US 20200143904A1

(19) United States

(12) Patent Application Publication

(10) Pub. No.: US 2020/0143904 A1

(43) Pub. Date: May 7, 2020

Shaver et al.

(54) PREDICTING MOLECULAR PROPERTIES OF MOLECULAR VARIANTS USING RESIDUE-SPECIFIC MOLECULAR STRUCTURAL FEATURES

(71) Applicant: **Just Biotherapeutics, Inc.**, Seattle, WA (US)

(72) Inventors: **Jeremy Martin Shaver**, Lake Forest Park, WA (US); **Randal Robert Ketchem**, Snohomish, WA (US)

(21) Appl. No.: **16/620,389**

(22) PCT Filed: **Jun. 8, 2018**

(86) PCT No.: **PCT/US2018/036777**

§ 371 (c)(1),
(2) Date: **Dec. 6, 2019**

Related U.S. Application Data

(60) Provisional application No. 62/517,048, filed on Jun. 8, 2017.

Publication Classification

(51) **Int. Cl.**

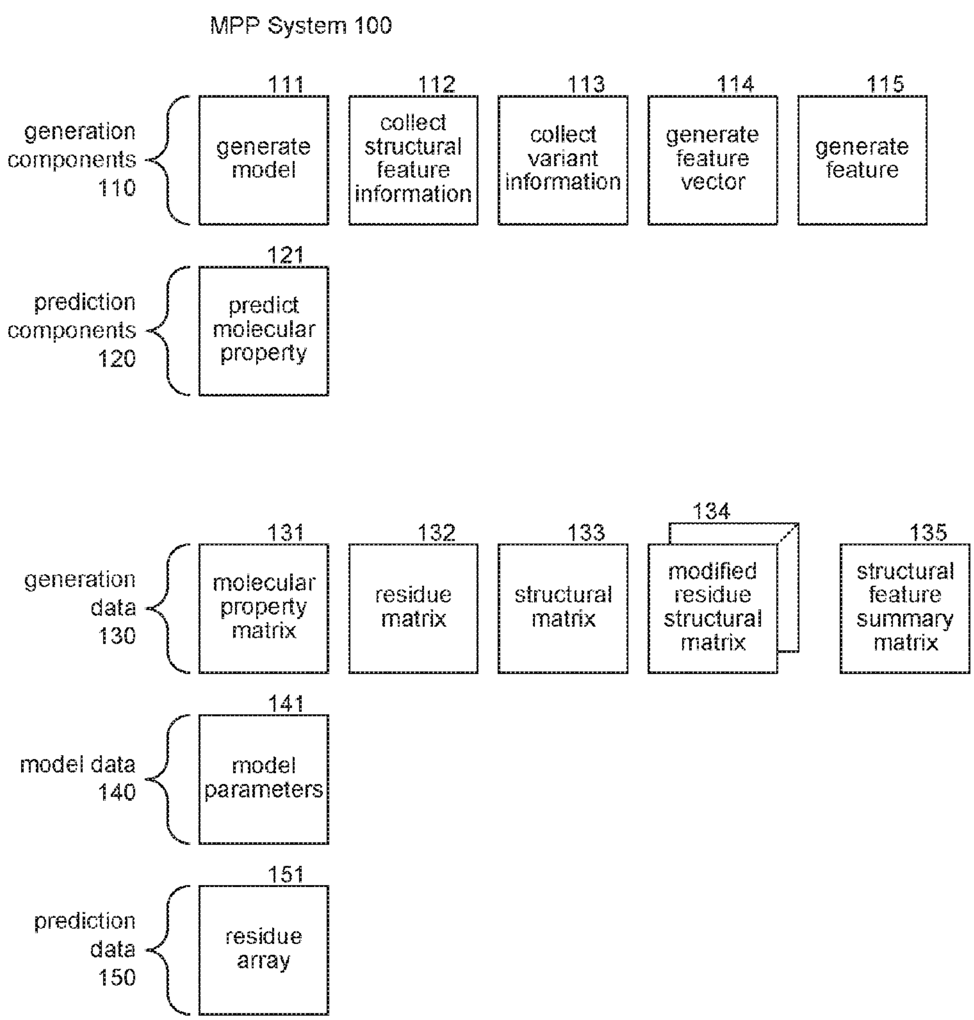
G16B 20/00	(2006.01)
G16B 30/00	(2006.01)
G16B 40/00	(2006.01)
G06F 30/20	(2006.01)

(52) **U.S. Cl.**

CPC ***G16B 20/00*** (2019.02); ***G16B 30/00*** (2019.02); *G06F 2111/10* (2020.01); ***G06F 30/20*** (2020.01); ***G16B 40/00*** (2019.02)

(57) **ABSTRACT**

A system for generating a model for predicting a molecular property of a variant of a molecule is provided. For each of a plurality of variants of the molecule, the system for each structural feature, aggregates the values for the structural features of the residues of the molecule that were modified to form the variant to form a feature vector for the variant. The system assigns the value for the molecular property of the variant to the feature vector wherein the feature vector and the assigned value form training data. The system then generates the model for predicting a value for the molecular property using the training data for the plurality of variants.



