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SignalDetectioninPharmacovigilance:AReviewofInformatics-driven ApproachesfortheDiscoveryofDrug-DrugInteractionSignalsinDifferent DataSources

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| article | info | abstract |
| *Keywords:*  MachineLearning  DataMining  AdverseDrug–DrugInteraction SignalDetection  Pharmacovigilance | | Theobjectiveofthisarticleistoreviewtheapplicationofinformatics-drivenapproachesinthepharmacovigilance fieldwithfocusondrug-druginteraction(DDI)safetysignaldiscoveryusingvariousdatasources.Signalcanbea newsafetyinformationornewaspecttoalreadyknownadversedrugreactionwhichispossiblycausallyrelated toamedication/medicationsthatwarrantsfurtherinvestigationtoacceptorrefute.Signalscanbedetected fromdifferentdatasourcessuchasspontaneousreportingsystem,scientificliterature,biomedicaldatabasesand electronichealthrecords.ThisreviewissubstantiatedbasedonthefactthatDDIsarecontributingtoapublic healthproblemrepresentedin6-30%adversedrugeventoccurrences.Inthisarticle,wereviewinformatics-drivenapproachesappliedbyauthorsfocusingonDDIsignaldetectionusingdifferentdatasources.Theaim ofthisarticleisnottolaboriouslysurveyallPVliterature.Asanalternative,wediscussedinformatics-driven methodsusedtodiscoverDDIsignalsandvariousdatasourcesreinforcedwithinstancesofstudiesfromPV literature.Theadoptionofinformatics-drivenapproachescancomplementandoptimizethepracticeofsafety signaldetection.However,furtherresearchesshouldbecarriedouttoevaluatetheefficiencyofthoseapproaches andtoaddressthelimitationsofexternalvalidation,implementationandadoptioninrealclinicalenvironments andbytheregulatorybodies. |

**1.Introduction**

*1.1.Pharmacovigilancebackground*

DrugsafetymonitoringidentifiedasPharmacovigilance(PV)isfor-mallydefinedbythe“WorldHealthOrganization(WHO)” as“thesci-enceandactivitiesrelatingtothedetection,assessment,understand-ingandpreventionofdrug-relatedproblems” [1].PVmaybeclassified intotwocategories:(1)preauthorizationPVconcerningtheinforma-tionadversedrugeventsaccumulatedfromclinicaltrialsettings(phase 0/IthroughphaseIII)[2];and(2)postmarketing/post-authorizationPV concerningthesafetyinformationcollectedduringpost-authorization lifecycle.Eventhoughpre-authorizationclinicalstudies(i.e.RCTs)are deliberatedasthelineamentofexplainingadrugefficacy,theydon’t usuallydetectwholesafetyconcernsofacertaindrugbeforeitsuse intherealworldduetowell-knownlimitations.Thoselimitationscan besummarizedintherestrictedsampleoftrialparticipantsinvolvedin

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thosestudiescomparedtothetotaltargetedpopulationwhomayexperi-encethedrugwhenevermarketed,thelimitedintervalofdrugexposure pereachstudyparticipantespeciallyifthedrugprojectedforchronic use,lackofpossiblyriskypatientsubpopulationswhoareusuallyomit-tedfromclinicaltrials(e.g.,patientswithimpairedorgans,elderlypa-tients,children,andchildbearingwomanwhomaybepregnantorlac-tatingmother,patientsonchemotherapy)[3].Furthermore,RCTscan’t detectrare/veryrareadversedrugreactions(ADRs)(withoccurrences of1/10000and1/100000,respectively)orlatentADRs(*>*6months) [4].Thatsaid,thedrugefficacyinformationfrompremarketingRCTs isgenerallymorecomprehensiveandreliable,whereascompletesafety profilescan’tbeestablished[4].Theseboundariesimposeobligationsof bothmarketingauthorizationholdersandregularityauthoritiestocon-tinuouslymonitor,collect,assess,anddrawconclusionsandappropriate actionstokeeppositivebenefit-riskratioaslongasthedrugexistsin market.

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*1.2.Drug-druginteractiondetection*

Oneoftheleadingcausesofglobalmorbiditiesandtreatmentfailure isinteractionbetweendrugagents.About30%ofunexpectedadverse drugeventsmaybeaccountedforDrug-druginteractions(DDIs)[5].In acknowledgmentofadversedrugeffectsisachiefreasonofproductat-tritioninlatestagesofthedrugdevelopmentcycle,theearlierdetection oftheinteractionprofilesofnoveldrugcandidatesisstillintractable. Inconventionaldrugdevelopmentprocess,manyofcandidatesofnovel therapeuticsareinvestigatedaforetriagingaslightquantityofeligi-blemolecules,ordinarilydependsonpriorscientists’experienceinthe therapeuticdomainandarenominatedforsubsequentlaboratoryand preclinicaltesting.Regulardrugdiscoveryprocessincludesthedelivery ofnewcandidatesfrombasicmedicinalscientistsintotestinginpre-clinicalphasesfollowedbyaconductionofdifferentclinicaltrials.Un-predictabledruginteractionsmayresultinserioushealthoutcomesand consequentlyundesirableinfluencesonthewholedrugdiscoverypro-gression.Accordingly,anincreasingdemandfordevelopinginformatics-basedframeworkstodiscoversafetycomprehensionintermsofclini-calpracticeandoriginateDDIsofnoveltherapeuticnomineesearlier indrugdevelopmentthroughmultidisciplinarylinkingbetweenclinical andpreclinicalinformation.[6].

Additionally,premarketingclinicalstudiesdon’tusuallyexplore DDIsbutratheremphasizeoninvestigatingtheefficacyandsafetyof individualmedications[7].Sincepatientsonpolypharmacyarenotusu-allyincludedinclinicaltrials.Furthermore,wheneverDDIsaredoubted, samplingbiasesandcohortsizesboundthecapabilityforidentifying rareadversereactions[8].Interactionsbetweendrugsmaytakeplace whensharingthesametargetproteins,pharmacologicalandmetabolic pathwaysleadingtoaffectingthesafetyand/orefficacyprofileofphar-maceuticalproducts.Inothermeans,theco-administrationmayconsid-erablyaffecttheefficacyand/orsafetyprofilesofadrugagent.Un-predictableDDIsarerecognizedonlythroughsignaldetectionprac-ticesandpostmarketinglifecycle[9].ThemagnitudeofaDDIseri-ousnesswarrantsdifferentregulatoryactionsgradingfromlabelinfor-mationchangesintomarketwithdrawals[10–12].Duetothelimita-tionsanddifficultiesinmonitoringinteractionprofilesofdrugs,mul-tipleinformatics-basedresearcheshavebeenemergedinrecentyears forDDIdiscoveryviaadoptingmachinelearning(ML)anddatamining methodsfromheterogeneousdatasources.

DDIscanbeclassifiedbyvariouscriteria.Withregardtoseverity, interactionsarefrequentlycharacterizedbythreecategoriesaccording toseverityinto(minor,moderateandmajor)[13].Thoseinteractions havingminimalclinicalconsequencesandminimalriskareclassifiedas minorDDIs.ModerateDDIiswithmoderateclinicalsignificance,usu-allyavoidthesecombinationsandtheymaybeusedonlyunderspecial circumstanceswithclosermonitoringandmayrequiredosagechanges. MajorDDIiswithhighclinicalsignificanceprobablyleadingtoseri-ousclinicaloutcomesshouldbeavertedduetonegativebenefit-risk ratios.

Intermsofmechanism,DDIsareclassifiedaseitherpharmacody-namic(PD)orpharmacokinetic(PK)[14].ItisnoteworthythatPD–basedDDIsmakeupasmallerclassthanPK-basedDDIs.APharmaco-dynamic(PD)interactionoccurswhenthepharmacologicaleffectofa drugisaffectedbyanotherasaresultof:1)directeffectattargetsite, (2)interferencewithbiologicalorphysiologicalsignalingpathways,re-sultinginadditive,orantagonisticeffects,orsynergistic/indirectphar-macologiceffect[15].Pharmacokinetic(PK)interactionoccurswhena druginfluencesthedispositionofanotherdruginthebodybyinterfering itsabsorption,distribution,metabolism,orelimination(ADME)proper-ties,causinganalteredplasmaconcentrationofthefirstdrugthatmay leadtodetrimentalconsequences(treatmentfailureortoxicity).Within thepharmacokineticprocesses,themetabolismpartcoversthelargest [16].Arecentstudy[17]hasestimatedthatthePK-basedDDIsoccurat metaboliclevelasfollows:(i)64%ofPK-relatedDDIsinvolveinduction orinhibitionofthehepaticcytochromesthatareaccountableformedi-

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**2.WidespreaddatasourcesinsupportofPharmacovigilance**

*2.1.PostmarketingPharmacovigilanceData:Spontaneousreporting systems*

PostmarketingPVdataaremainlyavailableinseveraluniquedata sourcesthroughSpontaneousreportingsystems(SRSs).Thistypeof spontaneousdataisthemainsourceforpostmarketingmonitoringun-tilnow.SRSsarelargedatabasesforcollectingindividualcasesafety reports(ICSRs)ofsuspectedadverseeventspassivelyreportedtoreg-ulatoryauthoritiesbypatients,healthcareprofessionals,andindustry. TheVigiBase(theWHO-UMCglobaldatabaseofICSRs)[19],USFood andDrugAdministration(FDA)adverseeventreportingsystem(FAERS) [20,21],theEuropeanEudraVigilance[22],andthe“vaccineadverse eventreportingsystems(VAERS)” [23]arethemostprominentICSRs managementsystems.

