# Molecular Descriptors Guide

Description of the Molecular Descriptors Appearing in the

PyDPI Software Package

Version1.0

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# 1 Descriptors of drugs

A small or drug molecule could be represented by its chemical structure. In the PyDPI software, we calculate ten types of molecular descriptors to represent drug molecules, including constitutional descriptors, topological descriptors, connectivity indices, E-state indices, autocorrelation descriptors, charge descriptors, molecular properties, kappa shape indices, MOE-type descriptors, and molecular fingerprints. These descriptors capture and magnify distinct aspects of chemical structures.

## 1.1 Molecular constitutional descriptors

1. Molecular weight (*Weight*)
2. Count of hydrogen atoms (*nhyd*)
3. Count of halogen atoms (*nhal*)
4. Count of hetero atoms (*nhet*)
5. Count of heavy atoms (*nhev*)
6. Count of F atoms (*ncof*)
7. Count of Cl atoms (*ncocl*)
8. Count of Br atoms (*ncobr*)
9. Count of I atoms (*ncoi*)
10. Count of C atoms (*ncarb*)
11. Count of P atoms (*nphos*)
12. Count of S atoms (*nsulph*)
13. Count of O atoms (*noxy*)
14. Count of N atoms (*nnitro*)
15. Number of rings (*nring*)
16. Number of rotatable bonds (*nrot*)
17. Number of H-bond donors (*ndonr*)
18. Number of H-bond acceptors (*naccr*)
19. Number of single bonds (*nsb*)
20. Number of double bonds (*ndb*)
21. Number of triple bonds (*ntb*)
22. Number of aromatic bonds (*naro*)

23. Number of all atoms (*nta*)
24. Average molecular weight (*AWeight*)
25. Molecular path counts of length 1 (*PC1*)
26. Molecular path counts of length 2 (*PC2*)
27. Molecular path counts of length 3 (*PC3*)
28. Molecular path counts of length 4 (*PC4*)
29. Molecular path counts of length 5 (*PC5*)
30. Molecular path counts of length 6 (*PC6*)

**Introduction:**

(1) The molecular weight (MW) is the sum of molecular weights of the individual atoms, defined as:

$$MW = \sum_{i=1}^{A} MW_i$$

And the average molecular weight (AWeight) is given as follows:

AWeight=MW/nAT

where nAT is the number of atoms

(2) The number of hydrogen (*nhyd*), carbon (*ncarb*), nitrogen (*nnitro*), oxygen (*noxy*), phosphorus (*nphos*), sulfur (*nsulph*), fluorine (*ncof*), chlorine (*ncocl*), bromine (*ncobr*), and iodine (*ncoi*) atoms are simply the total number of each of these types of atoms in the molecule.

The number of halogen atoms (*nhal*) is simply the sum of the counts of the halogen atoms; the number of heavy atoms (*nhev*) and hetero atoms (*nhet*) are defined the similar way.

(3) From descriptor 15 to 22, they are simply the number of ring, single bond, double bond, aromatic bond and H-acceptor, etc, in the molecule.

(4) From descriptor 25 to 30, they represent the number of path of length 1-6. The path of length *n* indicates the shortest distance equal *n* between two atoms in a topological molecular graph.

## 1.2 Topological descriptors

1. Weiner index (*W*)

2. Average Weiner index (*AW*)
3. Balaban's J index (*J*)
4. Harary number ($T_{hara}$)
5. Schiultz index ($T_{sch}$)
6. Graph distance index (*Tigdi*)
7. Platt number (*Platt*)
8. Xu index (*Xu*)
9. Polarity number (*Pol*)
10. Pogliani index (*Dz*)
11. Ipc index (*Ipc*)
12. BertzCT (*BertzCT*)
13. Gutman molecular topological index based on simple vertex degree (*GMTI*)
14. Zagreb index with order 1 (*ZM1*)
15. Zagreb index with order 2 (*ZM2*)
16. Modified Zagreb index with order 1 (*MZM1*)
17. Modified Zagreb index with order 2 (*MZM2*)
18. Quadratic index (*Qindex*)
19. Largest value in the distance matrix (*diametert*)
20. Radius based on topology (*radiust*)
21. Petitjean based on topology (*petitjeant*)
22. The logarithm of the simple topological index by Narumi (*Sito*)
23. Harmonic topological index proposed by Narnumi (*Hato*)
24. Geometric topological index by Narumi (*Geto*)
25. Arithmetic topological index by Narumi (*Arto*)