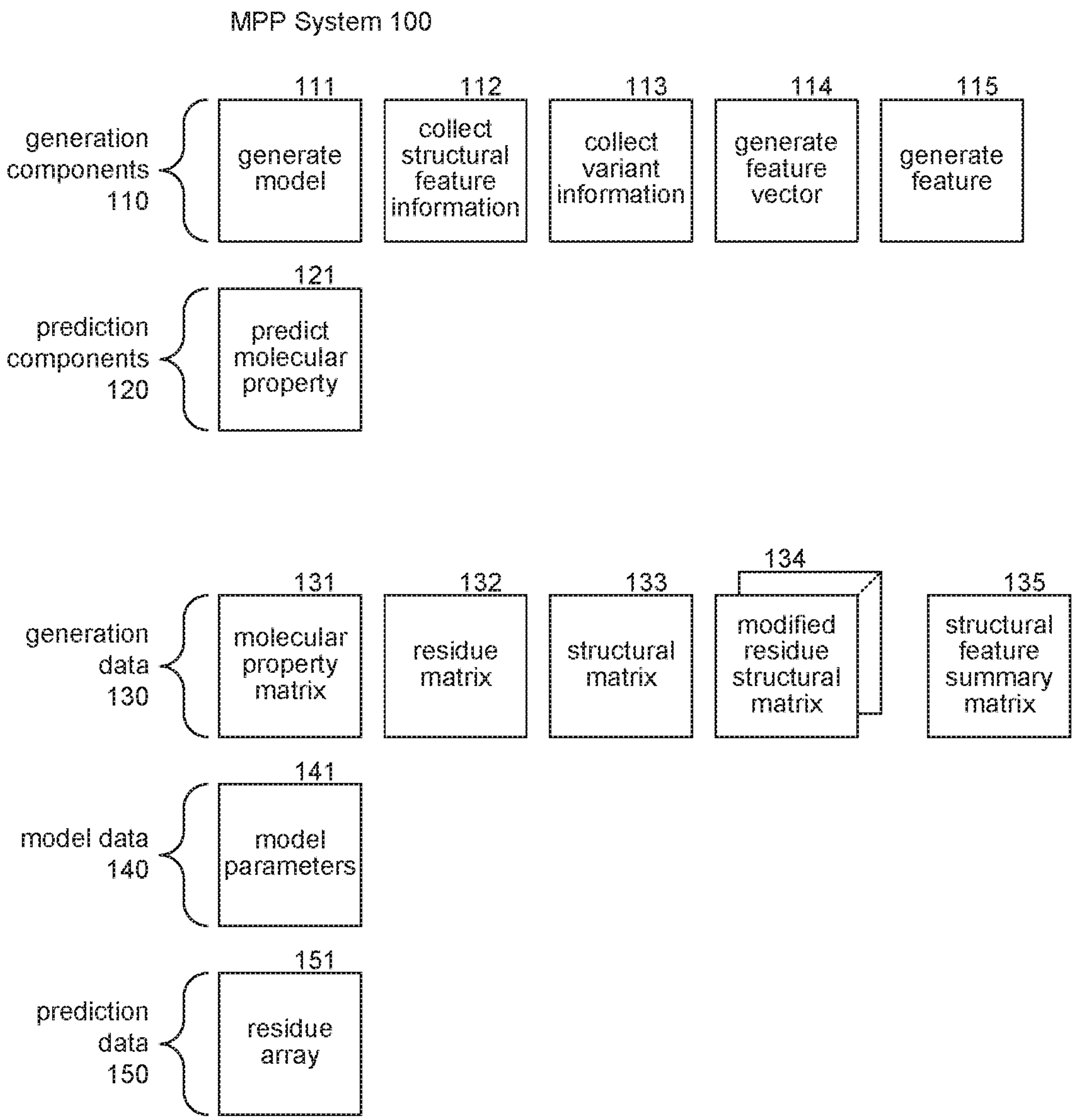

MPP System 100
generation components 110
111
generate model
112
collect structural feature information
113
collect variant information
114
generate feature vector
115
generate feature
prediction components 120
121
predict molecular property
generation data 130
131
molecular property matrix
132
residue matrix
133
structural matrix
134
modified residue structural matrix
135
structural feature summary matrix
model data 140
141
model parameters
prediction data 150
151
residue array

FIG. 1

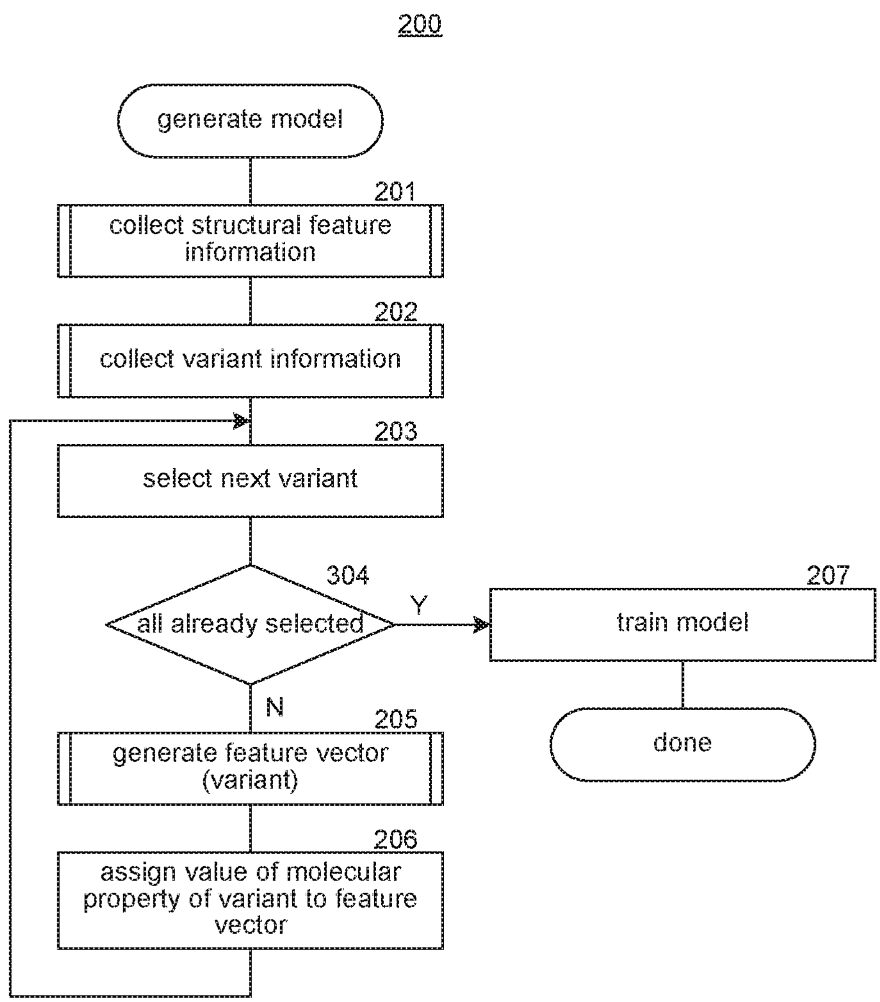

200
generate model
201
collect structural feature information
202
collect variant information
203
select next variant
304
all already selected
Y
207
train model
done
N
205
generate feature vector (variant)
206
assign value of molecular property of variant to feature vector

FIG. 2

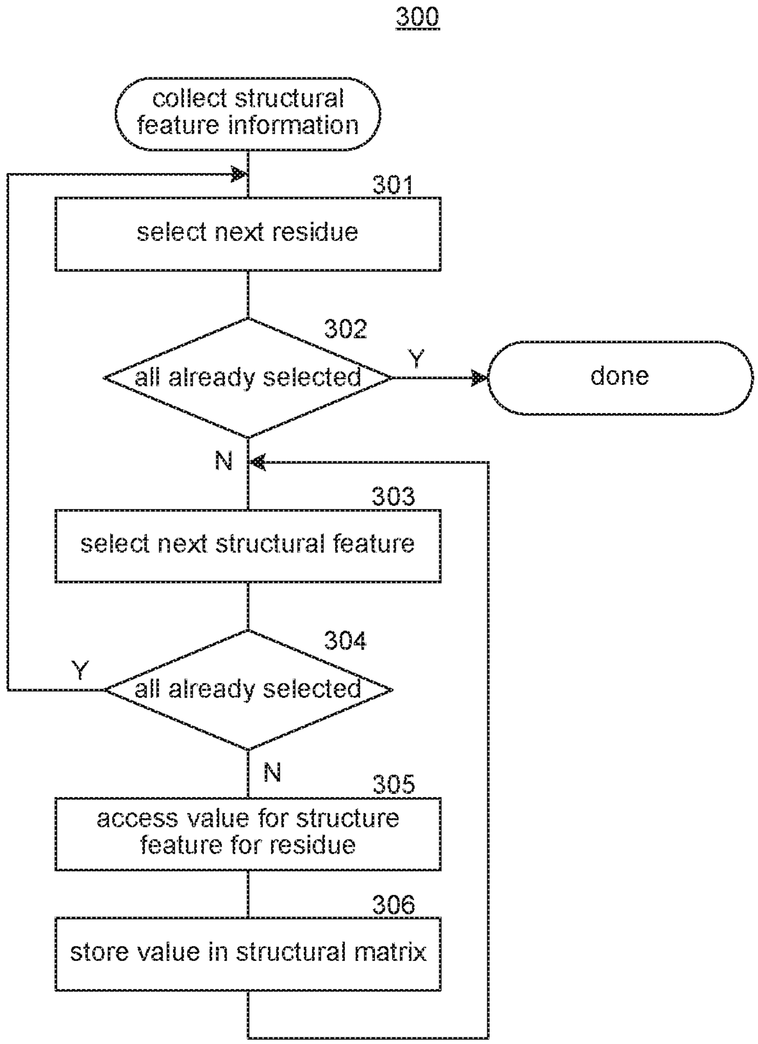

300
collect structural feature information
301
select next residue
302
all already selected
Y
done
N
303
select next structural feature
304
all already selected
Y
N
305
access value for structure feature for residue
306
store value in structural matrix