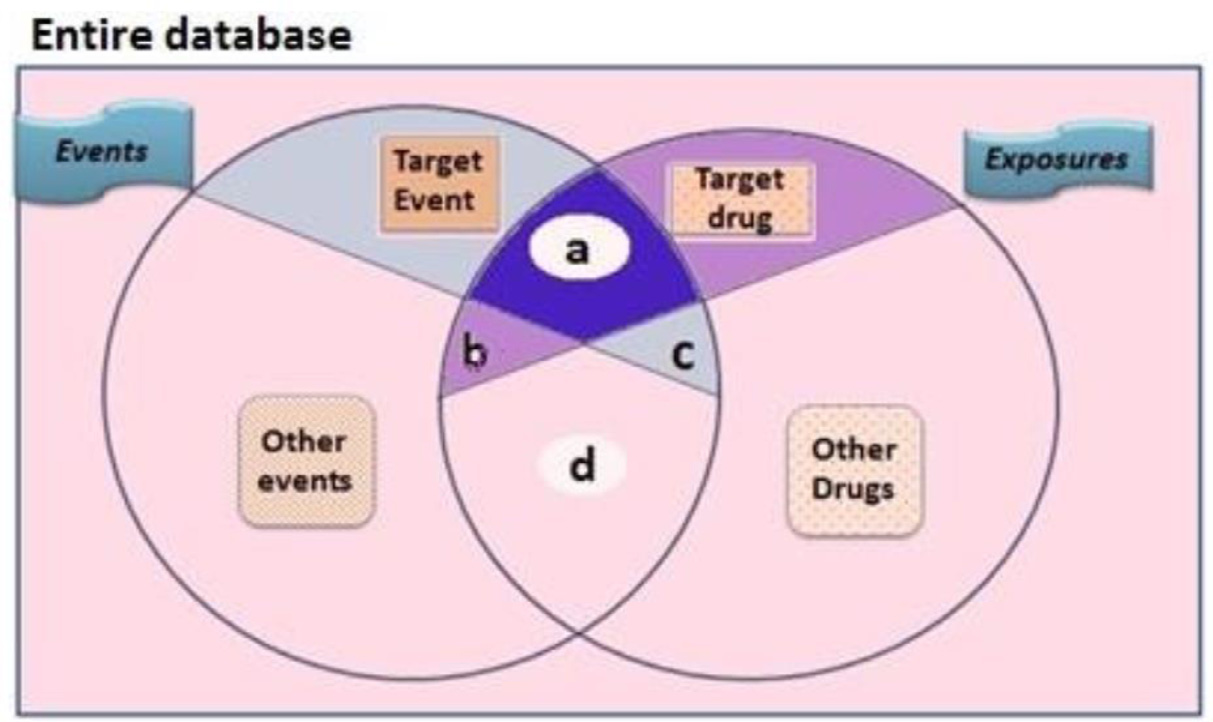
SuchkindofSRSsaredevelopedtoenablecontinuousmonitoringof pharmaceuticalandbiologicalproductswithinpharmacovigilancesys-tems[24].Generally,thestructureofSRSsadherestotheinternational safetyreportingguidanceissuedbytheInternationalConferenceonHar-monisation(ICHE2B)thatsetsstandardsforreportingindividualcase safetyreports(ICSR)[25].OthertypeofSRSsistheproprietarycom-panysafetydatabasesthatcontainICSRsofacompanypharmaceutical products.Theycansupportearlysafetysignaldetection.Themeritsof SRSsarerepresentedinprovidinginformationnecessaryforestablishing causalityassessmentfromrealdataand/ordevelopingmining/MLmod-elsthatmightnotbeavailableinotherdatasources.Forexamplebut notlimitedto,apparenttemporaltimerelationship,concomitantmed-ications,indications,de-/re-challengeinformation,somedemographic patientdata,andactiontaken&outcomeInformation.Despitemulti-benefitsofSRSswhichplayingacrucialroletosupportwisetherapeu-ticdecision-makinginregulatorybodies,theyhavewell-knownbound-aries.Thoselimitationscanbesummarizedinover-/under-reporting rates,limitedpastmedicalhistoryofpatients,falsesignalingduetomis-attributiontohiddenconfounders/riskfactors,andinabilitytoindicate realincidencerates.

*2.2.ElectronicHealthcareData*

Electronichealthcaredataconsistsofmultiplesourceslikeelectronic healthrecords(EHRs),administrativeandinsuranceclaimsdatabases. EHRsareakindoflongitudinalobservationalsystemswherepatients’medicalrecordsarecreatedfrommultiplesystemsinhealthcareor-ganization(s).ManyoftheEHRfieldsarecomposedofunstructured data(e.g.dischargesummaries,labtestfindings,nursenotifications, etc.)andnon-specificadverseevents.Naturallanguageprocessing(NLP) studiesshowhowusingEHRsdataviaadoptingtextminingapproaches canbebeneficialforextracting,encoding,anddetectingsafetysignals [26–29].ThemainbenefitofEHRsfromtheaspectofPVistheircapabil-itytoconductactivesurveillancefromreal-workdata[30–32].Merits distinguishEHRsystemsfromSRSscanrepresentedin:notcontaining duplicates,largelyunaffectedbyunder-orover-reportingastheytyp-icallyderivedautomatically,providingconsistentinformationonmost ofthesubject’sdrugexposureperiods,clinicallyrelevantevents(inde-pendentlyfromtheexposurestatus)andvaluableinformationonex-posedsubjectswithoutevents,andmuchmorecompleteassessment ofdrugexposureandcomorbiditystatus.Forthat,EHRsystemsmay generatesafetysignalsearlierthanSRSs.Nevertheless,theabovemen-tionedlimitationsconsiderthekeyboundariesforapplyinginregular PV.Otherlimitationscanberepresentedin:difficultytoaccessdueto privacyissues,andverychallengingpolicyandtechnicalissuestointe-grateEHRsfrommultiplesources.InEHRs,elevatedratesofamedical diagnosismayindicateasafetyissue(ifsubsequenttoprescription),so somestudieshavehypothesizedthatmetricsbasedonexploringlongi-tudinalobservationaldatasetfortemporalassociationsbetweenevents overtimeratherthanperson-countscouldproducemoreaccurateas-

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**Fig.1.VennDiagramillustratingtheentries{a,b,c,d}ofcon-tingencytable.**a,numberofreportscontainingboththesuspect drugandthesuspectadverseevent;b,numberofreportscontaining thesuspectdrugwithotheradverseevents(excepttheeventofin-terest);c,numberofreportscontainingthetargetadverseeventwith othermedications(exceptthedrugofinterest);d,numberofreports containingothermedicationsandotheradverseevents.

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| categorizedintotwogeneralclasses(frequentistandBayesian).Both categoriesutilizetheentriesofconfusionmatrix(asshownFig.1)to computethemagnitudeofstatisticalassociationbetweendrug-adverse-eventcombinations(DECs)inaPVdatabase[46].Theirprinciples dependonestimatingobserved-to-expectedreportingratiosfordrug-reactionpairsusingthetotalnumberofcasesinbackground[47–52]. Theyquantifytheunexpectednessofadverseeventbeingreportedto adrugordrugpair.AllDPAssharethesamebasicofdisproportion-atereportingbetweenobservedtoexpectedratios,despitetheydiffer incomputationpereach.WheneveraDEC’sDPAcomputationexceeds thepredefinedminimumthresholds,itwillbeflaggedasastatistical safetysignalthatrequiresfurtherclinicalassessment.Differentthresh-oldsareusedforthesealgorithmstoidentifysignificantsafetysignalsfor DECs.  *3.2.AssociationRuleMining*  BesidesDPAs,thereisanalgorithmcalled*associationrulemining* (abbreviatedasARM)[53].ARMisconsideredawell-knownmin-ingalgorithmfordisclosinginterestingpatternsconcealedwithinlarge databases.Thisalgorithmwasfirstadvancedsincemorethanadecade tobeappliedtothefieldofcomputerscience,thenexpandedtovarious sciences[54–56].SomestudieshaveadoptedARM-basedalgorithmsto detectadverseDDIpatternsusingSRSs[57].Apriorialgorithmisakind ofassociationrulesminingwhichoffersanappropriaterepresentation ofsparsedataforcomplexcomputations[53].Anyassociationrulecan beexpressedintheformof*𝑥*→ *𝑦*where*x*isanelementfromXitem-set,while*y*isanelementfromYitemset,notingthatx&yaredifferent items.Toestimatedirectionality,thegeneralApriorialgorithmworksin twosteps.Thekeyofprimarystepisbuiltoncountingafrequentitem setwhenanobservedassociationbetweenitemsexceedsthesupport threshold.Whilethesecondstepdependsongeneratingconfidentasso-ciationrulesfulfillingpredefinedminimumthresholds.Fromthescope ofPV,*𝑋* symbolizesanitemsetofmedicationsandysymbolizesanitem-setofadverse-reactions.Asignificantassociationruleindicatesthata specificDECexceedsminimumthresholdsofminimumconfidenceand support.ThesupportofaDEC*𝑆*(*𝑋*)istheobservednumeralsofreports having*𝑋*.Whilesupportofanassociationrule*𝑆*(*𝑋*→ *𝑌*)canbesym-bolizedas*𝑆*(*𝑋*∪ *𝑌*).Theconfidenceofanassociationrule*𝐶*(*𝑋*→ *𝑌*) indicates(*𝑆*(*𝑋*∪ *𝑌*))∕(*𝑆*(*𝑋*))(**1**).Confidencedefineshowfrequently objectsinYrepresentedinreportscontainingX.Confidenceenablesthe estimationofconditionallikelihood(*𝑃𝑟*(*𝑌*)∕(*𝑋*))(**2**)ofYinpresenceof X.Aninterestingassociationisflaggedwhenarulefulfillstheminimum thresholdsofbothsupport&confidence,howeversomestudieshave suggestedothermeasurestofiltersignificantDDIassociations[53]. | *3.3.Regression-basedApproaches*  Confoundersarehiddencovariatesthatmaybehiddenfactorslead-ingtoeitherflaggingspurioussafetysignalsordelayingthedetection ofsignificantones[58].Itisworthmentioningthatconfoundersmay inferariskfactorpredisposingtheadversereactionorakeytoidentify higherriskypatientsubpopulations.Asimplertypeofconfounderscan beseeninvariables(forexample,age,gender,andyear).Theymaybe handledeffectivelybythestratificationforeachstratumusingMantel–Haenszeladjustments[59,60].Nevertheless,adjustinghugenumeralsof possibleconfoundersmayresultinmissingsignaldetectioninatimely manner[61–63].Anotherlimitationisrepresentedinstratificationby gender,age-group,etc.wherethenumberofcasereportsarelowand theninfeasibletoconductsubgroupanalyses.Additionally,thereare otherformsofconfounderscalled“innocentbystander” responsiblefor theoccurrenceofadverseeventssuchasinteractingdrugsorindica-tionsofreportedcomedications.Unfortunately,usingMantel–Haenszel approachesforadjustingsuchkindofconfoundersisineffective[60]. Forlargenumbersofcovariates,adoptinglogistic-regression(LR)ap-proachismoreefficient[61].  LRextendslinearregressionfunctionbyasigmoidfunctiontoavalue intervalfrom0to1[62].LRcomputesRORbycategorizingdatabase’s recordsascase-controlrecordswhereacaseiscountedwheneverhav-ingadverse-eventofinterest,whereascontrolsarecountedwhenever recordshavingotheradverse-events.InthecontextofPV,twostudies havereportedadoptingLRmodelingusingSRSsaimingatDDIsignalde-tection[63,64].ThecomprehensionofLRcanbeexpressedaccording tothefollowingformula:  *̂𝑦*=*̂𝑝* ( *𝑥*1*,𝑥*2 ) =log*𝑝* 1−*𝑝*=*̂𝛽*0+*̂𝛽*1*𝑥*1+*̂𝛽𝑛𝑥𝑛*  (3)  Where*̂𝑦*denotespredictedoutcome;*̂𝛽*0=coefficientofslope; x0=Slope;*𝛽*n=coefficientofcovariatesn,Xn=numberofpredic-torsorfeaturescovariates.  **4.Paradigmsofdataminingandtextminingstudiesusing spontaneousreportingsystemsfordetectingDDIsignals**  Neverthelessthelimitationsofany“spontaneousreportingsystem (SRS)” inregularPVpractices,SRSsprovideprecioustoolindetecting previouslyunknownsafetyconcerns[65].DPAsrepresentthemostcom-monlyappliedalgorithmsintheareaofquantitativesignaldetection withinhealthauthoritiesandlargepharmaceuticalindustry[66,67]. TheShrinkagemeasureΩ,whichistheextensionofICmeasurefor thetriplets{drug-drug-AE},hasbeeninnovatedbyNorén*etal*.atUp-psalamonitoringCentre(UMC)toscreenpotentialDDIsignalsinthe |