**Introduction:**

(1) Weiner index (*W*)

$$W = (\sum d_{ij}) / 2$$

$d_{ij}$ is the entries of distance matrix D from H-depleted molecular graph.

(2) Average Weiner index (*AW*)

The average Weiner index is given by

$$WA = \frac{2W}{A(A-1)}$$

where A is the total number of atoms in the molecule, W and AW are described in more detail on pa 497 of the Handbook of Molecular Descriptors

(3) Balaban's J index (*J*)

$$J = \frac{B}{C+1}\sum_b (\sigma_i \sigma_j)_b^{-1/2}$$

where $\sigma_i$ and $\sigma_j$ are the vertex distance degree of adjacent atoms, and the sum run over all the molecular bond b, B is the number of bonds in the molecular graph and C is the number of rings. *J* are described in more detail on pa 21 of the Handbook of Molecular Descriptors

(4) Harary number ($T_{hara}$)

$$H = \frac{1}{2}\sum_i \sum_j d_{ij}^{-1}$$

The Harary index is a molecular topological index derived from the reciprocal distance matrix $D^{-1}$

(5) Schiultz index ($T_{sch}$)

$$MTI = \sum_{i=1}^{A} [(A+D)v]_i$$

It is a topological index derived from the adjacency matrix A, the distance matrix D and the A dimensional column vector v constituted by the vertex degree of the A atoms.

(6) Graph distance index (*Tigdi*)

The graph distance index is defined as the squared sum of all graph distance counts:

$$GDI = \sum_{k=1}^{D} ({}^k f)^2$$

where D is the topological diameter, ${}^k f$ is the total number of distances in the graph equal to k.

(7) Platt number (*Platt*)

Platt number is also known as the total edge adjacency index $A_E$, it is the sum over all entries of the edge adjacency matrix:

$$A_E = \sum_{i=1}^{B} \sum_{j=1}^{B} E_{ij}$$

where B is the number of edges in molecular graph

(8) Xu index (*Xu*)

It is a topological molecular descriptor based on the adjacency matrix and distance matrix; it is defined as:

$$Xu = \sqrt{A} \log \frac{\sum_{i=1}^{A} \delta_i \sigma_i^2}{\sum_{i=1}^{A} \delta_i \sigma_i}$$

where A is the number of atoms, $\delta$ is vertex degree and $\sigma$ is distance degree of all the atoms.

(9) Polarity number (*Pol*)

It is usually assumed that the polarity number accounts for the flexibility of acyclic structure; it is usually calculated on the distance matrix as the number of pairs of vertices at a topological distance equal to three. Some other polarity number also been defined based on different rules.

(10) Pogliani index (*Dz*)

$$D^Z = \sum_{i=1}^{A} \frac{Z_i^v}{L_i}$$

where A is the number of atoms, Z is the number of valence electrons and L the principal quantum number.

(11) Ipc index (*Ipc*)

Ipc index is the information for polynomial coefficients based information theory.

(12) BertzCT (*BertzCT*)

It is the most popular complexity index, taking into account both the variety of kinds of bond connectivities and atom types. It is defined as:

$$I_{CPX} = I_{CPB} + I_{CPA}$$

where $I_{CPB}$ and $I_{CPA}$ are the information contents related to the bond connectivity and atom type diversity

(13) Gutman molecular topological index based on simple vertex degree (*GMTI*)

$$S_G = \sum_{i=1}^{A} \sum_{j=1}^{A} \delta_i \delta_j d_{ij}$$

where $\delta_i \delta_j d_{ij}$ is the topological distance between vertex i and vertex j weighted by the product of the endpoint vertex degrees.