FIG. 3

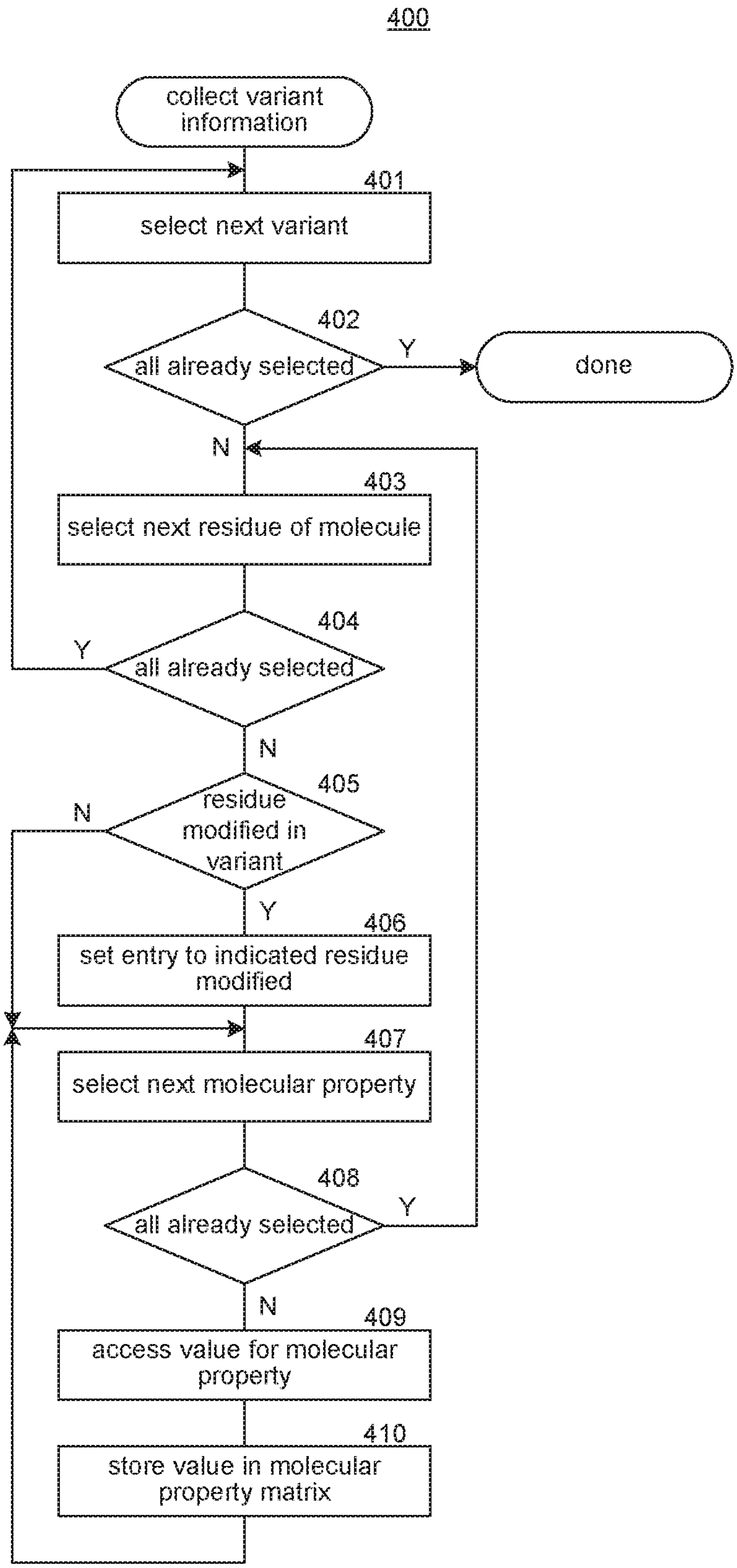

400
collect variant information
401
select next variant
402
all already selected
Y
done
N
403
select next residue of molecule
404
all already selected
Y
N
405
residue modified in variant
N
Y
406
set entry to indicated residue modified
407
select next molecular property
408
all already selected
Y
N
409
access value for molecular property
410
store value in molecular property matrix

