounds

CMPD_ID	name	I^q_1	I^q_2	I^q_3	I^q_4
8	Ciprofloxacin	33.562	0.236	0.352	0.705
28	Apigenin	29.885	0.27	0.407	0.789
50	Quercetin	34.277	0.276	0.413	0.819
54	Haloperidol	44.833	0.185	0.303	0.477
57	Nevirapine	25.731	0.284	0.406	0.916
169	Ursolic Acid	47.503	0.217	0.323	0.663
58	Mitoxantrone	60.8	0.236	0.363	0.671
61	Podofilox	41.071	0.211	0.314	0.644
66	(+)-Taxifolin	34.277	0.276	0.413	0.819
76	Chloroquine	42.46	0.26	0.414	0.696
107	Colchicine	51.672	0.287	0.423	0.882
114	Saquinavir	86.9	0.151	0.237	0.415
115	Indinavir	76.144	0.147	0.233	0.403
116	Amprenavir	69.801	0.221	0.342	0.621
117	Chrysin	27.677	0.282	0.42	0.837
129	Zidovudine	33.488	0.331	0.497	0.973
141	Lamivudine	23.582	0.349	0.519	1.03
150	Kaempferol	32.004	0.278	0.416	0.828
151	Luteolin	32.088	0.267	0.404	0.78
160	Cyclosporine	582.739	0.44	0.689	1.214
163	Ritonavir	103.789	0.161	0.256	0.435
164	Myricetin	36.608	0.275	0.412	0.817
168	Oleanolic Acid	47.52	0.215	0.32	0.653
193	Nifedipine	50.628	0.377	0.547	1.204
413	Sirolimus	159.248	0.178	0.28	0.488
483	Tenofovir	33.803	0.293	0.455	0.81
484	Adefovir	31.274	0.282	0.443	0.764
593	Delavirdine	52.159	0.166	0.267	0.439
625	Thiabendazole	18.185	0.311	0.458	0.935
713	Entecavir	29.767	0.29	0.43	0.875
729	Lopinavir	90.532	0.173	0.271	0.477
853	Zalcitabine	23.582	0.349	0.519	1.03
885	Emtricitabine	25.889	0.35	0.52	1.041
964	Disulfiram	60.801	0.685	1.063	1.887
991	Stavudine	25.889	0.35	0.52	1.041
7187	Costatolide	39.569	0.262	0.381	0.826
1460	Didanosine	23.687	0.29	0.432	0.863
6246	Ellagic Acid	29.481	0.287	0.412	0.927
7187	Costatolide	39.569	0.262	0.381	0.826
8260	Baicalein	29.825	0.28	0.418	0.83
9352	Naringenin	29.885	0.27	0.407	0.789
12014	Harman	18.019	0.355	0.502	1.146
13134	Palinavir	95.629	0.142	0.226	0.386
16901	Honokiol	36.232	0.315	0.478	0.909

good prediction models, since it presents values of Specificity and Sensitivity close to 50% (values for a random classifier). On the other hand, the Linear Neural Network (LNN) predictor based on 19 descriptors (LNN 19:19-1:1) is able to classify correctly above 76% of the cases in training and validation (see Table 5). This model presented high values of Sensitivity = Sn = 76.46 and Specificity = Sp = 77.13 in training and Sn = 77.30 and Sp = 75.67 in the external validation sets.

Figure 2 shows the AUROC values for the different ANN models. The LNN network shows values of AUROC = 0.82 in the training and external validation set. These values are typical of a classifier with a classification behavior different from a random classifier (AUROC = 0.5).[70] The sensitivity analysis allowed us to quantify (rank) and order (ratio) into a sequence the importance