(14) Zagreb index with order 1 (*ZM1*)

The first Zagreb index (Weighted by vertex degrees) is given by

$$M1 = \sum_a \delta_a^2$$

where *a* runs over the A atoms of the molecule and $\delta$ is the vertex degree.

(15) Zagreb index with order 2 (*ZM2*)

$$M2 = \sum_b (\delta_i \delta_j)_b$$

where b runs over all the bonds in the molecule

The Zagreb indices are described on pg 509 of Handbook of Molecular Descriptors

(16) Modified Zagreb index with order 1 (*MZM1*)

(17) Modified Zagreb index with order 2 (*MZM2*)

(18) Quadratic index (*Qindex*)

$$Q = \frac{\sum_g (g^2 - 2g)\, {}^g F + 2}{2}$$

Quadratic index also called normalized quadratic index, where *g* are the different vertex degree values and ${}^gF$ is the vertex degree count.

(19) Largest value in the distance matrix (*diametert*)

$$D = \max_i (\eta_i)$$

$$\eta_i = \max_j (d_{ij})$$

$\eta_i$ called atom eccentricity is the maximum distance from the *ith* vertex to the other vertices.

(20) Radius based on topology (*radiust*)

$$R = \min_i (\eta_i)$$

(21) Petitjean based on topology (*petitjeant*)

$$I_2 = \frac{D - R}{R}$$

(22) The logarithm of the simple topological index by Narumi (*Sito*)

$$S = \prod_{i=1}^{A} \delta_i$$

where A is the number of atoms, *Sito* is a molecular descriptor related to molecular branching proposed as the product of the vertex degrees.

(23) Harmonic topological index proposed by Narumi (*Hato*)

$$H = \frac{A}{\sum_{i=1}^{A} 1/\delta_i}$$

(24) Geometric topological index by Narumi (*Geto*)

$$G = \left( \prod_{i=1}^{A} \delta_i \right)^{1/A}$$

(25) Arithmetic topological index by Narumi (*Arto*)

$$A = \frac{\sum_{i=1}^{A} \delta_i}{A}$$

## 1.3 Molecular connectivity indices

1. Valence molecular connectivity Chi index for path order 0 (${}^{0}\chi^{v}$)
2. Valence molecular connectivity Chi index for path order 1(${}^{1}\chi^{v}$)
3. Valence molecular connectivity Chi index for path order 2(${}^{3}\chi^{v}$)
4. Valence molecular connectivity Chi index for path order 3(${}^{4}\chi^{v}$)
5. Valence molecular connectivity Chi index for path order 4(${}^{5}\chi^{v}$)
6. Valence molecular connectivity Chi index for path order 5(${}^{6}\chi^{v}$)
7. Valence molecular connectivity Chi index for path order 6(${}^{7}\chi^{v}$)
8. Valence molecular connectivity Chi index for path order 7 (${}^{8}\chi^{v}$)
9. Valence molecular connectivity Chi index for path order 8(${}^{9}\chi^{v}$)
10. Valence molecular connectivity Chi index for path order 9(${}^{10}\chi^{v}$)
11. Valence molecular connectivity Chi index for path order 10(${}^{11}\chi^{v}$)
12. Valence molecular connectivity Chi index for three cluster (${}^{3}\chi^{v}{}_{c}$)
13. Valence molecular connectivity Chi index for four cluster (${}^{4}\chi^{v}{}_{c}$)
14. Valence molecular connectivity Chi index for path/cluster (${}^{4}\chi^{v}{}_{pc}$)
15. Valence molecular connectivity Chi index for cycles of 3 (${}^{3}\chi^{v}{}_{CH}$)
16. Valence molecular connectivity Chi index for cycles of 4 (${}^{4}\chi^{v}{}_{CH}$)
17. Valence molecular connectivity Chi index for cycles of 5 (${}^{5}\chi^{v}{}_{CH}$)
18. Valence molecular connectivity Chi index for cycles of 6 (${}^{6}\chi^{v}{}_{CH}$)
19. Simple molecular connectivity Chi indices for path order 0 (${}^{0}\chi$)
20. Simple molecular connectivity Chi indices for path order 1 (${}^{1}\chi$)
21. Simple molecular connectivity Chi indices for path order 2 (${}^{2}\chi$)
22. Simple molecular connectivity Chi indices for path order 3 (${}^{3}\chi_{p}$)
23. Simple molecular connectivity Chi indices for path order 4 (${}^{4}\chi_{p}$)
24. Simple molecular connectivity Chi indices for path order 5 (${}^{5}\chi_{p}$)
25. Simple molecular connectivity Chi indices for path order 6 (${}^{6}\chi_{p}$)
26. Simple molecular connectivity Chi indices for path order 7 (${}^{7}\chi_{p}$)
27. Simple molecular connectivity Chi indices for path order 8 (${}^{8}\chi_{p}$)
28. Simple molecular connectivity Chi indices for path order 9 (${}^{9}\chi_{p}$)
29. Simple molecular connectivity Chi indices for path order 10 (${}^{10}\chi_{p}$)