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VigiBase[9].AuthorshaveshowntheprivilegesofΩ shrinkagemea-surecomparedtologisticregressionindetectinginterestingpatternsof DDIsignals.Itcanbecalculatedbyestimatingtheproportionbetween observedandexpectedfrequenciesasseeninthefollowingequation;

|  |  |  |
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| Ω =*𝑙𝑜𝑔*2 | *𝑛*111+*𝛼*  *𝐸*111+*𝛼* | (4) |
| WhereE111standsforthe“expected” incidencevalueofdrug-drug-eventcombinationwithinaPVdatabase;aisaconstantequalsto0.5; Ω025isthelowerboundaryof95%confidenceintervalwhichflaga statisticalDDIsignalwhenitsvalue≥0[9].In2013,Choi*etal.*have investigatedthefeasibilityofusingthenationalKoreanhealthinsurance systemnamed“HIRA” inidentifyingDDIsignals[68].Theyadopted theshrinkagemeasureOmegaΩ ontheICD-10codesofdiagnosesin associationwithastandardDDIdatasetofNSAIDanddiuretics.  AReportingratios(RR)wasused,asaconditionaldisproportionality analysis,toassesstheincreasedofuserssearchingforhyperglycemia-relatedtermsgiventhattheysearchedforbothpravastatinandparox-etine.Theresultsprovidedevidencetothepotentialityofpredictionof drugsafetysignalsfromsearchlogs.  Almenoff *etal*.haveexaminedtheBayesiandisproportionalitymea-sureMGPS(90%confidenceinterval)inscreeninginteractionprofiles betweenantihypertensivedrug“verapamil” andotherclassesofcar-diovascularmedications[69].Resultshaveshowntheusefulnessof MGPSdisproportionalityalgorithminminingDDIinterestingpatterns inpolypharmacyconditions.Schuemie*etal.*[70]proposedanapproach knownaslongitudinalGPS(LGPS)whichisamodificationoftheorig-inalMGPSapproach.LGPScomputedtheexpectednumberofmedi-caleventsduringdrugprescriptionsbasedonanaggregateunexposed patient-timeinexposedandunexposedpatients.Forprotectingagainst confoundingfromdominatingunexposedpatientssolongasthemajor-ityofthepatientsinapopulationdon’treceivespecificmedicine,au-thorssuggestedafilternamedObservationalProfilesofAdverseevents RelatedtoDrugs(LEOPARD)toeliminatespuriousassociationscaused byprotopathicbias.LGPShasbeenshowntooutperformrelatedmeth-ods,includingMGPS.  In2010,Harpaz*etal.*[71]haveproposedanenhancedApriorial-gorithmusingFAERSdataforthepurposeofdetectinginterestingDDI patterns.BecauseoftheunsuitabilityofclassicApriorimetricsfordrug safetyfield,RRRmeasurewasutilizedinstead,withsupplementaryfil-terthateachdrugpairinassociationtripletshouldhaveRRRscore higherthananyofeachdrugindividually.Thesecondfiltercriterion wasaimedtoeliminatespuriousDDIsignals.Resultsexhibitednearly 35%ofthedrug-drug-reactionassociationsrelatingtowell-knownDDI, thusindicatingtheprobablebenefitofcustomARMinflaggingpoten-tialDDIsignalsthatwarrantfurtherclinicalassessment.Anotherstudy, Ibrahim,H*etal*.[72]havepresentedanaugmenteddataminingal-gorithm“hybridApriori”,customizedtoPVapplications,wheredis-proportionalityPRRmeasurewasadoptedasinterestingnessmeasure todiscoverassociationpatternsofadverseDDIsfromFAERSdata.On theotherside,VanPuijenbroek*etal.*[73]haveconsideredanadjusted disproportionalitymeasureRORthroughimplementingamodeloflo-gisticregressionontheNetherlands’sPVdatabase“LAREB” toevalu-atetheadverseeffectsforthecoadministrationof“non-steroidalanti-inflammatorydrugs(NSAID)” and“diuretics” onworseningthesymp-tomsofcongestiveheartfailure(CHF)disease.Resultsimpliedthatus-ingNSAIDsthemselveshasnoroleinincreasingtheriskofCHF.While uponcoadministrationwithdiuretics,NSAIDshavecontributoryrolein aggravatingCHF.TheauthorshaveconcludedthatadoptingLRcanof-feradvantagesoverbivariatedisproportionalitymeasuresviaguarding againstfalsesignalsasaresultofconfoundingbyconcomitantmedica-tions.  Thakrar*etal*.haveillustratedtheprincipalofmultiplicativeandad-ditivemodelingindiscoveringDDIsignalsusingSRS[74].Thedesign ofmultiplicative/additiveframeworkwasbuiltonestimatingtheinter-actioncoefficient(*𝛿*)wheretheassociatedriskwithdrugpaircoadmin- | | |

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dardofknowninteractionsfromDrugBankandtheMediSpan® Drug TherapyMonitoringSystemTM(WoltersKluwerHealth,Indianapolis, IN).Inoverall,authors’methodachieved81.5%areaundertheReceiver OperatorCharacteristic(ROC)curveforsignalingknownDDIs.

Segura*etal*.[78]proposedtheshallowlinguistickerneltechnique forautomaticDDIsextractionfrombiomedicaltexts.Astherecogni-tionofdrugnamesisanessentialprerequisitestepfortheautomatic discoveryofDDIsfrombiomedicaltexts,authorsusedUMLSMetaMap Transfer(MMTx)tooltoautomaticallyidentifydrugentitiesoccurring inunstructuredtextualdocumentsofDDIsfromDrugBankdatabase. TheMMTxrecognizesandannotatesdrugentitiesaccordingtoUMLS semantictypes(e.g.,ClinicalDrug[clnd],PharmacologicalSubstance [phsu],andAntibiotic[antb]).Drug-DDIcorpuswascreated,annotated with3169DDIs,astheoutputofMMTxinXMLformat.Also,MMTx toolwasusedtoextractandlabelcandidatesofdrugpairswith1ifin-teractionexistsorlabeled0ifnointeractionexists.Theperformance ofproposedshallowlinguistickernel-basedtechnique,withaprecision of51.03%,arecallof72.82%andanF-measureof60.01%,confirmed theremarkableimpactofautomaticentityrecognitionontherelation extractiontask.