FIG. 4

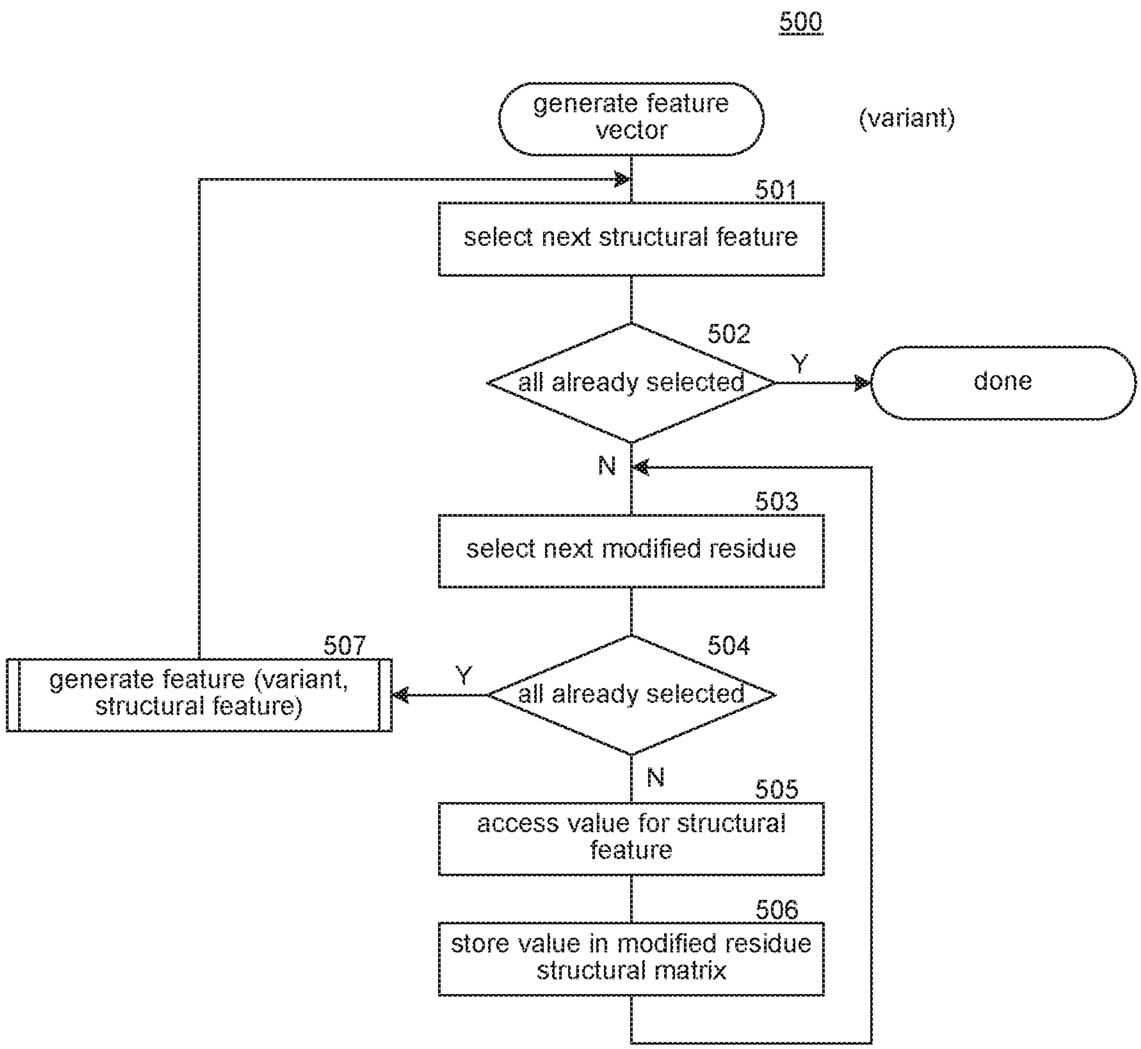

500
generate feature vector
(variant)
501
select next structural feature
502
all already selected
Y
done
N
503
select next modified residue
504
all already selected
Y
507
generate feature (variant, structural feature)
N
505
access value for structural feature
506
store value in modified residue structural matrix

FIG. 5

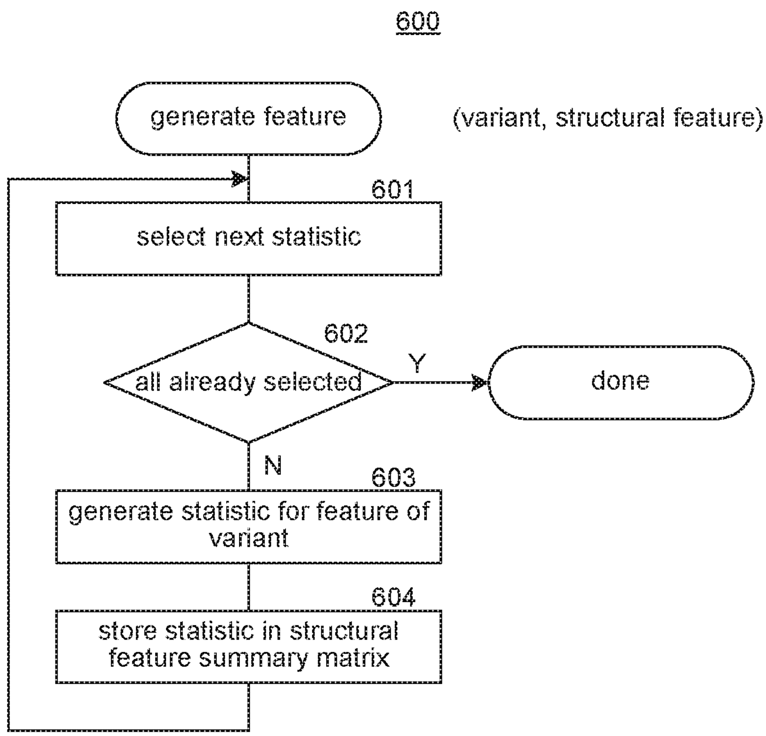

600
generate feature
(variant, structural feature)
601
select next statistic
602
all already selected
Y
done
N
603
generate statistic for feature of variant
604
store statistic in structural feature summary matrix

FIG. 6

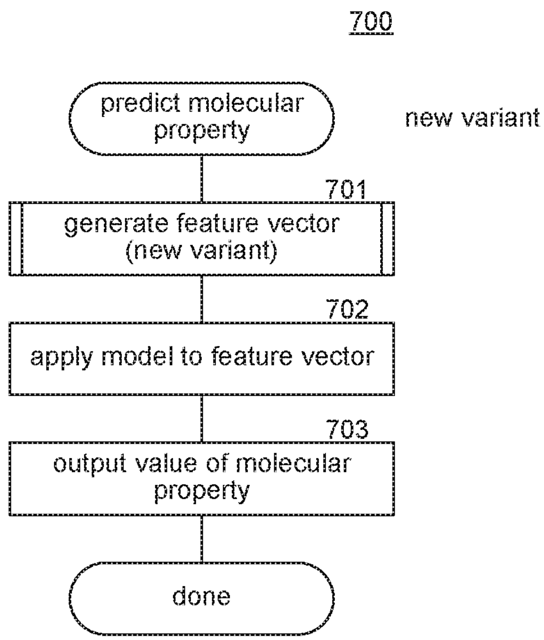

700
predict molecular property
new variant
701
generate feature vector (new variant)
702
apply model to feature vector
703
output value of molecular property
done

FIG. 7

PREDICTING MOLECULAR PROPERTIES OF MOLECULAR VARIANTS USING RESIDUE-SPECIFIC MOLECULAR STRUCTURAL FEATURES

BACKGROUND

[0001] Because the cost of developing breakthrough therapeutics based on modern biotechnology is so high, such therapeutics are not available to most people. A contributing factor to the high cost is that it is difficult to identify the molecular properties of new variants of a molecule such as an antibody. Although various tools are available to help in determining the molecular properties of molecules, they rely in large part in being able to synthesize the variant, which itself can be costly and time consuming.

BRIEF DESCRIPTION OF THE DRAWINGS

[0002] FIG. **1** is a block diagram illustrating components of the MPP system in some embodiments.

[0003] FIG. **2** is a flow diagram that illustrates the processing of a generate model component of the MPP system in some embodiments.

[0004] FIG. **3** is a flow diagram that illustrates the processing of a collect structural feature information component of the MPP system in some embodiments.

[0005] FIG. **4** is a flow diagram that illustrates the processing of a collect variant information component of the MPP system in some embodiments.

[0006] FIG. **5** is a flow diagram that illustrates the processing of a generate feature vector component of the MPP system in some embodiments.

[0007] FIG. **6** is a flow diagram that illustrates the processing of a generate feature component of the MPP system in some embodiments.

[0008] FIG. **7** is a flow diagram that illustrates the processing of a predict molecular property component of the MPP system in some embodiments.

DETAILED DESCRIPTION

[0009] A method and system for estimating molecular properties of new variants of a parent molecule (e.g., an antibody molecule) prior to synthesis of the new variants is provided. In some embodiments, a molecular property prediction ("MPP") system uses of various structural features of residues in a parent molecule (referred to as a molecule) in conjunction with molecular properties measured for a set of variants of the molecule. The MPP system supports predicting molecular properties of a new variant without having to calculate structural models for each of the variants. The MPP system also avoids creating the much more complicated "all molecules" model which attempts to predict molecular properties for any general antibody. The MPP system provides a prediction model that is more specific to a given molecule and more robust than the "all molecules" model. In some embodiments, the MPP system predicts molecular properties that include, but are not limited to, molecular characterizations such as antibody melting temperature ("Tm"), the percentage of high molecular weight expected during the expression and purification of the variant ("HMW"), chemical unfolding behavior, solubility, viscosity, and aggregation behavior (e.g., self-interaction nanoparticle spectroscopy—"SINS").

