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ConceptualAnalysis   
Chemistry-centricexplanationofmachinelearningmodels   
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Artificialintelligence(AI)isincreasinglybeingconsideredacross chemicaldisciplines,justasinmanyotherareasofscience,oftenwith highexpectationsfor“revolutionary” advances.Medicinalchemistry anddrugdesignareamongthefocalpointsofthesedevelopments[1–4]andthereisrisinginterestindeepneuralnetwork(DNN)architec-turesanddeeplearning(DL)forthegenerationofnovelcompoundsand predictionofvariousmolecularproperties[3,4].

Inchemoinformatics,medicinalchemistry,anddrugdesign,theterm AIistypicallyusedsynonymouslywithmachinelearning(ML),which representsonlyapartofthemethodologicalAIspectrum[5].However, MLalreadyhasalonghistoryinchemoinformaticsandmedicinalchem-istry,spanningmorethantwodecades,andiswidelyappliedformolecu-larpropertypredictionsaswellasthesearchfornovelactivecompounds [6].Neuralnetworks(NNs)werepopularearlyoninchemoinformatics, buthavebeenincreasinglyreplacedovertimewithotherapproaches [7]suchasthesupportvectormachine(SVM)[8]andrandomforest (RF)[9]algorithmsorBayesianmodeling[10],mostlyduetothein-trinsictendencyofNNstooverfitpropertypredictionmodelstrainedon moderatelysizeddatasets.WithDL,NNshavere-emergedinthisfield, forthemostpartasDNNarchitectures[11].

Incomputerscience,itisoftenobservedthatmethodologicalcom-plexitydoesnotscalewithpredictiveperformance[12]andthesame appliestomedicinalchemistryanddrugdesign[6].Although“bigdata”trendsarealsobeginningtoemergeinmedicinalchemistry[13],ML predictionsaretypicallybaseduponrelativelysmalldataregimesand well-definedmolecularrepresentations.Theseconditionsdonotplay intothestrengthsofDNNscomparedtootherareassuchasimageanal-ysisornaturallanguageprocessingwhereDLhasmadealargeimpactin recentyears[14,15].Accordingly,standardMLmethodsoftenperform comparablywellorbetterthanDNNsinpredictingbiologicalactivity andothermolecularproperties[6].

Ontheotherhand,DLoffersnewopportunitiesinchemoinformat-icsandmedicinalchemistrythatwerehardlypossibletoaddressina comparablewayuntilrecentlysuchas,forexample,inchemicalre-actionmodeling[1]orlarge-scalegenerative*denovo*compoundde-sign[3].IngenerativedesignandDNN-basedcompoundreposition-ing,successfulapplicationschartingnewterritoryarebeginningtoap-

pear[16]butotherclaimedadvancesremainoftenquestionable[17], partlyduetothelackofgenerallyacceptedevaluationcriteriaandstan-dardsforassessingchemicalnovelty[17].Eveninsuccessfuldesignap-plications,newlygeneratedorrepurposedchemicalentitiesareoften viewedcontroversiallyfromamedicinalchemistryperspective.Clearly, thefieldisinfluxbutML/DLinmedicinalchemistryanddrugdesign isstilllargelydominatedbymethodologicalconsiderations(whatcould bedone?)ratherthansuccessfulpracticalapplications(whathasbeen done?),whicharestillfarfrombeingroutine[18].

OneoftwoparticularlyrelevantaspectsconcerningMLinmedicinal chemistryemergingfromthediscussionaboveisthatavarietyofmeth-odsarebeingemployedforpropertypredictionandcompounddesign, rangingfromsimpledecisiontree-basedalgorithmsandprobabilistic modelingtocomplexDNNs,oftenwithcomparablesuccess.Theother importantaspectrelatestotherationalizationofpredictions,asfurther discussedinthefollowing.

Giventheoftencited“blackbox” characterofmostMLmodels [12,19],theirpredictionsaredifficulttorationalize.Inthepractice ofmedicinalchemistry,lackoftransparencyofpredictionsandmodel rationalizationcontinuetohindertheacceptanceofMLandlimitthe impactofpredictivemodelingonexperimentalprograms[6,18],de-spitethelongtraditionofMLinthisfield.Similarconsiderationsap-plytootherchemicaldisciplinesthatareprimarilyexperimentally driven.Ideally,onewouldliketoknowhowcertainandreliablea givenpredictionisandalsounderstanditinintuitivechemicalterms. Whileafewstudieshavepresentedapproachesforuncertaintyes-timationofMLpredictions[20,21],robustandgenerallyapplicable methodsarecurrentlynotyetavailable.However,incomputersci-enceandotherfields,thepotentialofexplainableorinterpretable MLisamuchdiscussedtopic[12,22,23],whichalsoisofhighrel-evanceforMLapplicationsinchemistry.Incomputerscience,inter-pretableMLreferstoalgorithmswhosepredictionscanbedirectly reconciled(suchasdecisiontrees)andexplainableMLtomethods enablingtherationalizationofblackboxmodels[12].However,in chemistry-relatedpublications,thesetermshavebeenusedmoreor lessinterchangeablyconcerningtherationalizationofmodelsandtheir decisions.