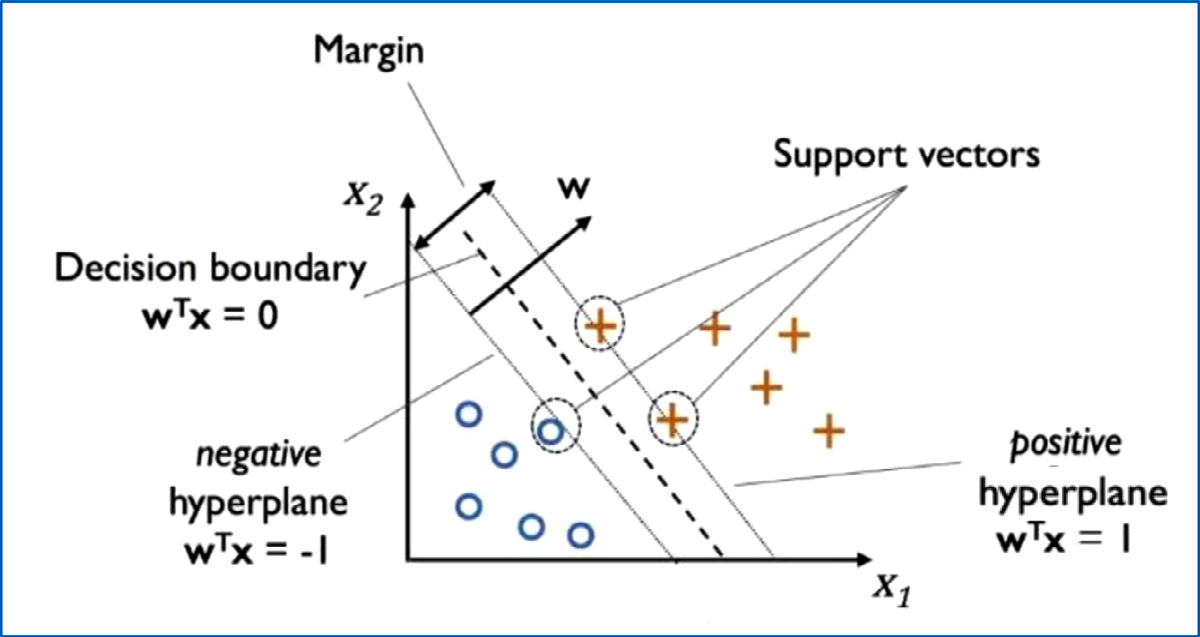
In2013,White*etal*.[79]havedemonstratedthattheinternetsearch logsthataregeneratedbyconsumersareabletoprovideearlyclues aboutDIAEs.Theauthorsconductedalargescalestudyofwebsearch logpayingattentiononspecificinteractionbetweenparoxetine(anan-tidepressant)andpravastatin(acholesterol-loweringdrug),whichwas recentlyreportedin2011tocausehyperglycemia.Yang*etal*.[80]pro-posedatextminingmethodologywheretheyusedsocialmediatoiden-tifyDDIpatternsbycombiningARMandlexicon-basedalgorithms.The authorsusedadatasourcecalled“MedHelp” asanexampleforanon-linehealthcareforums.Onlytripletswereconsideredwhereaseachco-occurrencewascountedforapairofinteractingdrugsassociatedwith anadverseevent.Theyexaminedthesignificanceoftheconstructed drug-drug-adverse-eventassociationsusing4metricsasfollows{sup-port,leverage,lift,andconfidence}[81].Somelimitationsrelatedto thepreviousmentionedmeasuresforexample,theleveragecouldbe verysmallorevennegativebecauseoftheverysmallofthreadsrelated toADRcomparedwiththetotalnumberofthreads.Forthat,authors adoptedanothermeasurecalledinteractionratiotocaptureDDIsignals throughwhichvariationofconfidencecanbecalculated.Thegenerated patternshaveproventhefeasibilityoftheproposedapproachinDDI signaldetectionfromDrugBankdatabase.

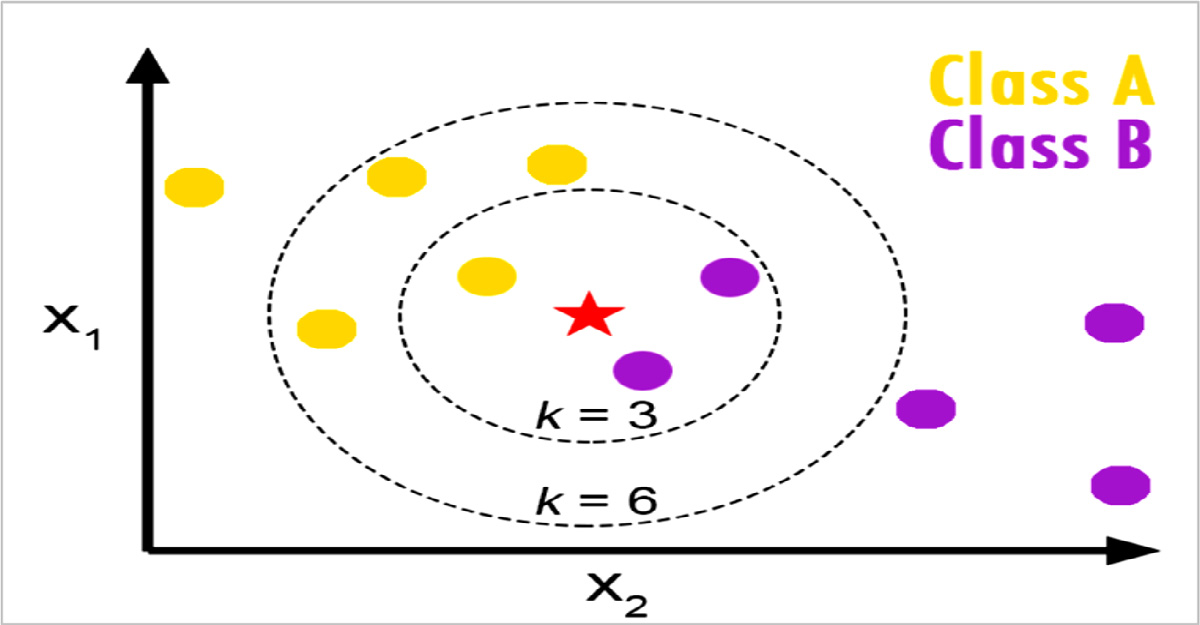
**5.Machinelearningapproachesforthepredictionofsafety signals**

Inrecentyears,researcheffortshavedirectedfromdataminingap-proachestowardsmachine-learning(ML)todiscoverDDIsearlyduring thedrugdiscoveryprocessbeforebecomingcommerciallyavailable.ML methodscanbecharacterizedintotwobroadcategories:supervisedand unsupervised[82].Insupervisedlearning,amodelisbuiltpriortothe analysiswherethemodellearnsfromlabeledinputdatainordertoesti-matespecificrelationshipsbetweenthefeaturesandthelabelsofthein-putdata.Then,thelearnedmodelisappliedtounseendatatopredictthe categoryorquantityofinterest.Classificationandregressionarevery commonsupervisedlearningtechniquesusedinbiomedicalresearch.It isworthmentioningthatregression-basedapproachesaretraditionally adoptedforeitherbiostatisticsordataminingpurposesasillustratedin section4.However,inseveralstudieseitherlinearorlogisticregression areconsideredasMLmodelsforbinary/multi-classpredictionofcon-tinuous/categoricalfeatures.SupervisedMLalgorithmsmaybeusedfor featureselection,classification,predictionorevaluatingtheefficiency ofsomeparameters[83].Incontrast,forunsupervisedlearning,theal-gorithmisapplieddirectlyonunlabeledinputdatatofindregularities, andthenamodelwillbebuiltaccordingtotheidentifiedpatterns.Clus-teringandbiclusteringalgorithmsarethemostcommonunsupervised MLtechniques[84].Thefollowingsubsectionsfrom5.1through5.5

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**Fig.2.Schematicrepresentationoflinearsupportvectorma-chinealgorithmconcept**.The*𝜔*denotesthenormalizedvectortothe decisionhyperplane;Horizontalandverticalaxes(X1andX2)symbol-izethefeaturespace(feature1&feature2).

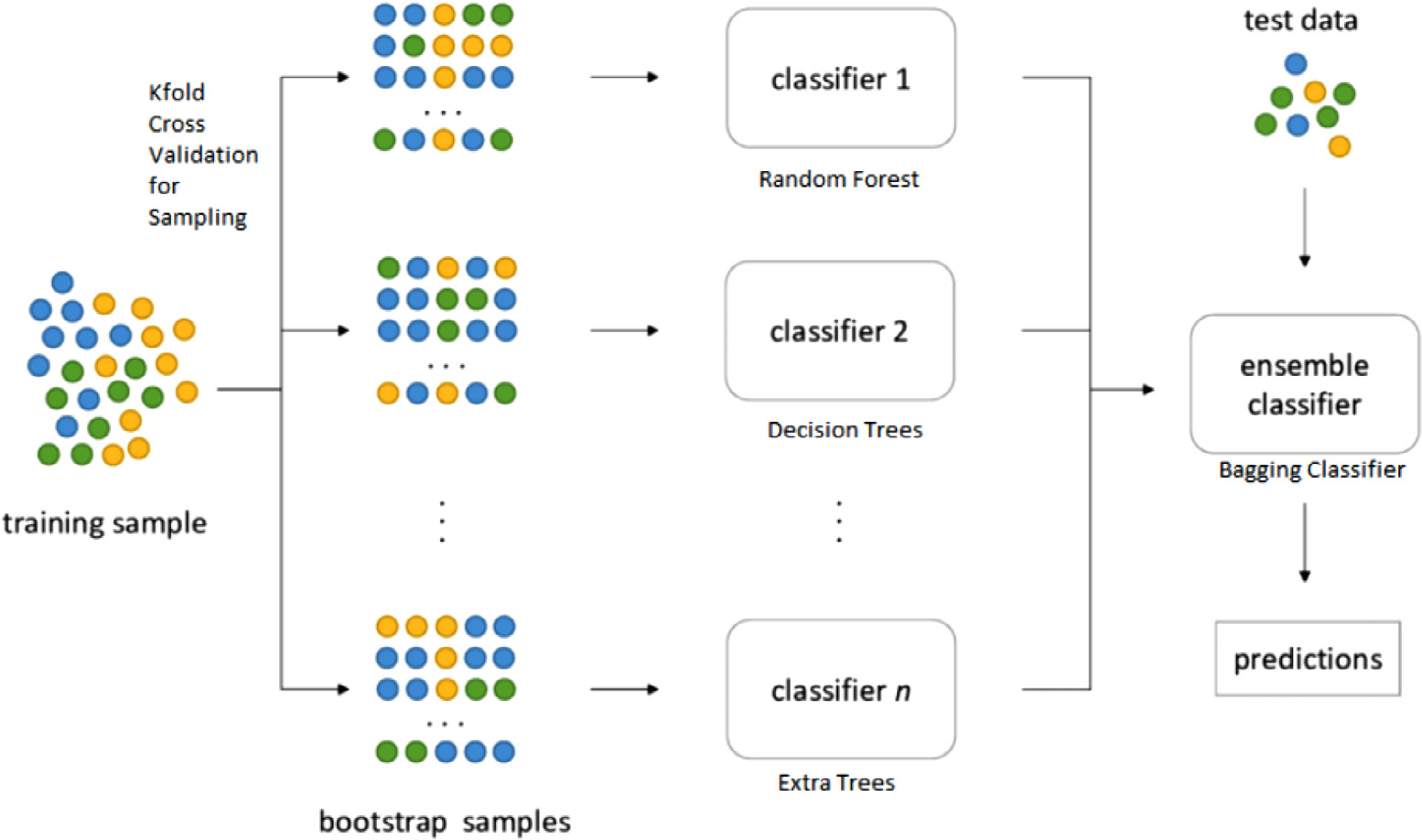
**Fig.3.**Schematicrepresentationofk-NearestNeighbor(KNN)algo-rithmconcept.Where,k=numberofneighbors;X1&X2aretheinput descriptors;Redstaristhequeryinstance[89].