30. Simple molecular connectivity Chi indices for three cluster ($^{3}\chi_{c}$)
31. Simple molecular connectivity Chi indices for four cluster ($^{4}\chi_{c}$)
32. Simple molecular connectivity Chi indices for path/cluster ($^{4}\chi_{pc}$)
33. Simple molecular connectivity Chi indices for cycles of 3 ($^{3}\chi_{CH}$)
34. Simple molecular connectivity Chi indices for cycles of 4 ($^{4}\chi_{CH}$)
35. Simple molecular connectivity Chi indices for cycles of 5 ($^{5}\chi_{CH}$)
36. Simple molecular connectivity Chi indices for cycles of 6 ($^{6}\chi_{CH}$)
37. mean chi1 (Randic) connectivity index (*mChi1*)
38. the difference between chi3c and chi4pc (*knotp*)
39. the difference between chi0v and chi0 (*dchi0*)
40. the difference between chi1v and chi1 (*dchi1*)
41. the difference between chi2v and chi2 (*dchi0*)
42. the difference between chi3v and chi3 (*dchi3*)
43. the difference between chi4v and chi4 (*dchi4*)
44. the difference between chiv3c and chiv4pc (*knotpv*)

**Introduction:**

1. Simple molecular connectivity index (No.19~36)

   The general formula for the molecular connectivity indices ($^{m}\chi_{t}$) is as follows:

$$^{m}\chi_{q}=\sum_{k=1}^{k}(\prod_{a=1}^{n}\delta_{a})_{k}^{-1/2}$$

   where *k* runs over all of the *mth* order sub-graphs constituted by *n* atoms; *K* is the total number of *mth* order sub-graphs present in the molecular graph and in the case of the path sub-graphs equals the *mth* order path count $^{m}P$. The product is over the simple vertex degrees of all the vertices involved in each sub-graph. The subscript "*q*" for the connectivity indices refers to the type of molecular sub-graph and *ch* for chain or ring, *pc* for path-cluster, *c* for cluster, and *p* for path. For the first three path indices ($^{0}\chi$, $^{1}\chi$, $^{2}\chi$), the calculation type, *p*, is often omitted from the variable name in the software.

2. Valence molecular connectivity indices (No.1~18)

   The valence connectivity indices ($^{m}\chi^{v}{}_{t}$) are calculated in the same fashion as the simple connectivity indices except that the vertex degree are replaced by the valence vertex degree, and the valence degree is given by: $\delta^v$=$Z^v$-$h$=$\sigma$+$\pi$+$n$-$h$. Where $Z^v$ is the number of valence electrons, $\pi$ is the number of electrons in *pi* orbital and *n* is the number of electrons in lone-pair orbitals.