[0010] In some embodiments, the MPP system generates a model for predicting a molecular property of a variant of a molecule. The MPP system accesses values for structural features of the residues of the molecule. For example, the structural features of a molecule may include participation of the residue in charge patches or hydrophobic patches and group diversity of neighboring residues. For each variant of the molecule, the MPP system accesses variant information indicating which residues in a sequence of residues of the molecule were modified to form the variant and a value for the molecular property of the variant. For each structural feature, the MPP system aggregates the values for the structural features of the residues of the molecule that were modified to form the variant to generate a feature vector for the variant. The MPP system assigns the value for the molecular property of the variant to the feature vector. The feature vector and the assigned value for each variant form training data. The MPP system then uses the training data to generate the prediction model for predicting a value for the molecular property. For example, the MPP system may use a linear regression technique, neural networks, random forest techniques, Lasso regression techniques, and partial least square regression techniques to generate the prediction model. The MPP system may generate a separate prediction model for each molecular property.

[0011] After the prediction model is generated, the MPP system can then use the prediction model to predict values for a molecular property for a new variant of the molecule without having to synthesize the new variant and provide information to help guide future variant creation and experimentations. The MPP system inputs an indication of the residues of the molecule that are to be changed (e.g., by substituting one amino acid for another). The MPP system generates a new feature vector for the variant in a manner similar to how the feature vectors of the training data are generated. The MPP system then applies the prediction model for a molecular property to the new feature vector to predict the value for the molecular property.

[0012] FIG. **1** is a block diagram illustrating components of the MPP system in some embodiments. The MPP system **100** includes generation components **110** prediction components **120**, generation data **130**, model data **140**, and prediction data **150**. The generation components include a generate model component **111**, a collect structural feature information component **112**, a collect variant information component **113**, a generate feature vector component **114**, and a generate feature component **115**. The generate model component **111** controls the overall generation of the model by invoking the collect structural feature information component **112**, the collect variant information component **113**, and the generate feature vector component **114** and then training the model. The collect structural feature information component **112** collects the values for the structural features for the residues of the molecule. The structural features information is stored in a structural matrix **133** that includes a row for each residue and a column for each feature with entries indicating the values of a feature for a residue of the molecule. The collect variant information component **113** collects information on the variants of the molecules that includes which residues of the molecule were modified and a value for each molecular property for the variant. The information relating to the modified variants is stored in a residue matrix **132** that includes a row for each variant and a column for each residue with the entries indicating whether that residue is modified in that variant. The information related to the values for the molecular property are stored in a molecular property matrix **131** that includes a row for each variant and a column for each molecular property with the entries indicating the values for each molecular property for each variant. The generate feature vector component **114** generates a feature vector of features for each variant. The feature vector for a variant includes, for each structural feature, one or more statistics generated from the values for that structural feature of the residues of that variant that were modified. To generate a feature vector for a variant, the generate feature vector component **114** may generate a modified residue structural matrix **134** for that variant that includes a column for each modified residue of that variant and a row for each feature with entries indicating the values for that structural feature in that residue for the molecule. The generate feature component **115** then aggregates the values from the modified residue structural matrix **134** for a variant. The generate feature component **115** may generate a structural feature summary matrix **135** that includes a row for each variant and a column for each feature with entries indicating the value for the feature that may be a statistic such as sum, mean, and standard deviation for that variant. Each row of the structural feature summary matrix **135** represents the feature vector for a variant. The generate model component then assigns to each feature vector of a variant the value of its molecular property from the molecular property matrix **131**.

[0013] The generate model component **111** then trains the prediction model using the feature vectors with their assigned values. The generate model component **111** stores the parameters learned during the training in a model parameters store **141**. Once the prediction model is generated, the value of a molecular property for a new variant can be predicted using a predict molecular property component **121**. The predict molecular property component inputs a residue array **151** that indicates for each residue of the molecule whether the corresponding residue in the new variant has been modified. The predict molecular property component **121** invokes the generate feature vector component to generate a new feature vector for the new variant. The predict molecular property component **121** then applies the model to the new feature vector to predict the value for the molecular property of the new variant.

[0014] The matrices below provide example values for the various matrices of the MPP system. The structural matrix is generated for variant **2**. The modified residue structural matrix includes the three rows of the structural matrix corresponding to the entries of the residue matrix that have values of "true." The structural feature summary matrix includes a row for each variant with a column for each statistic—the maximum, mean, and standard deviation for each of the hydrophobic area, the positive area, and solvent accessibility ("SA") structural features. For example, the maximum, mean, and standard deviation ("SD") of the positive area for variant **2** are 180, 60, and 84.853, respectively.

Molecular Property Matrix

[0015]

Molecular Property	
Variant	HMW
1	0.60083
2	0.87401
3	0.53155

Residue Matrix

[0016]

	Residue				
Variant	1	2	3	4	5
1	False	False	False	True	True
2	True	False	False	True	True
3	False	True	True	True	True

Structural Matrix

[0017]

Structural Feature			
Residue	hydrophobic area	positive area	SA
1	0	0	36.1
2	0	0	23.5
3	110	180	57.1
4	0	180	199.1
5	0	0	84.7

Modified Residue Structural Matrix (for Variant **2**)

[0018]

Structural Feature			
Residue	hydrophobic area	positive area	SA
1	0	0	36.1
4	0	180	199.1
5	0	0	84.7

Structural Feature Summary Matrix

[0019]

		Statistic								
		SA			hydrophobic area			positive area		
		max	mean	SD	max	mean	SD	max	mean	SD
Variant	1	199.1	141.9	57.2	0	0	0	180	90	90
	2	199.1	106.63	68.328	0	0	0	180	60	84.853
	3	199.1	91.1	66.014	110	27.5	47.631	180	90	90

[0020] The computing systems on which the MPP system may be implemented may include a central processing unit, input devices, output devices (e.g., display devices and speakers), storage devices (e.g., memory and disk drives), network interfaces, graphics processing units, and so on. The input devices may include keyboards, pointing devices, touch screens, gesture recognition devices (e.g., for air gestures), head and eye tracking devices, microphones for voice recognition, and so on. The computing systems may include desktop computers, laptops, tablets, servers, and so on. The computing systems may access computer-readable media that include computer-readable storage media and data transmission media. The computer-readable storage media are tangible storage means that do not include a transitory, propagating signal. Examples of computer-readable storage media include memory such as primary memory, cache memory, and secondary memory (e.g., DVD) and other storage. The computer-readable storage media may have recorded on it or may be encoded with computer-executable instructions or logic that implements the MPP system. The data transmission media is used for transmitting data via transitory, propagating signals or carrier waves (e.g., electromagnetism) via a wired or wireless connection.

[0021] The MPP system may be described in the general context of computer-executable instructions, such as program modules and components, executed by one or more computers, processors, or other devices. Generally, program modules or components include routines, programs, objects, data structures, and so on that perform particular tasks or implement particular data types. Typically, the functionality of the program modules may be combined or distributed as desired in various examples. Aspects of the MPP system may be implemented in hardware using, for example, an application-specific integrated circuit (ASIC) or field programmable gate array ("FPGA").