Table 3. Average Values of the Information Descriptors of Molecular Structure under Different Boundary Conditions

c_1	experimental measure	$N(c_j)$	$\langle I^q_1 \rangle$	$\langle I^q_2 \rangle$	$\langle I^q_3 \rangle$	$\langle I^q_4 \rangle$
IC_{50} (nM)	inhibitory concentration 50%	20332	64.303	0.209	0.324	0.587
EC_{50} (nM)	effective concentration 50%	14981	60.888	0.219	0.337	0.625
K_i (nM)	inhibitory constant	3736	78.878	0.180	0.282	0.501
IC_{95} (nM)	inhibitory concentration 95%	1290	59.295	0.189	0.296	0.521
IC_{90} (nM)	inhibitory concentration 90%	1118	54.730	0.226	0.338	0.682
ED_{50} (nM)	effective dose 50%	860	63.303	0.238	0.367	0.677
EC_{50} ($\mu g \cdot mL^{-1}$)	effective concentration	526	62.576	0.233	0.352	0.685
IC_{50} ($\mu g \cdot mL^{-1}$)	inhibitory concentration	335	147.952	0.254	0.406	0.687
EC_{90} (nM)	effective concentration	67	41.936	0.308	0.468	0.884
IC_{90} ($\mu g \cdot mL^{-1}$)	inhibitory concentration 90%	4	62.001	0.238	0.360	0.699
c_2	target protein	$N(c_j)$	$\langle I^q_1 \rangle$	$\langle I^q_2 \rangle$	$\langle I^q_3 \rangle$	$\langle I^q_4 \rangle$
CC-CKR-5	C–C chemokine receptor type 5	2304	62.466	0.152	0.243	0.405
CC-CKR-2	C–C chemokine receptor type 2	2009	64.050	0.170	0.273	0.448
CC-CKR-3	C–C chemokine receptor type 3	1206	56.723	0.156	0.253	0.410
CC-CKR-4	C–C chemokine receptor type 4	345	53.788	0.184	0.289	0.505
CXCR-4	C-X-C chemokine receptor type 4	332	147.452	0.178	0.278	0.497
HIV-1 RT	HIV-1 reverse transcriptase	4029	47.002	0.253	0.384	0.738
HIV-1 IN	HIV-1 integrase	1702	62.249	0.241	0.371	0.674
HIV-1 PR	HIV-1 protease	5946	89.711	0.184	0.288	0.513
GP160	envelope polyprotein GP160	34	45.879	0.224	0.353	0.611
c_3	organism	$Ni(c_2)$	$\langle I^q_1 \rangle$	$\langle I^q_2 \rangle$	$\langle I^q_3 \rangle$	$\langle I^q_4 \rangle$
HIV-1	HIV-1	34544	64.299	0.221	0.340	0.630
mmu	*Mus musculus*	68	64.004	0.157	0.251	0.423
hsa	*Homo sapiens*	6128	65.954	0.162	0.259	0.430
HIV-2	HIV-2	1030	81.747	0.198	0.311	0.547
HIV	HIV	1479	52.782	0.203	0.314	0.578
c_4	assay	$N(c_j)$	$\langle I^q_1 \rangle$	$\langle I^q_2 \rangle$	$\langle I^q_3 \rangle$	$\langle I^q_4 \rangle$
1033994	antiviral activity against HIV1	282	44.250	0.261	0.398	0.752
708445	effective concentration required for the inhibition of HIV-1 IIIB in MT-4 cells	176	102.090	0.158	0.251	0.424
859312	inhibitory activity was determined against HIV type 1 protease	175	112.916	0.164	0.258	0.450
659084	inhibitory conc for displacement of [125I]-MIP-1 alpha from human CCR5 in CHO cell	141	73.162	0.131	0.210	0.345
763303	inhibition of HIV-1 protease	118	72.588	0.177	0.269	0.515
974332	displacement of [125I]MIP1alpha from human CCR5 expressed in CHO cells	109	57.925	0.137	0.219	0.367
660813	inhibitory activity against recombinant human Chemokine receptor type 3 (CCR3) expressed in Chinese hamster ovary cells	108	57.228	0.154	0.248	0.406
833931	inhibitory activity against wild type HIV-1 LAI cell line	106	46.897	0.306	0.459	0.906

of the different chemoinformatics vs pharmacoepidemiology inputs. This kind of model may be useful to predict different situations of interest in pharmacoepidemiology. For instance, the model is able to identify when the same drugs present a strong effect on population epidemiology for different counties $(L_{aq}(c_j)_{pred} = 1)$. Table 6 shows the predictions for some cases with the LNN model. In the table we can see that the model predicts $L_{aq}(c_j)_{pred} = 1$ for Nevirapine[75] in different counties, which is a drug $L_{aq}(c_j)_{obs} = 1$ for these counties. In Table SM4 of the Supporting Information, we provide the results predicted with the LNN model for all the cases in training and external validation series.