The valence connectivity indices are described on page 86 of the Handbook of Molecular Descriptors. The connectivity indices are described in detail in the literature.

3. The remains connectivity indices are simple combination of the above simple connectivity indices and valence connectivity indices.

## 1.4 Kappa shape descriptors

1. Kappa alpha index for 1 bonded fragment ($^1\kappa_\alpha$)
2. Kappa alpha index for 2 bonded fragment ($^2\kappa_\alpha$)
3. Kappa alpha index for 3 bonded fragment ($^3\kappa_\alpha$)
4. Kier molecular flexibility index (*phi*)
5. Molecular shape Kappa index for 1 bonded fragment ($^1\kappa$)
6. Molecular shape Kappa index for 2 bonded fragment ($^1\kappa$)
7. Molecular shape Kappa index for 3 bonded fragment ($^1\kappa$)

**Introduction:**

(1) Kappa alpha index

The first order kappa shape index ($^1\kappa$) is given by

$$^1k = 2\,^1P_{\max}\,^1P_{\min} / (^1P_i)^2 = A(A-1)^2 / (^1P_i)^2$$

where $P_i$=# of paths of bond length *i* in the hydrogen suppressed molecule and A is the number of non hydrogen atoms in the molecule.

The second order kappa shape index ($^2\kappa$) is given by

$$^2k = 2\,^2P_{\max}\,^2P_{\min} / (^2P_i)^2 = (A-1)(A-2)^2 / (^2P_i)^2$$

The kappa shape indices are described on pg 248 of the Handbook of Molecular Descriptors.

The first order kappa alpha shape index ($^1\kappa_\alpha$) is given by

$$ {}^{1}k_{a} = \frac{(A+a)(A+a-1)^{2}}{({}^{1}P+a)^{2}} $$

where

$$ a = 1 - \frac{r_{x}}{r_{x(sp^{3})}} $$

where $r_x$ is the covalent radius of the atom being evaluated and $r_{x(sp^{3})}$ is the covalent radius of a carbon *sp*$^{3}$ atom (0.77Å).

The second order kappa alpha shape index (${}^{2}\kappa_{\alpha}$) is given by

$$ {}^{2}k_{a} = \frac{(A+a-1)(A+a-2)^{2}}{({}^{2}P+a)^{2}} $$

The third order kappa alpha shape index (${}^{3}\kappa_{\alpha}$) is given by

$$ {}^{3}k_{a} = \frac{(A+a-1)(A+a-3)^{2}}{({}^{3}P+a)^{2}} \qquad \text{if A is odd} $$

$$ {}^{3}k_{a} = \frac{(A+a-3)(A+a-2)^{2}}{({}^{3}P+a)^{2}} \qquad \text{if A is even} $$

The kappa shape indices are described on page 250 of the Handbook of Molecular Descriptors.

The kappa flexibility index (*phi*) is given by

$$ phi = \frac{{}^{1}k_{a}\,{}^{2}k_{a}}{A} $$

The kappa flexibility index is described on page 178 of the Handbook of Molecular Descriptors.

## 1.5 Electrotopological State Indices

1. Sum of E-State of atom type: sLi (*S1*)
2. Sum of E-State of atom type: ssBe (*S2*)
3. Sum of E-State of atom type: ssssBe (*S3*)
4. Sum of E-State of atom type: ssBH (*S4*)
5. Sum of E-State of atom type: sssB (*S5*)
6. Sum of E-State of atom type: ssssB (*S6*)
7. Sum of E-State of atom type: sCH3 (*S7*)
8. Sum of E-State of atom type: dCH2 (*S8*)
9. Sum of E-State of atom type: ssCH2 (*S9*)
10. Sum of E-State of atom type: tCH (*S10*)
11. Sum of E-State of atom type: dsCH (*S11*)
12. Sum of E-State of atom type: aaCH (*S12*)
13. Sum of E-State of atom type: sssCH (*S13*)
14. Sum of E-State of atom type: ddC (*S14*)
15. Sum of E-State of atom type: tsC (*S15*)
16. Sum of E-State of atom type: dssC (*S16*)
17. Sum of E-State of atom type: aasC (*S17*)
18. Sum of E-State of atom type: aaaC (*S18*)
19. Sum of E-State of atom type: ssssC (*S19*)
20. Sum of E-State of atom type: sNH3 (*S20*)
21. Sum of E-State of atom type: sNH2 (*S21*)
22. Sum of E-State of atom type: ssNH2 (*S22*)
23. Sum of E-State of atom type: dNH (*S23*)
24. Sum of E-State of atom type: ssNH (*S24*)
25. Sum of E-State of atom type: aaNH (*S25*)
26. Sum of E-State of atom type: tN (*S26*)
27. Sum of E-State of atom type: sssNH (*S27*)
28. Sum of E-State of atom type: dsN (*S28*)
29. Sum of E-State of atom type: aaN (*S29*)