|  |  |
| --- | --- |
| ThemainadvantageofKNNalgorithmisitscapabilitytoarbitrar-ilyapproximateanydatadistribution.Howeveritsdemeritscanbe abridgedasfollows:(i)ComputationallychallengingasKNNusesall datapointsoftheloadedtrainingdatasetforconductingqueries;(ii)the numberofdataneededtobescaledgrowsexponentiallywithdimension byincreasingthedatasetsize.Itisknownasthe“curseofdimensional-ity”.  *5.3.RandomForestClassifier*  Ensemblelearningisageneralmeta-approachthatcombinespredic-tionsfrommultipleMLmodelstoachievebetterpredictiveperformance. OneofthepowerfulMLalgorithmbasedonbaggingensemblelearning israndomforestclassifier(abbreviatedas“RFC”).Itwasdevelopedby LeoBreiman[92].Baggingisoneofthemainstandardstrategiesusedin ensemblelearningtechniquesthatfitsmanydecisiontreesondifferent samplesofthesamedatasetandaveragesthepredictions(seeFig.4) [93].  RFCisasupervisedlearningalgorithmthatisbasedontheinfras-tructureofdecisiontreealgorithmandtoclassifyeithercategoricalor continuousfeatures[94].Itestimatesnumbersofdecisiontreeclassi-fierswhichfitonvarioussubsetsofatrainingdatasettoaugmentthe predictiveperformanceandmanageoverfittingcomparedto“Decision treealgorithm” (refertoFig.5).Theconsiderednumberoffeaturesat eachsub-treeequalstothesquarerootofthenumberoffeaturesinthe inputtrainingdataset.Then,itaveragesthescoresofeachdecisiontree topredicttheclassofthetestdatasetinstance[95,96].  Besidesthehighvarianceassociatedwithtreeclassifiersduetosub-stantialchangeinthetrainingdatasetresultinginverydifferentsub-treesandbeingnon-interpretable,RFCisstillprivilegedasarelatively fasttrainingmodelthatrequireslittledatapreparationcanbeadopted formultidimensionalproblems[97,98]. | *5.4.ArtificialNeuralNetworks*  ArtificialNeuralNetworks(ANN)areasetofalgorithmsdeveloped toimitatetheneuronsinhumanbrainthataredesignedtorecognize patternsindatawhichmaybeusedforclassificationorclusteringprob-lems[99,100].TherearetwomaincategoriesofANN:(i)simpleneural networks;(ii)deeplearningneuralnetworks(refertoFig.6).Wehere outlinethegeneralANNarchitecturesandcommonactivationfunctions withtakingintoconsiderationdeeplearningneuralnetworksareoutof scopeoftheunderlyingreviewwhereANNs.  TherearetwospecificarchitecturesforANNs:(1)Feed-forwardneu-ralnetworksand(2)Feedback/Recurrentneuralnetworks.*Feed-forward neuralnetworks*arethemostcommonarchitectureofANNinpractical applications.Inthisarchitecture,theinformationtravelsinonedirec-tiontowardstheoutputlayerwithoneormultiplehiddenlayers.While *Feedback/recurrentneuralnetworks(RNNs)*aremoreflexibleandmuch difficulttoanalyzethanfeed-forwardnetworks.RNNscanprocessvari-ablelengthinputsbyprocessingthemintimesteps,allowingtheoutput ofdeeperlayerstobefedbacktopreviouslayersinsubsequenttime steps.ThereforethistypeofANNistypicallyutilizedinsequentialand time-seriestasks.  Fig.7showsschemeofaninterfacialneuronwhereasequenceof threeoperationscanberepresentedasfollows:(1)takeaninputfeature *𝑖*foravector*𝑋* andassignitaweight,thensumthoseinputstoobtain modulatedfeaturescomingtothebodyoftheneuron,andfinallyhave anactivationfunction*𝑓* “*Perceptron*” thattransformsthosemodulated featuresintotheultimateoutput/class[96].  Therearevarioustypesofactivationfunctionsbutthemostcom-mononesusedinANNmodelingareHeavisidestepfunction[101],Sig-moidfunction[102],HyperbolicTangentfunction(Tanh)[103],Recti-fiedLinearUnit(ReLU)[104],Softmaxfunction[105].Heavisidestep functionistheclassicandsimplestANNactivationfunctionwithbi- |

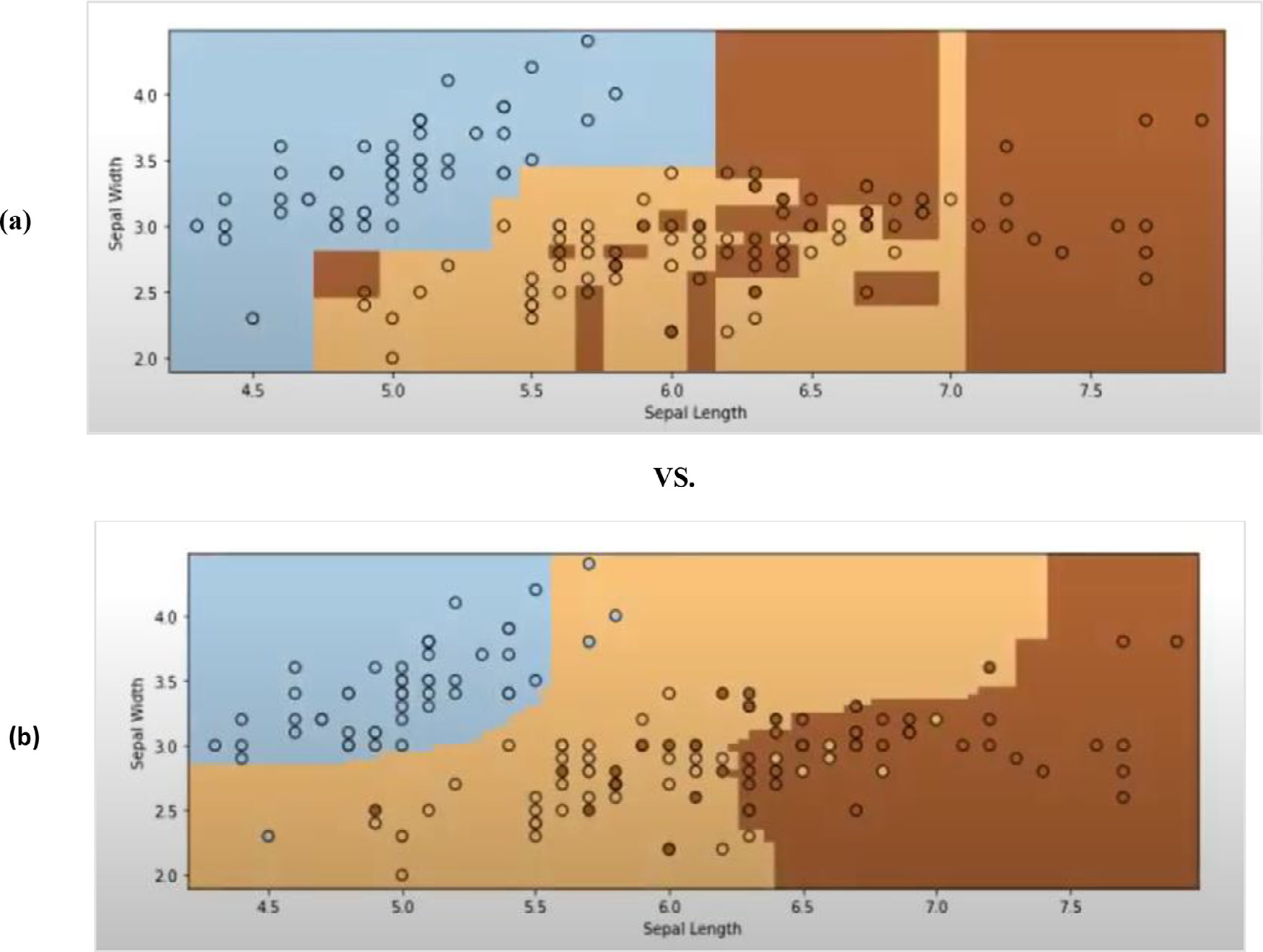
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**Fig.4.**Schematicrepresentationofbag-



gingensemblelearningconcept.