[0022] In some embodiments, the actual molecular properties are measured for each previously synthesized variant (i.e., that are used for training) and are referred to as the "Y values." A separate value is collected for each variant (rows) and each molecular property (e.g. Tm, HMW, SINS—as columns) in the molecular property matrix **131**.

[0023] In some embodiments, the residue matrix **132** is a Boolean matrix that describes which residue(s) were modified in the parent molecule to create the given variant. Each row of this matrix represents one variant and each column a Boolean vector indicating if a given residue was mutated.

[0024] In some embodiments, the structural features of the molecule for each residue that is available for modification in the molecule is stored in the structural matrix **133**. The structural matrix **133** contains columns representing the individual structural features and rows as the residues. The structural matrix **133** may be derived from a structural model of the molecule by extracting for each residue, value for structural features such as:

- **[0025]** participation of the residue in positive or negative charge patches or hydrophobic patches
- **[0026]** group diversity of neighboring residues (e.g. number of hydrophobic, acidic, basic, or neutral residues within a given distance—distance based on the tertiary structure)
- **[0027]** solvent accessibility of the residue (high at the surface of the molecule)
- **[0028]** nearness to region/chain interfaces (e.g. distance to Fv and constant domain interface)
- **[0029]** secondary structure environment
- **[0030]** original (in molecule) and new residue (in variant) length or size
- **[0031]** original and new residue pKa (i.e., acidity)

[0032] A goal of the MPP system may be to identify a subset of structural features that can be used to estimate a given molecular property for both the set of previously synthesized variants (known as a calibration set) and to estimate the molecular property for new variants (without the synthesis and measurement of the molecular property of those variants). The MPP system starts by using the residue matrix **132** to extract the rows of the structural matrix **133** for residues that were modified for a given variant. The modified residue structural matrix **134** for a variant has as many rows as the number of residues modified for that variant. The modified residue structural matrix **134** is compressed down into a single row by applying a set of statistical metrics to each column including, but not necessarily limited to: sum, mean, standard deviation, skew, kurtosis, minimum, maximum, product, and sum and mean of the log of absolute values (e.g., logs post-multiplied by original value sign either summed or averaged). The result of applying each of these operations on each original structural feature column is that the statistic is turned into a new column. Accordingly, there are 10 new columns (e.g., given the set of 10 statistical metrics above) for each original structural feature. The MPP system thus captures the molecular variation of the set of modified residues without having to specifically list the residues. After iterating over all variants, the MPP system generates a structural feature summary matrix **135** in which each row is a variant and the columns are the statistical summary of each set of modified structural features. Next, the structural feature summary matrix **135** is either used in a dimension-reducing regression or classification model (e.g., partial least squares, or neural network with reducing hidden-layer nodes) to predict the Y values (e.g., molecular properties), or it is used in a variable selection method (e.g., a genetic algorithm, or correlation-based selection) to reduce the number of variables. In the latter case, only the selected variables are used in a regression or classification model.

[0033] In some embodiments, the MPP system may support molecule-generalized models. Because each molecule has a different starting value for a given molecular property, and because each molecule may be differently sensitive to the characteristics of the modified residues, models as described above are expected to only be applicable to the specific parent molecule. However, some property predictions can be made less molecule-specific by adding molecule-encoding variables or doing a priori corrections, for example, by making the Y values be relative to the parent molecule. In such cases, multiple structural feature summary matrices for different molecules may be combined along with their corresponding Y values and processed in a single model. For example, a combined structural feature summary matrix may include a column to identify the parent molecule of a variant. In such a case, the MPP system may use deep-learning style models such a neural network with multiple hidden layers.

[0034] FIG. **2** is a flow diagram that illustrates the processing of a generate model component of the MPP system in some embodiments. The generate model component **200** is invoked to generate the model for a molecule for use in predictions. In block **201**, the component invokes the collect structural feature information component to collect the structural features of the molecule. In block **202**, the component invokes the collect variant information component to collect variant information for each variant that is used to generate the model. In blocks **203**-**206**, the component loops generating the feature vector for each variant. In block **203**, the component selects the next variant. In decision block **204**, if all variants have already selected, then the component continues at block **207**, else the component continues at block **205**. In block **205**, the component invokes the generate feature vector component passing an indication of the variant. In block **206**, the component assigns the value of the molecular property for the variant to the feature vector to form the training data of the feature vector and the assigned value. The component then loops to block **203** to select the next variant. In block **207**, the component trains the prediction model using the training data and completes.

[0035] FIG. **3** is a flow diagram that illustrates the processing of a collect structural feature information component of the MPP system in some embodiments. The collect structural feature information component **300** is invoked to collect the structural features for the molecule. In block **301**, the component selects the next residue of the molecule. In decision block **302**, if all the residues have already been selected, then the component completes, else the component continues at block **303**. In block **303**, the component selects the next structural feature of the residue. In decision block **304**, if all the structural features for the selected residue have already been selected, then the component loops to block **301** to select the next residue, else the component continues at block **305**. In block **305**, the component accesses the value for the structural feature for the selected residue. In block **306**, the component stores the value in the structural matrix **133** and then loops to block **303** to select the next structural feature.

[0036] FIG. **4** is a flow diagram that illustrates the processing of a collect variant information component of the MPP system in some embodiments. The collect variant information component **400** is invoked to collect the molecular properties of the variants along with an indication of which residues were modified. In block **401**, the component selects the next variant. In decision block **402**, if all the variants have already been selected, then the component completes, else the component continues at block **403**. In block **403**, the component selects the next residue of the molecule. In decision block **404**, if all the residues have already been selected, then the component loops to block **401** to select the next variant, else the component continues at block **405**. In decision block **405**, if the residue is modified in the variant, then the component continues at block **406**, else the component continues at block **407**. In block **406**, the component sets the entry for the selected variant and the selected residue in the residue matrix **132** to indicate that the residue has been modified in the selected variant. In block **407**, the component selects the next molecular property. In decision block **408**, if all the molecular properties have already been selected, then the component loops to block **403** to select the next residue in the molecule, else the component continues at block **409**. In block **409**, the component accesses the value for the molecular property. In block **410**, the component stores the value in the molecular property matrix **131** and then loops to block **407** to select the next molecular property.

[0037] FIG. **5** is a flow diagram that illustrates the processing of a generate feature vector component of the MPP system in some embodiments. A generate feature vector component **500** is invoked to generate a feature vector for a passed variant. In block **501**, the component selects the next structural feature. In decision block **502**, if all the structural features have already been selected, then the component completes, else the component continues at block **503**. In block **503**, the component selects the next modified residue for the passed variant. In decision block **504**, if all the modified residues have already been selected, then the component continues at block **507**, else the component continues at block **505**. In block **505**, the component accesses the value for the selected structural feature. In block **506**, the component stores the value in the modified residue structural matrix **134** for the variant and then loops to block **503** to select the next modified residue. In block **507**, the component invokes a generate feature component to generate the features for the variant from the value for the selected structural feature stored in the modified residue structural matrix **134** and then loops to block **501** to select the next structural feature.