30. Sum of E-State of atom type: sssN (*S30*)

31. Sum of E-State of atom type: ddsN (*S31*)

32. Sum of E-State of atom type: aasN (*S32*)

33. Sum of E-State of atom type: ssssN (*S33*)

34. Sum of E-State of atom type: sOH (*S34*)

35. Sum of E-State of atom type: dO (*S35*)

36. Sum of E-State of atom type: ssO (*S36*)

37. Sum of E-State of atom type: aaO (*S37*)

38. Sum of E-State of atom type: sF (*S38*)

39. Sum of E-State of atom type: sSiH3 (*S39*)

40. Sum of E-State of atom type: ssSiH2 (*S40*)

41. Sum of E-State of atom type: sssSiH (*S41*)

42. Sum of E-State of atom type: ssssSi (*S42*)

43. Sum of E-State of atom type: sPH2 (*S43*)

44. Sum of E-State of atom type: ssPH (*S44*)

45. Sum of E-State of atom type: sssP (*S45*)

46. Sum of E-State of atom type: dsssP (*S46*)

47. Sum of E-State of atom type: sssssP (*S47*)

48. Sum of E-State of atom type: sSH (*S48*)

49. Sum of E-State of atom type: dS (*S49*)

50. Sum of E-State of atom type: ssS (*S50*)

51. Sum of E-State of atom type: aaS (*S51*)

52. Sum of E-State of atom type: dssS (*S52*)

53. Sum of E-State of atom type: ddssS (*S53*)

54. Sum of E-State of atom type: sCl (*S54*)

55. Sum of E-State of atom type: sGeH3 (*S55*)

56. Sum of E-State of atom type: ssGeH2 (*S56*)

57. Sum of E-State of atom type: sssGeH (*S57*)

58. Sum of E-State of atom type: ssssGe (*S58*)

59. Sum of E-State of atom type: sAsH2 (*S59*)

60. Sum of E-State of atom type: ssAsH (*S60*)

61. Sum of E-State of atom type: sssAs (*S61*)

62. Sum of E-State of atom type: sssdAs (*S62*)

63. Sum of E-State of atom type: sssssAs (*S63*)

64. Sum of E-State of atom type: sSeH (*S64*)

65. Sum of E-State of atom type: dSe (*S65*)

66. Sum of E-State of atom type: ssSe (*S66*)

67. Sum of E-State of atom type: aaSe (*S67*)

68. Sum of E-State of atom type: dssSe (*S68*)

69. Sum of E-State of atom type: ddssSe (*S69*)

70. Sum of E-State of atom type: sBr (*S70*)

71. Sum of E-State of atom type: sSnH3 (*S71*)

72. Sum of E-State of atom type: ssSnH2 (*S72*)

73. Sum of E-State of atom type: sssSnH (*S73*)

74. Sum of E-State of atom type: ssssSn (*S74*)

75. Sum of E-State of atom type: sI (*S75*)

76. Sum of E-State of atom type: sPbH3 (*S76*)

77. Sum of E-State of atom type: ssPbH2 (*S77*)

78. Sum of E-State of atom type: sssPbH (*S78*)

79. Sum of E-State of atom type: ssssPb (*S79*)

80-158. maximum of E-State value of specified atom type (*Smax1~Smax79*)