Last, we used this LNN-ALMA model to generate/predict a complex network of the AIDS prevalence in the US at county level with respect to the preclinical activity of anti-HIV drugs in preclinical assays. The network is bipartite with two classes of nodes (counties vs drugs). In this sense, it is a multiscale network similar to the bipartite networks of drugs vs target proteins reported by other groups.[76−80] However, the drug nodes of the present network contain information about the drug structure as well as all the assay conditions (target protein, organism, assay protocol, experimental measure). In addition, the other set of nodes is typical of a social network because they contain

information about the income inequality in the county. Therefore, this complex network is multiscale, linking information about drugs, targets, assays, and society in the same line of thinking expressed by Barabasi et al.[81] The links of this complex network are the outputs $L_{aq}(c_j)_{pred} = 1$ of our model. That is why we analyzed 43,249 data points to fit the model and predict the complex network at the same time. Consequently, we have to include values of AIDS prevalence in 2,310 US counties vs ChEMBL results for 21,582 unique drugs, 9 viral or human protein targets, 4,856 protocols, and 10 possible experimental measures. In Figure 3, we illustrate the subnetwork of AIDS prevalence vs anti-HIV drug preclinical activity for the state of Texas. We include some examples of drugs like Efavirenz (ChEMBL223228) and Saquinavir (ChEMBL114) with observed and predicted $L_{aq}(c_j)_{obs} = L_{aq}(c_j)_{pred} = 1$ effects on AIDS prevalence in the counties of Kendall, Jasper, and Victoria, respectively.

We used the sensitivity analysis of the ANN module implemented in STATISTICA to detect the parameters with the higher contribution to the model. We can conduct the sensitivity analysis on the inputs to one ANN by a STATISTICA Neural Networks algorithm. The sensitivity analysis ranks the order of input importance by treating each input variable in turn as if it were "unavailable".[82] It is defined a missing value substitution procedure, which allows predictions to be made in

Table 4. Values of $I^a_0(t)$ for Some Counties of Different States

state(s)	county name	$D_a{}^a$	$G_a{}^b$	$I^a_0(t)$
AL	Autauga County	181	0.405	0.15898072
AL	Baldwin County	188	0.439	0.15695808
AR	Arkansas County	165	0.467	0.15442902
AR	Ashley County	97	0.447	0.15631254
AZ	Apache County	124	0.488	0.15205113
AZ	Cochise County	134	0.435	0.15725717
CA	Alameda County	396	0.456	0.15551203
CA	Amador County	114	0.399	0.15921181
CO	Adams County	179	0.403	0.15906207
CO	Alamosa County	78	0.474	0.15368107
CT	Fairfield County	375	0.537	0.14500381
CT	Hartford County	434	0.458	0.15532361
FL	Alachua County	383	0.516	0.14827275
FL	Baker County	380	0.429	0.15767582
GA	Appling County	105	0.422	0.15811815
GA	Atkinson County	256	0.447	0.15631254
HI	Hawaii County	199	0.458	0.15532361
HI	Honolulu County	201	0.422	0.15811815
IA	Boone County	58	0.407	0.15889508
Ia	Ada County	101	0.435	0.15725717
ID	Bannock County	100	0.429	0.15767582
IL	Adams County	65	0.453	0.15578751
IN	Adams County	21	0.380	0.15968223
IN	Allen County	136	0.428	0.15774207
KS	Allen County	44	0.394	0.15937449
KS	Atchison County	57	0.434	0.15732946
KY	Allen County	71	0.42	0.1582353
KY	Anderson County	76	0.376	0.15972937
KY	Barren County	56	0.455	0.15560481
LA	Acadia Parish	174	0.452	0.15587743
LA	Allen Parish	550	0.434	0.15732946
LA	Ascension Parish	178	0.409	0.15880517
MA	Berkshire County	102	0.462	0.15493541
MD	Allegany County	180	0.446	0.15639665
MD	Calvert County	124	0.369	0.15976727
ME	Hancock County	73	0.437	0.15710961
MI	Allegan County	74	0.402	0.15910113
MI	Barry County	44	0.392	0.15943186