[0038] FIG. **6** is a flow diagram that illustrates the processing of a generate feature component of the MPP system in some embodiments. The generate feature component **600** is passed an indication of a variant and a structural feature and generates a feature for the feature vector for the variant for each statistic based on the structural feature. In block **601**, the component selects the next statistic. In decision block **602**, if all the statistics have already been selected, then the component completes, else the component continues at block **603**. In block **603**, the component generates the selected statistic for the structural feature of the variant based on values in the modified residue structural matrix **134** for the passed variant. In block **604**, the component stores the statistic in the structural feature summary matrix **135** and then loops to block **601** to select the next statistic.

[0039] FIG. **7** is a flow diagram that illustrates the processing of a predict molecular property component of the MPP system in some embodiments. The predict property component **700** is invoked to predict a molecular property of a new variant. The new variant is indicated by the residues that have been modified. In block **701**, the component invokes a generate feature vector component to generate a feature vector for the new variant based on the modified residues as indicated by the residue array **151**. In block **702**, the component applies the prediction model to the feature vector to generate a value for a molecular property for the new variant. In block **703**, the component outputs of value of the molecular property and then completes.

[0040] The following paragraphs describe various embodiments of aspects of the MPP system. An implementation of the MPP system may employ any combination of the embodiments. The processing described below may be performed by a computing device with a processor that executes computer-executable instructions stored on a computer-readable storage medium that implements the MPP system.

[0041] In some embodiments, a method performed by a computing system for generating a model for predicting a molecular property of a variant of a molecule is provided. The method accesses values for structural features of residues of the molecule. For each of a plurality of variants of the molecule, the method accesses variant information indicating which residues in a sequence of residues of the molecule were modified to form the variant and a value for the molecular property of the variant. For each of the plurality of variants of the molecule, the method also, for each structural feature, aggregates the values for the structural features of the residues of the molecule that were modified to form the variant to form a feature vector for the variant. For each of the plurality of variants of the molecule, the method assigns the value for the molecular property of the variant to the feature vector wherein the feature vector and the assigned value form training data. The method then generates the model for predicting a value for the molecular property using the training data for the plurality of variants. In some embodiments, the method further predicts a value for the molecular property of a new variant by accessing new variant information indicating which residues in the sequence of residues of the molecule were modified to form the variant; for each structural feature, aggregates the values for the structural feature of the residues of the molecule that were modified to form the new variant to form a new feature vector for the new variant; and applies the model to the new feature vector to predict the value for the molecular property of the new variant. In some embodiments, the model is generated using a linear regression technique using the training data as input. In some embodiments, the model is generated by learning a neural network using the training data as input. In some embodiments, the generating of the model includes reducing dimensions of the training data. In some embodiments, the molecule is a protein. In some embodiments, a variant is formed by replacing an amino acid of the molecule with a different amino acid. In some embodiments, the molecular property is selected from a group consisting of antibody melting temperature, percentage of high molecular weight, chemical unfolding behavior, solubility, viscosity, and aggregation behavior. In some embodiments, the structural features are selected from a group consisting of participating of a residue in charge patches or hydrophobic patches, group diversity of neighboring residues, solvent accessibility of a residue, nearness to region/chain interfaces, secondary structural environment, sizes of residue in the molecule and the variant, and acidity of a residue in the molecule and the variant. In some embodiments, the aggregating of the values for a structural feature generates statistics selected from a group consisting of sum, mean, standard deviation, skew, kurtosis, minimum, maximum, product, sum of log of absolute values, and mean of log of absolute values.

[0042] In some embodiments, a computing system for predicting a value for a molecular property of a new variant of a molecule is provided. The computing system includes one or more computer-readable storage medium storing computer-executable instructions and one or more processors for executing the computer-executable instructions stored in the one or more computer-readable mediums. The computer-executable instructions control the computing system to access new variant information indicating which residues in a sequence of residues of the molecule were modified to form the new variant. For each of a plurality of structural features of residues of the molecule, the computer-executable instructions control the computing system to aggregate the values for the structural feature of the residues of the molecule that were modified to form the new variant to form a new feature vector for the new variant. The computer-executable instructions further control the computing system apply a model to the new feature vector to predict the value for the molecular property of the new variant. The model is generated using training data comprising feature vectors derived from value of structural features of variants of the molecule and the values of the molecular property of those variants. In some embodiments, the computer-executable instructions further control the computing system to access values for structural features of residues of the molecule. For each of a plurality of variants of the molecule, the computer-executable instructions control the computing system to access variant information indicating which residues in a sequence of residues of the molecule were modified to form the variant and a value for the molecular property of the variant; for each structural feature, aggregate the values for the structural features of the residues of the molecule that were modified to form the variant to form the feature vector for the variant; and assign the value for the molecular property of the variant to the feature vector wherein the feature vector and the assigned value form the training data. The computer-executable instructions control the computing system to generate the model for predicting a value for the molecular property using the training data for the plurality of variants. In some embodiments, the model is generated using a linear regression technique using the training data as input. In some embodiments, the model is generated by learning a neural network using the training data as input. In some embodiments, the computer-executable instructions further control the computing system to reduce dimensions of the training data. In some embodiments, the molecule is a protein. In some embodiments, a variant is formed by replacing an amino acid of the molecule with a different amino acid. In some embodiments, the molecular property is selected from a group consisting of antibody melting temperature, percentage of high molecular weight, chemical unfolding behavior, solubility, viscosity, and aggregation behavior. In some embodiments, the structural features are selected from a group consisting of participating of a residue in charge patches or hydrophobic patches, group diversity of neighboring residues, solvent accessibility of a residue, nearness to region/chain interfaces, secondary structural environment, sizes of residue in the molecule and the variant, and acidity of a residue in the molecule and the variant. In some embodiments, the computer-executable instructions control the computing system to aggregate the values for a structural feature further generate statistics selected from a group consisting of sum, mean, standard deviation, skew, kurtosis, minimum, maximum, product, sum of log of absolute values, and mean of log of absolute values.

[0043] Although the subject matter has been described in language specific to structural features and/or acts, it is to be understood that the subject matter defined in the appended claims is not necessarily limited to the specific features or acts described above. Rather, the specific features and acts described above are disclosed as example forms of implementing the claims. Accordingly, the invention is not limited except as by the appended claims.

1-20. (canceled)

21. A method comprising:

generating, by a computing system including one or more processing units and one or more non-transitory computer-readable storage media, a structural matrix for a variant protein, the variant protein having a modified residue at a position of the variant protein that is different from an initial residue at a corresponding position of a parent protein and the structural matrix indicating respective first values of individual structural features for residues of the variant protein;

modifying, by the computing system, the structural matrix to generate a modified structured matrix for the variant molecule, the modified structural matrix indicating a subset of the first values that corresponds to one or more residues of the variant protein that have been modified with respect to initial residues of the parent protein;

performing, by the computing system, one or more statistical operations with respect to the subset of the first values to produce one or more second values for the one or more statistical operations;

generating, by the computing system, a structural feature summary matrix that includes the one or more second values in association with the variant protein and a number of additional values for the one or more statistical operations in association with a plurality of additional variant proteins;

determining, by the computing system and based on the structural feature summary matrix, a subset of the individual structural features included in the structural matrix;

assigning, by the computing system, a value of a molecular property for the variant protein to the subset of the first values included in the modified structural matrix;

producing, by the computing system, training data indicating that the value of the molecular property for the variant protein is assigned to the subset of the first values and indicating a number of additional values of the molecular property assigned to additional sets of values for the individual structural features, individual additional sets of values corresponding to respective additional variants of the parent protein;

generating, by the computing system, a model to predict values for the molecular property for new variant proteins that correspond to the parent protein, the model including one or more parameters that correspond to the subset of the individual structural features;

accessing, by the computing system, new variant information indicating one or more modified residues of a new variant protein that are different from one or more residues of the parent protein at one or more corresponding positions;

generating, by the computing system, a second modified structural matrix that indicates additional values for the individual structural features for the one or more modified residues; and

applying, by the computing system, the model to the second modified structural matrix and to the new variant information to determine an additional value of the molecular property for the new variant protein.