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Inmedicinalchemistry,thereisanurgentneedforMLmodelra-tionalization.Althoughthereluctanceofmedicinalchemiststorelyon blackboxpredictionsintheircompounddesignandoptimizationefforts isawidespreadphenomenon,onlyalimitednumberofinvestigations haveaddressedtheexplanationorinterpretationofMLpredictionsin thecontextofstructure-activityrelationship(SAR)analysis[24].With increasinguseofcomplexDNNarchitecturesinthefield[3,4],this widensthegapbetweenmodelavailabilityandacceptanceandfurther limitstheimpactofML.

Foractivitypredictionmodels,availablerationalizationstrategies typicallyaimtoidentifymolecularrepresentationfeaturesthatde-termineindividualpredictions,mostlyinamodel-dependentmanner. Theseapproachespredominantlyemployfeatureweightingtechniques torationalizepredictionsofkernel-based[25,26]orBayesian[27]clas-sificationmodels.Inaddition,weightgradientsacrossdifferentNNlay-erscanalsobedeterminedtotracedeterminantsofpredictionsandex-plain(D)NNmodels.However,thesegradientstendtobeunstable,fre-quentlyresultingindifferentinterpretationsofverysimilarpredictions [28].

Inadditiontomodel-dependenttechniques,model-independent methodscanalsobeconsidered,whichareprincipallypreferredbe-causetheyareapplicabletoanyMLmodel,regardlessofthecom-plexityoftheunderlyingalgorithm.Moreover,model-independentap-proachestypicallydonotrequirebalancingperformanceandinter-pretabilityacrossdifferentmodels[29].However,withsensitivityanal-ysis[30],onlyonemodel-independentapproachhasuntilrecentlybeen appliedtopropertypredictionsinchemoinformatics.Thismethodol-ogywasadaptedaboutadecadeagotostudytheinfluenceofsys-tematicfeaturevaluechangesonactivitypredictionsusingMLmod-els[31,32].Sensitivityanalysisgenerallyreliesonfeatureperturbation tostudyensuingeffects.Inparticular,partialderivativeswereused toassesstheimpactoflocalperturbationsoffragmentdescriptorson modelpredictions[32].Sensitivityanalysisbecomesrapidlyinfeasi-blewithincreasingmodeldimensionality,whichlimitsitsapplicability. Hence,thismethodologyhasbeenmoreorlessabandonedinthefield orsubstitutedbyapproximationsthatbettersummarizeperturbations effects.

Ourgrouphasconsideredalternativeapproacheswithpotentialfor MLmodel-independentrationalizationfromdifferentviewpointsinclud-ingbroadapplicability,quantitativeassessmentofpredictions,andease ofvisualinterpretation.Inlightofthesecriteria,theconceptof*Shap-leyvalues*[33,34]fromcooperativegametheory[34,35]hasbecome ourmethodologyofchoice.Shapleyvalueswereoriginallyintroduced in1953[33]toquantitativelyaccountforcontributionsofindividual playersformingateam.Thesevaluesprovideaquantitativeassessment ofcooperativecontributionstoateam’sultimatesuccess(totalgain). Accordingly,theyspecifyapartitionofmeritamongindividualplayers bycalculatingtheaverageofallcontributionsmadebyagivenplayer indifferentteamconstellations.

TheShapleyvalueconceptisreadilytransferabletoMLbyapplying thefollowinganalogies:Thegameateamengagesincanperceivedas apredictiontaskforasingleinstance(e.g.,acompound).Themeritfor thistaskisgivenbythedifferencebetweenitspredictionandtheaver-agepredictionofallinstances.Theplayersparticipatinginthegameare featuresvaluesoftheinstancethatcooperate(actinconcert)toobtain themeritforagivenprediction.TheresultingShapleyvalueofagiven featureisthenobtainedastheaveragecontributionofafeatureover allpossiblefeaturecombinations.Accordingly,Shapleyvaluesaccount forthepartitionofcontributionsoverindividualfeaturescomprisinga featurevectororset(suchasamolecularrepresentation).Akeyaspect oftheShapleyvalueconceptthatsetsitapartfrommodel-dependent featureweightingmethodsisthatnotonlythecontributionoffeature presencetoagivenpredictioncanbequantified,butalsothecontribu-tionoffeatureabsence.