$^a D_a$ is the AIDS prevalence rate in the county a^{th} in 2010. $^b G_a$ is the Gini income-inequality measure of the US county in 2010.

the absence of values for one or more inputs. To define the sensitivity of a particular variable X, the first run uses the network on a set of test cases and accumulates the network error. In the second step, the network is employed again using the same cases but replacing the observed values of X with the value estimated by the missing value procedure, and again it calculated the accumulated network error. By removing the variable X, it is expected for some deterioration in error to occur. Therefore, the measure of sensitivity is the ratio of the error with missing value substitution to the original error. The more sensitive the network is to a particular input, the greater the deterioration is expected, and therefore the greater the ratio. The elimination of a variable with ratio ≤1 improves or has no effect on the performance of the ANN. After the sensitivities are calculated, they are ranked in order. In Table 7 we can see that the model shows a higher relevance to the information about the molecular structure, parameters of type I^q_k. Second, the model ranks the information about the organism used to measure the biological activity, parameters of type $\Delta I^q_k(c_3)$. The third type of relevant input is

the experimental measure used to quantify the activity of the drug, parameters of type $\Delta I^q_k(c_1)$. The fourth ranked inputs in order of importance are parameters of type $\Delta I^q_k(c_2)$, which quantify the target protein. The fifth type of input quantifies information about the assay protocol used to test the drug. The last effect introduced in the model was the information about income inequality in the county $I^a_0(t)$. Thus, the sensitivity analysis shows that the model is ranked according to the importance of factors in the following order (AIDS epidemiology/anti-HIV drug) ≈ structure of drug > organism in preclinical assay > experimental measure of activity > drug target > pharmacological assay > county income inequality. Table 7 depicts the parameters in decreasing order of their contribution to the model (higher contribution => higher ratio => lower rank). The five parameters with higher contribution are the following: I^q_2, I^q_4, $\Delta I^q_2(c_3)$, $\Delta I^q_2(c_1)$, I^q_3. The parameters of higher contribution for each type of information are the following: I^q_2 with rank = 1, $\Delta I^q_2(c_3)$ rank = 3, $\Delta I^q_2(c_1)$ with rank = 4, $\Delta I^q_2(c_2)$ with rank = 13, $\Delta I^q_2(c_4)$ with rank = 15, and $I^a_0(t)$ with rank = 17 (shown in boldface in Table 7).

We retrained the model using only these parameters, but the new ANN fails to generate good predictive models with Sp and Sn < 50%. It means that the model provides a greater importance to the chemical structure and pharmacological information (branch A), with respect to county information (branch B), but it needs all the parameters. This could be explained taking into consideration that branch A includes the higher number of input factors (information considered), whereas branch B includes only one input factor, the income-inequality in the county with respect to the state. We should also note that the only epidemiological feature used as input to calculate the Shannon information indices of the county was the G_a measure of income inequality. The G_a measure of income-inequality is widely used as a descriptor to approach the study of the epidemiology of different diseases.[83,84] The values of $G_a \approx 0$ are characteristic of societies with near-to-ideal equalitarian distribution of income, whereas values of $G_a \approx 1$ are typical of inequality in income distribution.[85] Gant et al.[86] found a positive value of the Pearson
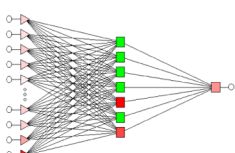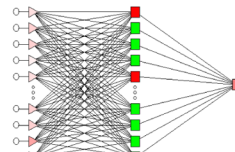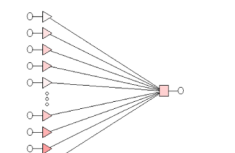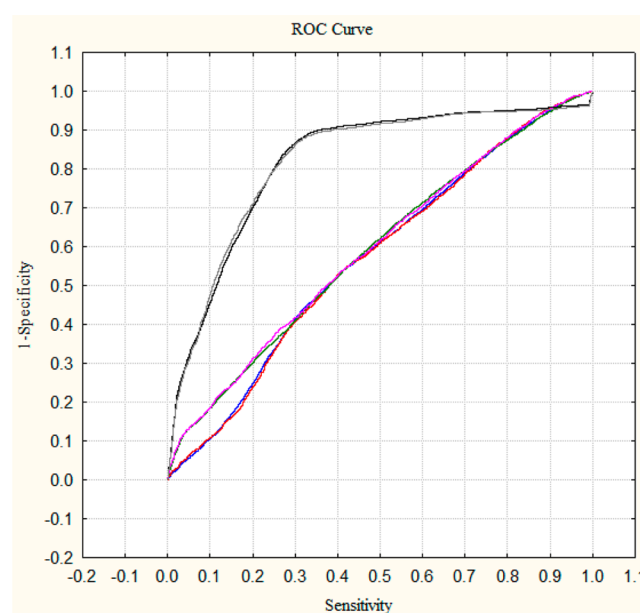