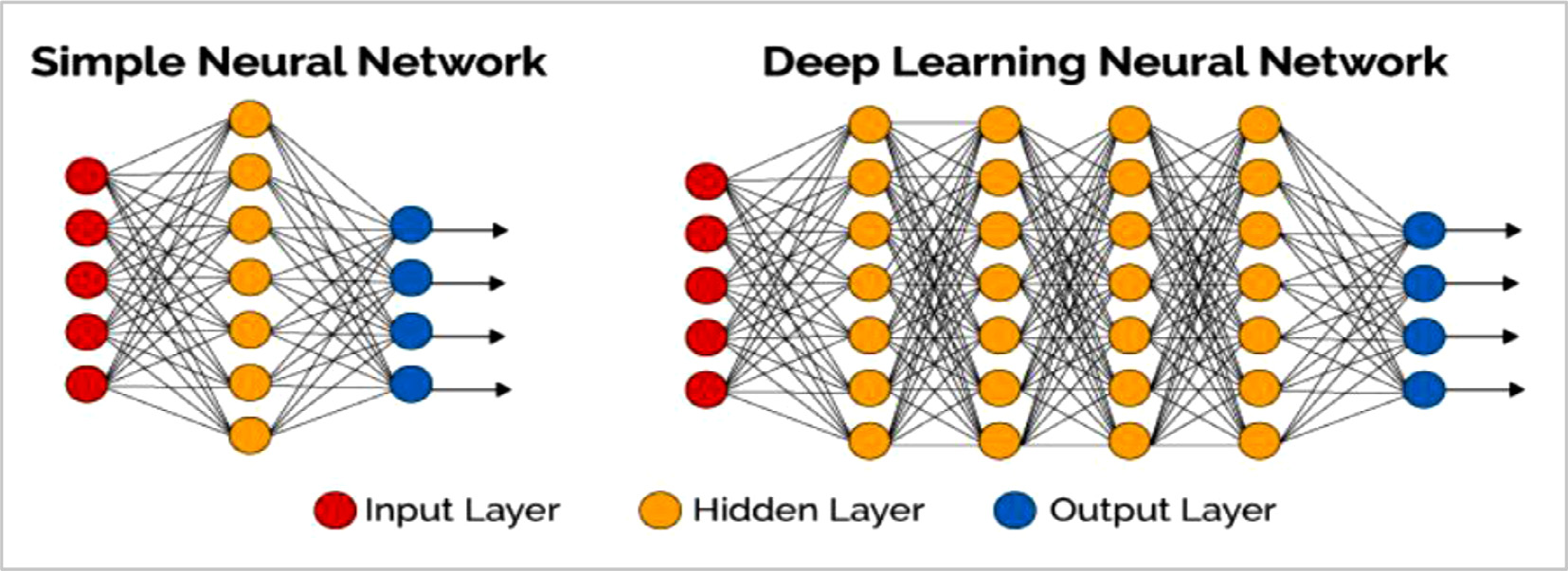
**Fig.5.**Comparisonof(a)decisionboundariesofdecisiontreeclassifierversus(b)decisionboundariesofrandomforestclassifieronclassicexample“Irisdataset”.

naryoutcomethatwasfirstdevelopedbyFrankRosenblatt(Referto the“bluecircle” inFig.7above).Itoutputs0ifthescoreis≤0,and1 otherwise.

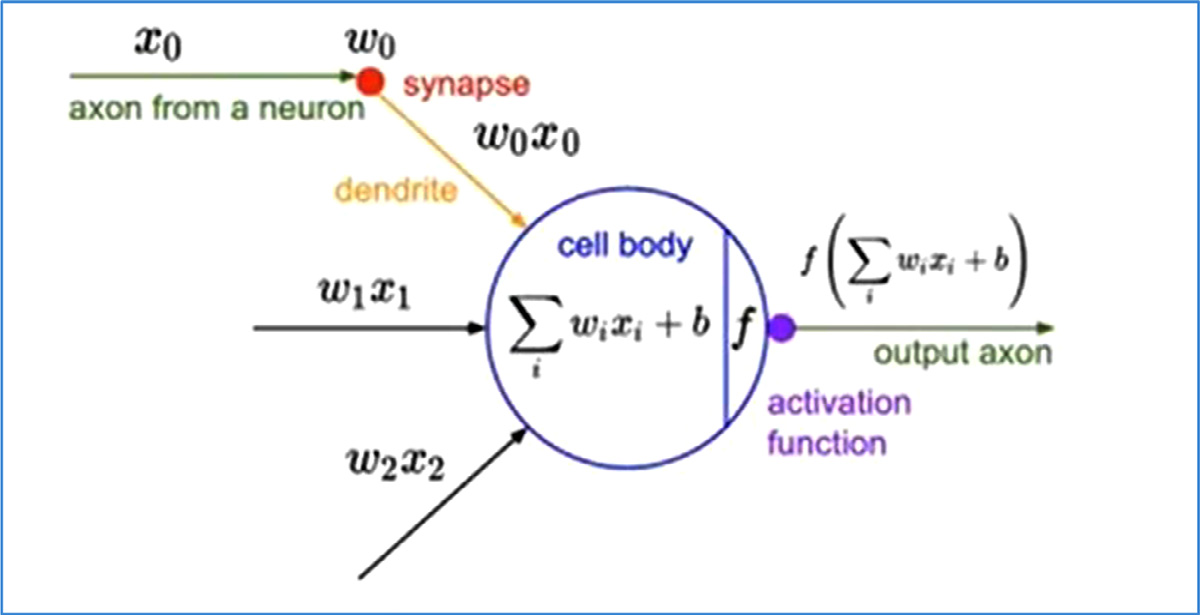
Sigmoidisanon-linearactivationfunctionwhichisalsoknownas“Logisticfunction”.Itprovidesasmoothanddifferentiatedgradient curve.Sigmoidistypicallyusedastheactivationfunctioninbinary classificationproblemswhereitspredictionoutputisnormalizedinto therange[0–1].LikeSigmoid,Hyperbolictangentactivationfunction isusedinbinaryclassificationproblems.Nonetheless,itiszerocentric

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**Fig.6.**Maintypesofartificialneuralnetworks(ANN).



**Fig.7.**Schematicrepresentationof“Perceptronlearningrule” toim-itateanartificialneurontobiologicalneuron.*𝑋𝑖*:Inputfeatureito avector*𝑋*inasingleneuron;*𝑊𝑖*:assignedweightforeachinput featurei.

|  |  |
| --- | --- |
| *5.5.NaiveBayes*  NaiveBayes(NB)isoneofthesimplestsupervisedMLalgorithms thatissuitableforbinaryandmulticlassclassificationofcategoricalin-putfeatures.NBisbasedonBayes’theoremtoestimateposteriorproba-bilitywiththeassumptionofindependencebetweenfeatures[106].The comprehensionofNBasaprobabilisticclassifiercanbeexpressedasin thefollowingequation:  *𝑃*(*𝑐*|*𝑥*)=*𝑃*(*𝑥*~~|~~*𝑐*)*𝑃*(*𝑐*) Where*𝑃*(*𝑐𝑥*)denotestheposterior/conditionalprobabilityofclass (9)  (target)givenpredictor(feature);*𝑃*(*𝑐*)isthepriorprobabilityofclass; *𝑃*(*𝑥𝑐*)symbolizesthelikelihoodwhichistheprobabilityofpredictor givenclassand*𝑃*(*𝑥*)representsthepriorprobabilityofpredictor. ThemeritofNBmodelingisthatitiseasytobuildwithnocompli-catediterativeparameterestimation.Itisparticularlyusefultoimple-mentonlargedatasets[107].However,themainlimitationofNBisthe assumptionthatallthepredictorfeaturesarecompletelyindependent.  **6.ParadigmsofmachinelearningstudiesforpredictionofDDI signals**  Inthelightofprinciplesofthestate-of-artMLalgorithmsdescribed throughoutsection5,inthissection,wepresentparadigmsofMLstudies reportedinbiomedicalliterature.TwomaintypesofMLapproaches-(network-based[108–111]andsimilarity-based[17,112–120])**-**have beenadoptedbyresearchersforthepurposesofpredictingDDIsafety signals.  *Regardingnetwork-basedMLmethods,*theyhavebeenproposedbyre-searchersfordifferentobjectives,includingDDIprediction,drug-target-interaction(DTI)prediction,adversedrugreactionprediction,ordrug repurposing[121]*.*FordiscoveringunknownDDIsignals,thestrate- | giesofnetwork-basedMLapproachesdependoninferringdrugsimi-laritiesbetweennetworknodesorlearningabouttopologicalfeatures ofthenetworkstructure[122,123].Thoseknowledgenetworkscanbe constructedbyextractingandintegratingexistingdrugknowledgefrom oneormultipledatasources(e.g.chemical,biological,target,genomic, pharmacologicaldatabases)leadingtovariousshapesofnetworks(e.g. drug-drug,drug-target,protein-protein,pharmacodynamic,drug-gene, phenotypic,pharmacokinetic,etc.)[124].  Cami*etal.,*[108]suggestedapredictivepharmacointeractionnet-works(PPIN)frameworktopredictDDIsbyutilizingthenetworktopo-logicalstructureforallknownDDIsofaknowledgedatabase“Mul-tumVantageRx”,acommercialavailabledatabaseofcuratedDDIs andrelatedsideeffects.Basedonintrinsicandtaxonomicproperties ofdrugsnodesandedgesrepresentinginteractionbetweennodes,the PPINhasreported48%sensitivity,90%specificityand81%areaun-derthereceiveroperatingcharacteristiccurve(AUROC).Ontheother hand,Huang*etal.*,[109]haveconductedastudybasedonprotein-protein-interaction(PPI)networkforsystematicpredictionofPDDDIs. Theydesignedtwometricsofnetworktopologytointegratepheno-typic&genomicsimilaritiesbetweendrugpairs.NumerousPDDDIs havebeendiscoveredwithhighaccuracyscore(0.82)andmodestre-callscore(0.62).In2014[111],Cheng*etal.,*adoptedaheterogeneous network-assistedinference(HNAI)frameworkforlarge-scaleprediction ofligand–receptorDDIs.Theirworkdependedonintegratingdrugphe-notypic,therapeutic,chemical,andgenomicproperties.Theytested fiveMLalgorithms:NaiveBayes,DecisionTree,3-nearestneighbors (or3NN),logisticregressionandsupportvectormachinetopredict DDIs.ThekeyfindingoftheHNAImodelwasareasonableareaun-derthereceiveroperatingcharacteristic(ROC)curve(AUC)(0.67)as evaluatedusingfive-foldcross-validation.In2019,Cheng*etal.*[110] havereportedanetwork-basedmethodforpredictingbeneficialdrug-combinationsdiscriminatedfromadverseDDIsforFDA-approvedan- |

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tihypertensivedrugs.Threetypesofexperimentallyevidencedclinical datasources(FDA-approveddruglabels,DatabaseofClinicaltrials.gov, andpublishedpreclinicalstudies)wereutilized.Inthisstudytwotopo-logicalmeasureswereadoptedforcapturingassociationsbetweenele-mentsofdiseaseanddrug–targetnetworksinthehumanprotein–protein interactome.Network-basedproximitymeasurewasusedtocapturethe topologicallinkingbetweentwodrug–targetmodules,whereas,Z-score wasusedtogetclosenessamongdiseaseanddrugnetworks.Asare-sult,sixdifferentrelationshipsofdrug-drug-diseasemodulescouldbe distinguishedbycombininganumberofdecisionrules.