159-237. minimum of E-State value of specified atom type (*Smin1~Smin79*)

**Introduction:**

The E-State value for a given non hydrogen atom *i* in a molecule is given by its intrinsic state ($I_i$) plus the sum of the perturbations on that atom from all the other atoms in the molecule:

$$S_k = I_k + \sum_{i=1}^{A} \Delta I_{ki}$$

where the intrinsic state ($I_k$) is given by

$$I_k = \frac{(2/N)^2 \delta_k^v + 1}{\delta_k}$$

where N=principle quantum number (which is equal to the element's period or row in the element table).

The perturbation of atom *k* due to atom *i* is given by

$$\Delta I_{ki} = \frac{(I_i - I_k)}{{r_{ki}}^2}$$

where

$$r_{ki} = d_{ki} + 1$$

$d_{ki}$ is the number of bonds that separate atom *k* from atom *i*.

The atom type non hydrogen indices (SX) are obtained by summing the E-State values for all the atoms of a given type *t* that are present in the molecule.

$$SX = \sum S(t)$$

In addition, the symbol present in molecular descriptors, *s*, *d*, *t* and *a* indicate single bond, double bond, triple bond and aromatic bond, respectively.

## 1.6 Autocorrelation descriptors

The Broto-Moreau autocorrelation descriptors (ATSdw) are given by

$$ATSdw = \sum_{i=1}^{A} \sum_{j=1}^{A} \delta_{ij} \omega_i \omega_j$$

where *d* is the considered topological distance (i.e. the lag in the autocorrelation terms), $_{\mathrm{ij}}$ is the Kronecker delta function ( $_{\mathrm{ij}}$=1 if $d_{ij}$=d, zero otherwise), and $w_i$ and $w_j$ are the weights (normalized atomic properties) for atoms *i* and *j* respectively. The normalized atomic mass, van der Waals volume, electronegativity, or polarizability can be used for the weights. To match Dragon, the Broto-Moreau autocorrelation descriptors are calculated in the Software as follows:

$$ATS\mathrm{d}w=\ln\left(1+\sum_{i=1}^{A}\sum_{j=1}^{A}\delta_{ij}\cdot w_i\cdot w_j\right)$$

The Moran autocorrelation descriptors (MATSdw) are given by

$$MATS\mathrm{d}w=\frac{\frac{1}{\Delta}\cdot\sum_{i=1}^{A}\sum_{j=1}^{A}\delta ij\cdot\left(w_i-\overline{w}\right)\left(w_j-\overline{w}\right)}{\frac{1}{A}\sum_{i=1}^{A}\left(w_i-\overline{w}\right)^2}$$

where $\overline{w}$ is the average value of the property for the molecule and $\Delta$ is the number of vertex pairs at distance equal to $d$ .

The Geary autocorrelation descriptors are given by

$$GATS\mathrm{d}w=\frac{\frac{1}{2\Delta}\cdot\sum_{i=1}^{A}\sum_{j=1}^{A}\delta ij\cdot\left(w_i-w_j\right)^2}{\frac{1}{A-1}\sum_{i=1}^{A}\left(w_i-\overline{w}\right)^2}$$

The 2D autocorrelation descriptors are described on page17-19 of the Handbook of Molecular Descriptors.

### 1.6.1 Moreau-Broto autocorrelation descriptors

1. Broto-Moreau autocorrelation of a topological structure-lag1/weighted by atomic masses (*ATSm1*)
2. Broto-Moreau autocorrelation of a topological structure-lag2/weighted by atomic masses (*ATSm2*)
3. Broto-Moreau autocorrelation of a topological structure-lag3/weighted by atomic masses (*ATSm3*)
4. Broto-Moreau autocorrelation of a topologicalstructure-lag4/weighted by atomic masses (*ATSm4*)
5. Broto-Moreau autocorrelation of a topological structure-lag5/weighted by atomic masses (*ATSm5*)
6. Broto-Moreau autocorrelation of a topological structure-lag6/weighted by atomic masses (*ATSm6*)
7. Broto-Moreau autocorrelation of a topological structure-lag7/weighted by atomic masses (*ATSm7*)
8. Broto-Moreau autocorrelation of a topological structure-lag8/weighted by atomic masses (*ATSm8*)