Figure 2. ROC curve analysis of LNN (gray color) vs MLPs (other colors) classifiers.

Table 5. Linear vs Nonlinear ANN Models

ANN models	Data sets	Training set		Validation set	
	Observed	$L_{aq} = 0$	$L_{aq} = 1$	$L_{aq} = 0$	$L_{aq} = 1$
MLP 13:13-7-1:1	Parameter [a]	Sn	Sp	Sn	Sp
	Predicted	55.79	56.17	56.52	55.67
	$L_{aq} = 0$	13469	3637	4534	1237
	$L_{aq} = 1$	10670	4661	3487	1554
	AUROC	0.57		0.57	
MLP 16:16-11-1:1	Parameter [a]	Sn	Sp	Sn	Sp
	Predicted	56.13	56.20	56.63	55.67
	$L_{aq} = 0$	13550	3634	4543	1237
	$L_{aq} = 1$	10589	4664	3478	1554
	AUROC	0.59		0.59	
LNN 19:19-1:1	Parameter [a]	Sn	Sp	Sn	Sp
	Predicted	76.46	77.13	77.30	75.67
	$L_{aq} = 0$	18458	1897	6201	679
	$L_{aq} = 1$	5681	6401	1820	2112
	AUROC	0.82		0.82	

[a]Parameter, Sp = Specificity, Sn = Sensitivity. Columns: observed classifications; Rows: predicted classifications.