22. The method of claim **21**, comprising:

determining a respective first value of the individual structural features for the modified residue using a structural model of the variant protein.

23. The method of claim **21**, wherein the parent protein and the variant protein include antibodies and determining a value of an individual structural feature for the modified residue includes determining a distance between the modified residue and a constant region of the variant protein or determining a distance between the modified. residue and a variable region of the variant protein.

24. The method of claim **2**,**1**, comprising:

synthesizing the variant protein; and

measuring the value of the molecular property for the variant protein.

25. The method of claim **21**, wherein the new variant information includes an array that indicates for each residue of the new variant protein whether a respective residue in the new variant protein has been changed with respect to a residue at a corresponding location in the parent protein.

26. A computing system comprising:

one or more processing units; and

one or more non-transitory computer-readable storage media storing computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

generate a structural matrix for a variant molecule, the variant molecule having modified residues that are different from initial residues at corresponding first positions parent molecule and the structural matrix indicating respective first values for individual structural features for residues of the variant molecule;

modify the structural matrix to generate a modified structural matrix for the variant molecule, the modified structural matrix indicating a subset of the first values that corresponds to the modified residues;

assign a value of a molecular property for the variant molecule to the subset of the first values included in the modified structural matrix;

generate a model to predict values for the molecular property for new variant molecules that correspond to the parent molecule;

generate a second modified structural matrix that indicates second values for the individual structural features for residues of a new variant molecule that are different from residues of the parent molecule at corresponding second positions; and

apply the model to the second modified structural matrix to determine an additional value of the molecular property for the new variant molecule.

27. The computing system of claim **26**, wherein the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

perform one or more statistical operations with respect to the subset of the first values to produce one or more third values for the one or more statistical operations;

generate a structural feature summary matrix that includes the one or more third values in association with the variant molecule and includes a number of additional values for the one or more statistical operations in association with a plurality of additional variant molecules; and

determine based on the structural feature summary matrix, a subset of the individual structural features included in the structural matrix.

28. The computing system of claim **27**, wherein the model includes one or more parameters that correspond to the subset of the individual structural features.

29. The computing system of claim **26**, wherein:

the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to generate new variant information that includes an array indicating, for each residue of the new variant molecule, whether a respective residue in the new variant has been changed with respect to a residue at a corresponding location in the parent molecule; and

the additional value of the molecular property for the new variant molecule is generated based on the new variant information.

30. The computing system of claim **26**, wherein the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

determine a value for a structural feature relating to diversity of residues neighboring a variant residue of the variant molecule by:

determining a number of hydrophobic residues within a first distance of the variant residue;

determining a number of acidic residues within a second distance f the variant residue;

determining a number of basic residues within a third distance of the variant residue; and

determining a number of neutral residues within a fourth distance of the variant residue;

wherein the first distance, the second distance, the third distance, and the fourth distance are based on a tertiary structure of the variant molecule.

31. The computing system of claim **26**, wherein the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

determine a value for a structural feature of a variant residue of the variant molecule by:

determining that the variant residue is located in a positively charged region of the variant molecule; or

determining that the variant residue is located in a negatively charged region of the variant molecule.

32. The computing system of claim **26**, wherein:

the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

generate a feature vector by aggregating values for structural features corresponding to each modified residue in the variant molecule that is different from an initial residue of the parent molecule at respective corresponding positions; and

produce training data by assigning the value of the molecular property for the variant molecule to the feature vector; and

the model is generated using the training data.

33. The computing system of claim **2**,**6**, wherein:

the one or more non-transitory computer-readable storage media store additional computer-executable instructions that, when executed by the one or more processing units, cause the computing system to:

obtain input indicating changes to residues of the parent molecule to produce a number of modified residues for a new variant molecule; and generate a feature vector by determining individual values for respective structural features for each modified residue of the number of modified residues; and

the additional value of the molecular property for the new variant molecule is determined based on the feature vector.

34. method comprising:

generating, by a computing system including: one or more processing units and one or more non-transitory computer-readable storage media, a structural matrix for a variant molecule, the variant molecule having modified residues that are different from initial residues at corresponding first positions of a parent molecule and the structural matrix indicating respective first values for individual structural features for residues of the variant molecule;

modifying, by the computing system, the structural matrix to generate a modified structural matrix for the variant molecule, the modified structural matrix indicating a subset of the first values that corresponds to the modified residues;

assigning, by the computing system, a value of a molecular property for the variant molecule to the subset of the first values included in the modified structural matrix;

generating, by the computing system, a model to predict values for the molecular property for new variant molecules that correspond to the parent molecule;

generating, by the computing system, a second modified structural matrix that indicates second values for the individual structural features for residues of a new variant molecule that are different from residues of the parent molecule at corresponding second positions; and

applying, by the computing system, the model to the second modified structural matrix to determine an additional value of the molecular property for the new variant molecule.

35. The method of claim **34**, comprising:

determining a first value of a first structural feature of a modified residue of the variant molecule by determining an accessibility of the modified residue to a solvent based on proximity of the modified residue to a surface of the variant molecule; and

determining a second value of a second structural feature of the modified residue by determining a pKa value of the variant molecule with respect to a pKa value of the parent molecule.

36. The method of claim **34**, comprising:

performing one or more statistical operations with respect the subset of the first values to produce one or more third values for the one or more statistical operations;

generating a structural feature summary matrix that includes the one or more third values in association with the variant molecule and includes a number of additional values for the one or more statistical operations in association with a plurality of additional variant molecules; and

determining based on the structural feature summary matrix, a subset of the individual structural features included in the structural matrix.

37. The method of claim **36**, wherein the model includes one or more parameters that correspond to the subset of the individual structural features.

38. The method of claim **36**, wherein the one or more statistical operations include at least one of determining for the subset of the first values: a sum, a mean, a standard deviation, a skew, a kurtosis, a minimum, a maximum, a product, a sum of log of absolute values, or a mean of log of absolute values.

39. The method of claim **34**, wherein the molecular property includes antibody melting temperature, chemical unfolding behavior, solubility, viscosity, aggregation behavior, or percentage of high molecular weight.

40. The method of claim **34**, comprising:

obtaining input indicating changes to residues of the parent molecule to produce a number of modified residues for a new variant molecule;

generating a feature vector by determining individual values for respective structural features for each modified residue of the number of modified residues; and

wherein the additional value of the molecular property for the new variant molecule is determined based on the feature vector.

* * * * *