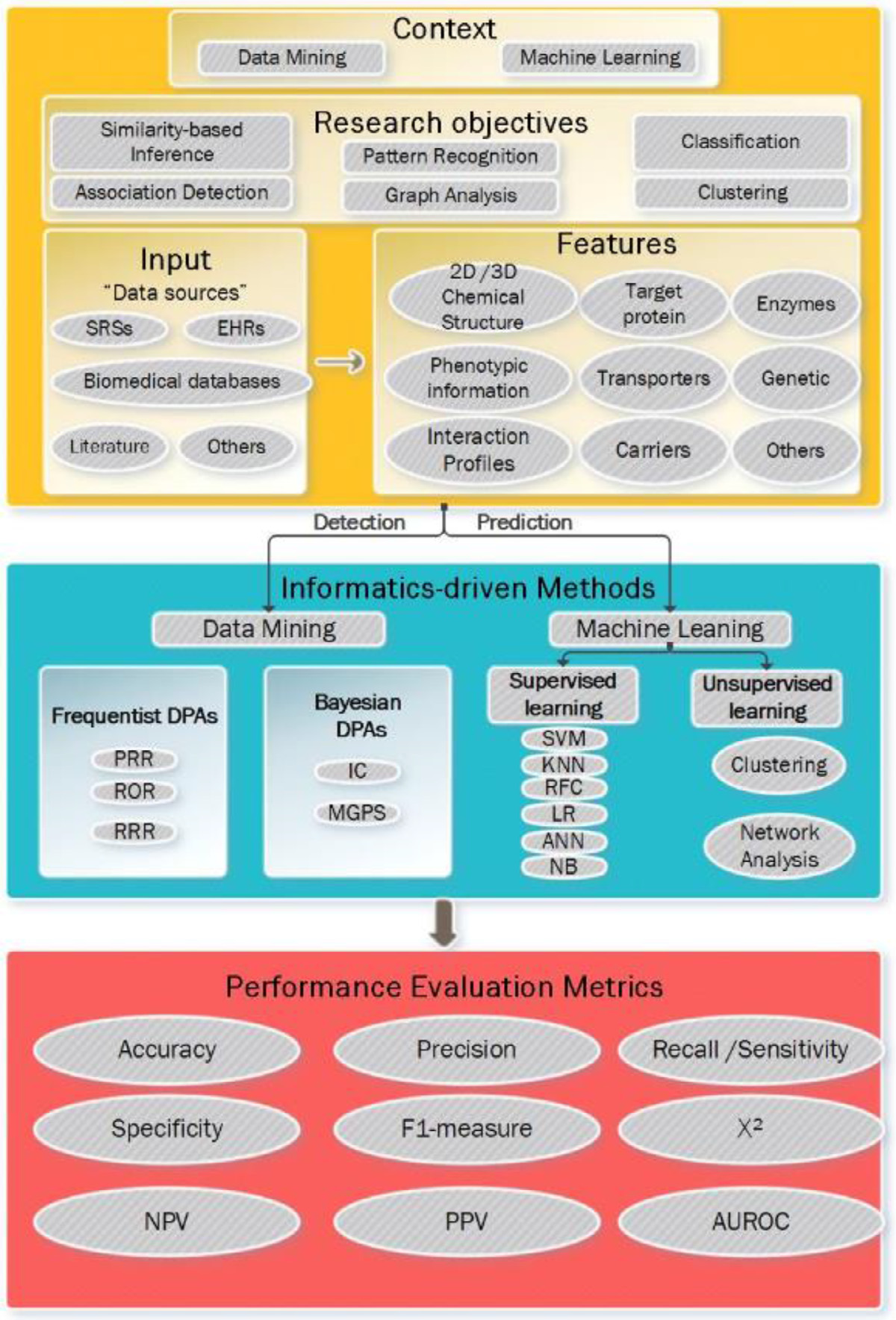
Inrecentyears,Similarity-basedMLframeworkshavebeengreatly adoptedforclassificationtasksinthefieldofpharmacovigilance,par-ticularlyDDIpredictioncomparedtofeaturevector-basedframeworks. Similarity-basedmethodspostulatethatsimilartreatmentsmayad-verselyinteractwiththesamedrug.ASimilarity-basedMLframework ideallycomposesoffivephasesthatcanbesummarizedasfollows: (i)Featurecapturingfromoneormoredatasources;(ii)Constructing featurematricesusuallyshowrelationshipsbetweenadrugandfea-turedescriptorsexpressingvariousrelationshipsbetweeninteracting drugsfromvariousperspectives.Thesefeaturedescriptorsmayreflect thechemicalpropertiesofadrug(e.g.2dchemicalsubstructures,3d pharmacophores,anatomicaltherapeuticchemical“ATC” codes,etc.). Theymayalsorepresentpharmacodynamic/pharmacokineticproper-tiesofadrug(e.g.targetproteins,metabolizingenzymes,transporter proteins,andcarrierproteins).Moreover,descriptorsmayrevealsome pharmacogenomics/clinicalproperties(e.g.geneprofile,interaction-profile,adverse-drug-event(ADE)profile,etc.);(iii)Computingfeature similarityscoresbetweenbit-vectorsusingvarioustypesofsimilarity indices[125–134];(iv)Implementingthepredictionphasebyadopting well-establishedMLalgorithms;(v)Evaluatingpredictiveperformance resultsoftheSimilarity-basedMLframework.

Thosesimilarity-basedMLframeworkshaveanumberofnotable meritscomparedtonetwork-basedorfeaturevector-basedframeworks: (1)Theydonotrequirefeatureengineeringthatisusuallyacomplex procedure;(2)Existingsimilarityindices(e.g.Tanimotocoefficient)are well-developedandbroadlyused;(3)higherpredictiveperformance outcomes.

Ferdousi*etal.,*[17]haveconductedarecentstudyforcomputational predictionofDDIsbasedonthesimilaritiesofthebiologicalelements betweendrugpairsextractedfromtwopublicallyavailabledatabases (DrugBank&KEGG).Theycompared12similaritymeasuresfortheir abilitytorecallpositiveDDIs(i.e.knownDDIs).Then,theyselectedthe mostreliablebinary-similaritymeasure.Theycouldextract250,000po-tentialDDIscategorizedas(low,moderate,high,veryhigh)according totheirpredictionscores.Theyqualitativelyvalidatefewofthepre-dictedDDIassociationsandnoquantitativeperformanceevaluationhas beenmade.Vilar,S.*etal.,*[112–115]haveconductedaseriesofstud-iesbuiltonsimilarity-basedmodelingusingDrugBankasadatasource. TheuseofdrugstructuralsimilarityinformationforDDIpredictiongave anoverallprecisionof0.26,sensitivityof0.68,andspecificityof0.96 [112].Vilar,S.*etal.*,[113]havesuccessfullyappliedasimilarity-based modelforDDIpredictionbasedontheinteractionprofilefingerprints (IPFs).Adatabaseof17,230DDIcandidatesalongwiththeirpotential pharmacologicaleffectshasbeenprovidedforsupportingdecisionin DDIdetectionandpharmacovigilance(PV)dataanalysis.Thismethod hasreportedprecisionvaluesrangingfrom0.4–0.5.Whereasin2014 [114],Vilar,S.*etal.*,havepresentedaprotocolintegratingfivesim-ilarityfingerprintsofdrugpairsinpurposeoflarge-scaleDDIpredic-tion.ThestudyreportedarobustAUROC*>*0.95.Vilar,S.*etal.,*[115] haveextendedtheirworkin2015targetingspecifictypeofadverse DDIsusingFDAPVdatabase(FAERS).Theirsimilarity-basedmethod dependedoncapturingchemicalandpharmacologicalfeatures.Their resultsshowedenhancedsensitivity,specificityandprecisionincom-parisontothedataminingalgorithmproportionalreportingratio“PRR”traditionallyappliedonPVdatabases.Likewise,Sornalakshmi*etal.*, [116]includeddifferentsimilaritymeasuresrepresentedin2Dchem-

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**Fig.8.Amulti-layeredinformatics-drivenframeworkfordiscov-eringdrug-druginteractionssafetysignals.**SRS:SpontaneousRe-portingSystem;EHR:ElectronicHealthRecords;PRR:Proportional ReportingRatio;ROR:RelativeOddsRatio;RRR:RelativeReport-ingRatio;IC:InformationComponent;MGPS:Multi-GammaPoison Shrinker;SVM:SupportVectorMachine;KNN:K-nearestneighbor; RFC:RandomForestClassifier;LR:Logisticregression;ANN:Artifi-cialNeuralNetwork;NB:NaïveBayes;***𝑿***2:Chi-Square;NPV:Neg-ativePredictiveValue;PPV:PositivePredictiveValue;AUROC:Area undertheROCCurve.