Table 6. Predictions of Some Cases with the LNN Network

CMPD_ID	$L_{aq}(c_j)_{obs}$	$L_{aq}(c_j)_{pred}$	c-level	measure	name	target	organism	assay_ID	state_county
1172035	1	1	0.37192	IC_{50} (nM)	Nifeviroc	CC-CKR-5	hsa	1174016	MO_Laclede
1172035	1	1	0.41989	IC_{50} (nM)	Nifeviroc	CC-CKR-5	hsa	1174015	MO_Macon
1201187	1	1	0.43568	IC_{50} (nM)	Maraviroc	CC-CKR-5	hsa	1034062	MI_Tuscola
1201187	1	1	0.44035	IC_{50} (nM)	Maraviroc	CC-CKR-5	hsa	1019461	MN_Nicollet
129	1	1	0.36238	IC_{50} (nM)	Zidovudine	HIV	HIV	640394	IN_Hancock
175691	1	1	0.55885	IC_{95} (nM)	Rilpivirine	HIV	HIV	1930128	WA_Mason
175691	1	1	0.52729	IC_{95} (nM)	Rilpivirine	HIV	HIV	1930283	WA_Pacific
308954	1	1	0.32563	IC_{50} (nM)	Etravirine	HIV	HIV	1006144	GA_Gordon
308954	1	1	0.31279	IC50 (nM)	Etravirine	HIV	HIV	1006139	GA_Lumpkin
57	1	1	0.40037	ED_{50} (nM)	Nevirapine	HIV-1	HIV-1	709947	TX_Dawson
57	1	1	0.45551	ED_{50} (nM)	Nevirapine	HIV-1	HIV-1	709946	TX_Denton
114	1	1	0.34536	IC_{50} (nM)	Saquinavir	HIV-1	HIV-1	755976	IL_Whiteside
114	1	1	0.34894	IC_{50} (nM)	Saquinavir	HIV-1	HIV-1	868005	CA_Mono
114	1	1	0.32824	IC_{50} (nM)	Saquinavir	HIV-1	HIV-1	866135	CA_Placer
129	0	0	0.17658	EC_{50} (nM)	Zidovudine	HIV-1	HIV-1	884233	NC_Durham
129	0	0	0.18634	EC_{50} (nM)	Zidovudine	HIV-1	HIV-1	688523	NC_Edgecombe
141	0	0	0.16086	EC_{50} (nM)	Lamivudine	HIV-1	HIV-1	1263166	GA_Crisp
141	0	0	0.15857	EC_{50} (nM)	Lamivudine	HIV-1	HIV-1	1263167	GA_DeKalb
141	0	0	0.13955	EC_{50} (nM)	Lamivudine	HIV-1	HIV-1	1263157	GA_Dooly
484	0	0	0.26125	EC_{50} (nM)	Adefovir	HIV-1	HIV-1	1831866	OH_Hocking
484	0	0	0.17849	EC_{50} (nM)	Adefovir	HIV-1	HIV-1	1831858	OH_Jackson
1163	0	0	0.14076	EC_{50} (nM)	Atazanavir	HIV2	HIV-2	991367	MO_Polk
1163	0	0	0.09766	EC_{50} (nM)	Atazanavir	HIV2	HIV-2	991368	MO_Taney
1163	0	0	0.15377	IC_{50} (nM)	Atazanavir	HIV2	HIV-2	1262836	TN_Putnam
222559	0	0	0.23747	IC_{50} (nM)	Tipranavir	HIV2	HIV-2	1264851	TX_Camp
222559	0	0	0.20195	IC_{50} (nM)	Tipranavir	HIV2	HIV-2	1262828	TX_Cass
625	0	0	0.26799	EC_{50} (nM)	Thiabendazole	HIV-1	HIV-1	689145	WI_Jefferson

correlation coefficient $\rho = 0.40$ between AIDS diagnosis rates and G_a for 1,560 US counties between 2006 and 2008. However, they also found a positive correlation ($\rho = 0.52$) with proportion unmarried − ages >15 years. The AIDSVu data presented an average value of $G_a = 0.435$ and a standard deviation of only 0.03. The AIDSVu data set analyzed in this work presents an even weaker correlation ($\rho = 0.31$) between AIDS diagnosis rates in 2010 and G_a for the 2,310 US counties studied in this work. It
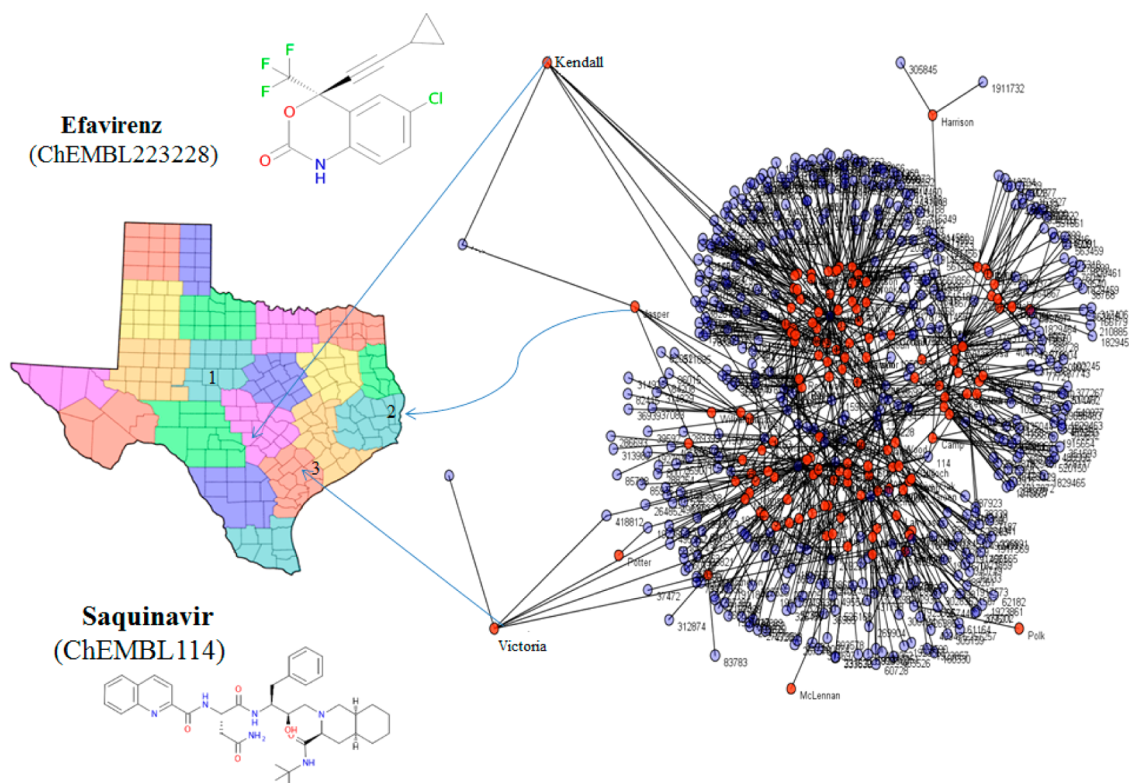
Figure 3. Predicted subnetwork of AIDS prevalence vs anti-HIV drug preclinical activity for Texas.