Forfeaturesetsofincreasingsize,systematiccalculationsofShapley valuesonthebasisofallpossiblefeaturecombinationsbecomecom-

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resultingchangeofaprediction[41].ThisisincontrasttoSHAPthat doesnotrelyonatomremoval(i.e.,introductionofaperturbationat thestructurallevel),butassessescollaborative(i.e.,combination-based) contributionsofrepresentationfeatures.TheSimilarityMapsapproach doesnotrequirefeaturemappingbutcannotquantifycontributionsof featureabsence.Inaddition,single-atomperturbationsmightnotsignif-icantlymodifyamodel’spredictionbutaffectstructuralintegrity. Anotherconceptuallydistinctapproachinvolvesfeatureweighting ofmultiplemodelsgeneratedwiththesameMLalgorithm,providing thebasisforthedeterminationof*featureimportancecorrelation*[42]. Fortarget-basedcompoundactivityclasses,thismeasureyieldedmodel-internaldatasetsignaturesandrevealedsimilarcompoundbinding characteristicsofproteinsaswellasfunctionalrelationships.Strong featureimportancecorrelationbetweencompoundactivityprediction modelsindicatedfunctionalsimilaritiesbetweendifferenttargetsthat werenotrelatedtocompoundbinding[42].ForRFmodelsderivedfor morethan200targets,theGiniimpurity(GI)criterion[43]servedas ameasureofnode-basedrecursivepartitioningquality.GIisametric frominformationtheorydefinedinEq.(1):

GI= ∑*𝑝𝑖* (1−*𝑝𝑖* ) (1)

Here,*𝑝𝑖*isthefrequencyforclass*i*atagivennode,and*n*is2for binaryclassification.Accordingly,GIforagivenfeatureisequivalent tothemeandecreaseinGI,i.e.,thenormalizedsumofallimpurity decreasevaluesfornodesintheRFwheresplittingwasbasedonthat feature.Thus,increasingvaluesindicateincreasingfeatureimportance fortheRFmodel[43].Correlationorstatisticalassociationacrossfea-tureimportancevaluesfromdifferentmodelsisthenquantifiedusing correlationcoefficients.

Featureimportancecorrelationanalysisonlyrequiresmodel-internal information,butdoesnotdependonmodelexplanations.Feature weightsorimportancevaluescanbeextractedusingmultiplestrategies, dependingontheunderlyingMLalgorithm.Moreover,incontrastto SHAP-basedanalysisofindividualpredictions,featureimportancecor-relationanalysisisbaseduponglobalmodelassessment,takingmany compoundsintoaccount.WhileSHAPandfeatureimportancecorrela-tionanalysisareconceptuallydistinct,thesemethodsarecomplemen-taryandcanbecombinedforMLmodelassessment.Itisanticipated thatincreasingeffortswillbeexpandedinchemoinformaticstodevelop methodsformodelexplanationinordertofurtherincreasetheaccep-tanceofMLinthepracticeofmedicinalchemistry.

**DeclarationofCompetingInterest**

Theauthorsdeclarethattheyhavenoknowncompetingfinancial interestsorpersonalrelationshipsthatcouldhaveappearedtoinfluence theworkreportedinthispaper.

**AppendixA**

*SHAPtheory*

Theprincipalgoalofanexplanationmodel*g*istolocallyapprox-imateandtherebysimplifyacomplexmodel*f*thatisdifficulttoun-derstand.Additivefeatureattributionmethodsgenerateanexplanation modelviaalinearfunctionofbinaryvariables,givenbyEq.(2):

*𝑔*(*𝑥*′)=*𝜙*0+∑*𝜙𝑖𝑥*′ (2)

where*𝑥*′∈ {0*,*1}*𝑀*,*M*isthenumberofinputfeatures,and*𝜙𝑖*∈ ℝ.The presenceorabsenceofafeaturevalueimpactingthepredictionrepre-sentsafeaturecontribution(*𝜙𝑖*).Accordingly,aweightmustbeassigned toeachvariableforwhichtheLIMEmethodology[37]canbeapplied andfurtherextended.

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(iv)Aweightedlinearregressionmodel*g*istrainedtopredict*f(x)*. ThemodelcoefficientsareShapleyvaluescorrespondingtofea-tureimportanceestimates.

Samplingallpossiblefeaturesubsetsisavoidedthroughpermuta-tionofthefeaturevectorbysettingfeaturesonandoff.Afeatureis assignedalargeweightifitsreplacementwithanartificialvalueleads toasignificantchangeinmodeloutput.Weightsofartificialsamples aredeterminedasthenumberoffeatureadditionsequencesofagiven subsetbytheSHAPkernel.Coefficientsfromlocallinearregressionpro-videfeatureweightsasShapleyvalues,whichindicatehowimportant afeatureisforagivenpredictionincludingthedirection(sign)offea-tureinfluence.Theexpectedexplanatoryvalueiscalculatedasthemean ofthemodeloutputprobability(numericalvalue)overtrainingsetin-stances.Foragiveninstance,themodeloutputisthencalculatedasthe sumoftheexpected(base)valueandallSHAPfeaturevalues.

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