**Table1**   
**SummaryofthePerformanceMetricsofMachineLearningandDataMiningmethodsadoptedinthestudiesdescribed in**sections4**and**6**,respectively.**AUCROC:AreaundertheReceiverOperatorCharacteristiccurve;DDI:drug-druginteraction; SRS:spontaneousreportingsystem;ARM:Associationrulemining;SVM:Supportvectormachine;IPF:Interactionprofile fingerprint;PPIN:Protein-proteininteractionnetwork.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Method(Measurements) |  |  |  |  |
| ResearchObjective | BestSensitivity | BestPrecision | BestSpecificity | BestAccuracy | BestAUROC |

**DataminingmethodsforDDISignaldetectionimplementedtoSRSdata**

|  |  |  |
| --- | --- | --- |
| Associationpattern recognition(ARM) | HybridApriori(0.81) [72] | HybridApriori(0.85)  [72] |

**MachinelearningmethodsforDDISignaldetectionimplementedintobiomedicalknowledgedatabases**

|  |  |  |  |
| --- | --- | --- | --- |
| Classification  Similarity-based  modeling | MolecularStructure  Fingerprint(0.96)  [112]  PPIN(0.96)  [106] | PPIN(0.81) [109] | SVM(0.93)[117] IPF(0.96)  [113] |
| Networkanalysis |

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|  |  |  |
| --- | --- | --- |
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| experimental/clinicalinvestigationsmaybeneededtoprovidefurther evidencesforconfirmingaDDIsignal.Severalfactorshaveimpacton detectingDDIsignalswhereimportantonesmaybemissedorspuri-ousassociationsaremorelikelytobeproduced.Theseinfluencescan besummarizedin:minimaldemographicdata,duplicatedreports,no informationregardingpatientexposure,underreportingthatmayarti-ficiallyincreaseexpectedriskestimatesofthedrugs,verbatimmedical terms,unstandardizeddrugnames,etc.Accordingly,optimizingcurrent dataminingtechniqueswithchosenthresholdsaimingatovercoming rawdatachallengesandcapturingDDIsignalswithhighersensitivity andprecisioniscrucial.Also,researchershaveshownARManditsex-tendedalgorithmsasgoodchoicesforhandlingthesparseofpostmar-ketingPVdatawithinSRSswherestrongassociationpatternscouldbe generatedtoeasilyrecognizehigherorderofDrug-AEassociations.On theotherside,adoptingEHRsasacomplementarysourceforroutine PVpracticesgenerallyandDDIsignaldetectionspecificallyischalleng-ing.Thismaybeattributedtotheontologyproblems,heterogeneityof datafromvarioussourcesandpatients’informationaremainlybeing intextualformats,besidesconfoundingbyco-medications,riskfactors and/orcomorbidities.Hence,developingNLPapproachesandtobein-tegratedwithregressionmethodscanbeanoptiontohandleontology problemsalongwithmanagingconfounders.AnotheravenueofNLPcan beadoptedinregularPVdatainpurposesofreducingthelargespace ofdrug-drug-eventassociationsinherentlypresentinSRSsandallowing furtherprocessinginthecontextofDDIsignaldetection[134].  WhereasfromMLperspective,PPINframeworkprovidesabetter overallperformanceconcerningbothaccuracyandspecificitycompared toothermethods.While,SVMappearstohavethebestoverallDDIpre-dictiveperformanceintermsofAUROCcomparedtoothersupervised MLinpredictingDDIsignals[135–140].However,SVMhasinherited limitationsrepresentedinthetimelapseofmodelrunningandtheblack boxnaturelimitingtheinterpretationofthepredictionoutcomes.Inre-centyears,thedawnofadoptingsupervisedMLinPVsignaldetection hasresultedfromtheevolutionofmultipleusefulbiomedicalknowl-edgeresourcesasgoldstandardsoflabeledDDIs(e.g.DrugBank[141], KEGG,Micromedex),besidesusingtheseresourcestoassessthepredic-tiveperformanceofsupervisedMLavenues.  TheuseofsupervisedMLhasitslimitssuchasclassimbalance,sparse features,lowoverlappingandconsistencybetweendifferentDDIsre-sources[142].Therefore,advancementsinincorporatingunsupervised MLapproachesinDDIsdiscoverystudies,improvementsofDDIcor-poraannotation,andestablishingstandardizedguidelinesforestablish-ingDDIgoldreferencedatasetsareprobablyessentialstepstodevelop morerealisticMLframeworksduringdrug-development,aswellas,pre-marketingphases.Otherdirectionsofdevelopmentstobeimplemented intoroutinePVpracticesarerepresentedinhowMLmaycontribute inboostingDDIsignaldetectionfromSRSdataand/orpredictingtheir types/changeinseverity,combiningmorethanonedatasources(e.g. EHRs,patientsupportprograms,prospectivesurveys,randomizedcon-trolledtrials,etc.)ratherthanrestrictingtoSRSdata,assessingMLal-gorithmicperformancebyconstructingreliabletestsets,inadditionto advancingframeworksforincreasingtransparencyorexplainabilityof MLoutputs.  Accordingtotheabovementionedillustrationsandbeyondthestruc-turedPVdatasources,theexponentialincreaseofthescientificliter-aturecomplicatestheexplorationofsuchbiomedicalcorpora[143]. Biomedicalcorporaenablesconstructinglearningdatasetsofmedically relatedtermsthatembedpriorknowledgeandaidinthepragmaticuse ofcertainwordswithinspecificcontexts[120].Informatics-basedmeth-ods,inparticulartextminingandMLframeworkshavegreatapplicabil-ityinthisregardtoaidinextracting,analyzingandclassifyingbiological informationdesignatedinscientificpublications.Duringthepastyears, biomedicalcorporahavepresentedavaluablePVdatasourceforthe detectionandanalysisofDDIsignals.Theunstructurednatureofthis typeofdatasourcesischallenging.NaturalLanguageProcessing(NLP) approachesarecrucialinthiscontexttoannotate,standardizeandmap | relevantmedicalterminologiesandgenericdrugnamesiscrucialfor implementingreliablecomputationalmodels. |
| **8.Concludingremarks** |
| Theavailabilityoffreelyavailablesafetydatasourcesalongwith theadoptionofnovelDMand/orMLmethodshasadvancedthePV domain.Inthisreview,weparticularlyfocusondevelopmentsinin-formaticstechniquesinthecontextofDDIsignals.Wehaveshowna portfolioofPVresources,DMandMLapproachestechniquesproposed todiscoveradverseDDIsignals.Eachmethodmayre-stimulateinterest toevolveDDIsurveillancepracticesbyofferingdifferentprospects.To thebestweknow,theunderlyingpaperisthefirstreviewcombining machinelearninganddataminingmethodstodisclosepotentialsignals ofDDIsindrugsafetysurveillance.PossiblecausalDDIsassociationsare experimentedduringdrugdevelopmentcycle,thenmonitoredviapost-marketingPVsystemsafterbeinginmarket.Developingbetterpredic-tivemethods,toflagpotentialDDIsignals,becomesofgreatimportance toindustryandregulatorybodies[144,145].  TheblackboxnatureofMLmethodsisoneoftheirmajorlimita-tionsleadingtodifficultyininterpretingofwhatfeaturesareimpor-tantand/orinterpretingthemodelresults.However,generally,adopting informatics-drivenmethodstobeimplementedinregulardrugdevelop-mentprocesswillbevaluable.Sincethiswillenablegreaterlinkage betweenbasicexperimentalplatformsandcontrolledclinicalsettings earlyduringdrugdevelopmentphases,thenempoweringtheanalysisof importantsafetyconcernsforinvestigationaldrugsatearlierstageslead-ingtomoreefficienttriagefornoveldrugcandidatesforfurtherstepsin thedevelopmentprocess[146].Boostedpredictiveapproachescanbe achievedbyintegratingstructuralandbiologicalknowledgewithen-richedsafetydatasets[147]**.**Previousstudieshaveshownbenefitsfrom linkingdrugs’phenotypic,therapeutic,structural,andgenomicinforma-tioninrevealingDDIpatternsinbothdrugdiscoveryandpostmarketing PVprocesses[148–150].  Innovativeparadigmshavearisenfromexploitingvariousdata sourcescomparedtoconventionalPVpractices,permittingfortheac-tivemonitoringofDDIdrugprofiles.Asspontaneoussystemsarecon-sideredthebiggestassemblyofrealworlddatafordistinguishingDDIs [151–154].Thediscoveryofhigher-orderdrug–eventcombinationsis morechallengingthanidentifyingsignalsofsingledrug–eventpairsdue tothelimitationofunder-reportingratesinlargeSRSs.Althoughthe DDIdetectionresearchshiftedawayfromSRSsutilizationintoother datasourcesintherecentyears,thiscouldn’treplacethemainroleof SRSsinregularPV.Accordingly,moreeffortsarerequiredinpurposes ofevolvingmethodsforroutineDDIsdiscoveryacrossdifferentsafety datasources.  Also,themainchallengeinDDIsignaldetectionstudiesisthelack ofwell-establishedguidancesforassessinginformatics-drivenmethods performance.Principally,thisisduetothelackofreferencestandardfor interactionsafetyprofilesofthewholemarketeddrugproducts[155]. Hence,researchersshouldconductmorestudieswithpurposesforac-quiringbettercomprehensiontothelandscapesofmultivariateassoci-ationmeasuresalongwithestimatingcorrespondingpredictiveperfor-mance.Furthermore,developingapproachestargetingtheestimationof optimalDDIsignaldetectionthresholdsthatachievebalancedtrade-off betweensensitivityandspecificitywithdecreasingfalsesignalscanbe avaluableperspective.  Inconclusion,informatics-drivenapproachesdon’tprovecausality association,butinsteadtheycanbevaluablecomplementarytoolto flaghypothesesofDDIcombinationsandsupportsignalassessment. Comprehensiveclinicaljudgmentwillalwaysendurefundamentalfor establishingcausalrelationshipsbetweendrugsandsafetyconcerns. |
| **DeclarationofCompetingInterest** |
| Theauthorsdeclarethattheyhavenoknowncompetingfinancial interestsorpersonalrelationshipsthatcouldhaveappearedtoinfluence theworkreportedinthisreviewpaper. |

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[[24]](http://refhub.elsevier.com/S2667-3185(21)00005-2/sbref0024)[IvanovS,LaguninA,FilimonovD](https://vaers.hhs.gov/data.html)[,PoroikovV.Assessmentofthecardiovascularad-](http://refhub.elsevier.com/S2667-3185(21)00005-2/sbref0024)

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