Table 7. Sensitivity Analysis for the LNN Network

index	name of information indices and their MA operators[a]	ratio	rank
I^q_2	Balaban V-index for drugs	532.48	**1**
I^q_4	Balaban X-index for drugs	336.91	2
$\Delta I^q_2(c_3)$	MA of V-index of drugs assayed in the same organism	263.34	3
$\Delta I^q_2(c_1)$	MA for V-index of drugs with the same experimental measure	254.03	4
I^q_3	Balaban Y-index for drugs	194.36	5
$\Delta I^q_4(c_3)$	MA of X-index of drugs assayed in the same organism	169.38	6
$\Delta I^q_4(c_1)$	MA for X-index of drugs with the same experimental measure	158.25	7
$\Delta I^q_3(c_3)$	MA for Y-index of drugs with the same organism	94.37	8
$\Delta I^q_3(c_1)$	MA for Y-index of drugs with the same experimental measure	94.09	9
I^q_1	Balaban U-index for drugs	10.56	10
$\Delta I^q_1(c_1)$	MA for U-index of drugs with the same experimental measure	5.55	11
$\Delta I^q_1(c_3)$	MA for U-index of drugs with the same organism	5.08	12
$\Delta I^q_2(c_2)$	MA for V-index of drugs with the same protein target	1.09	13
$\Delta I^q_4(c_2)$	MA for X-index of drugs with the same protein target	1.02	14
$\Delta I^q_2(c_4)$	MA for V-index of drugs tested in the same assay	1.01	15
$\Delta I^q_3(c_2)$	MA for Y-index of drugs tested with the same protein target	1.01	16
$I^a_0(t)$	Shannon information index based on the Gini coefficient	1.01	17
$\Delta I^q_4(c_4)$	MA for X-index of drugs tested in the same assay	1.01	18
$\Delta I^q_3(c_4)$	MA for Y-index of drugs tested in the same assay	1.0	19

[a]MA = Moving Average operator of Box-Jenkins.

may indicate that possibly we should include other factors in branch B in order to collect additional epidemiological information relevant to the present problem. In upcoming papers we will continue working on the strategy described here, including other information indices of the molecules, other epidemiological factors, different disease transmission matrices, and using different types of machine learning algorithms.

4. CONCLUSIONS

We developed a model called LNN-ALMA to generate complex networks of the AIDS prevalence in the US counties with respect to the preclinical activity of anti-HIV drugs. The best classifier found was the LNN; the inputs of this classifier are based on Balaban information indices. Consequently, this model may be useful to predict the most effective drugs to treat HIV in different populations (from the US counties) with a given epidemiological prevalence. In future work, we will continue to improve the models, and we will include other information indices, social and economic factors, machine-learning techniques, etc.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The additional tables include the information indices for all the molecules, averages of information indices of the molecules, information indices for the all the US counties, and the results of the LNN model. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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