9. Broto-Moreau autocorrelation of a topological structure-lag1/weighted by atomic van der Waals volumes (*ATSv1*)

10. Broto-Moreau autocorrelation of a topological structure-lag2/weighted by atomic van der Waals volumes (*ATSv2*)

11. Broto-Moreau autocorrelation of a topological structure-lag3/weighted by atomic van der Waals volumes (*ATSv3*)

12. Broto-Moreau autocorrelation of a topological structure-lag4/weighted by atomic van der Waals volumes (*ATSv4*)

13. Broto-Moreau autocorrelation of a topological structure-lag5/weighted by atomic van der Waals volumes (*ATSv5*)

14. Broto-Moreau autocorrelation of a topological structure-lag6/weighted by atomi van der Waals volumes (*ATSv6*)

15. Broto-Moreau autocorrelation of a topological structure-lag7/weighted by atomic van der Waals volumes (*ATSv7*)

16. Broto-Moreau autocorrelation of a topological structure-lag8/weighted by atomic van der Waals volumes (*ATSv8*)

17. Broto-Moreau autocorrelation of a topological structure-lag1/weighted by atomic Sanderson electronegativities (*ATSe1*)

18. Broto-Moreau autocorrelation of a topological structure-lag2/weighted by atomic Sanderson electronegativities (*ATSe2*)

19. Broto-Moreau autocorrelation of a topological structure-lag3/weighted by atomic Sanderson electronegativities (*ATSe3*)

20. Broto-Moreau autocorrelation of a topological structure-lag4/weighted by atomic Sanderson electronegativities (*ATSe4*)

21. Broto-Moreau autocorrelation of a topological structure-lag5/weighted by atomic Sanderson electronegativities (*ATSe5*)

22. Broto-Moreau autocorrelation of a topological structure-lag6/weighted by atomic Sanderson electronegativities (*ATSe6*)

23. Broto-Moreau autocorrelation of a topological structure-lag7/weighted by atomic Sanderson electronegativities (*ATSe7*)

24. Broto-Moreau autocorrelation of a topological structure-lag8/weighted by atomic Sanderson electronegativities (*ATSe8*)

25. Broto-Moreau autocorrelation of a topological structure-lag1/weighted by atomic polarizabilities (*ATSp1*)

26. Broto-Moreau autocorrelation of a topological structure-lag2/weighted by atomic polarizabilities (*ATSp2*)

27. Broto-Moreau autocorrelation of a topological structure-lag3/weighted by atomic polarizabilities (*ATSp3*)

28. Broto-Moreau autocorrelation of a topological structure-lag4/weighted by atomic polarizabilities (*ATSp4*)

29. Broto-Moreau autocorrelation of a topological structure-lag5/weighted by atomic polarizabilities (*ATSp5*)

30. Broto-Moreau autocorrelation of a topological structure-lag6/weighted by atomic polarizabilities (*ATSp6*)

31. Broto-Moreau autocorrelation of a topological structure-lag7/weighted by atomic polarizabilities (*ATSp7*)

32. Broto-Moreau autocorrelation of a topological structure-lag8/weightedbyatomic polarizabilities (*ATSp8*)

## 1.6.2 Moran autocorrelation descriptors

33. Moran autocorrelation-lag1/weighted by atomic masses (*MATSm1*)

34. Moran autocorrelation-lag2/weighted by atomic masses (*MATSm2*)

35. Moran autocorrelation-lag3/weighted by atomic masses (*MATSm3*)

36. Moran autocorrelation-lag4/weighted by atomic masses (*MATSm4*)

37. Moran autocorrelation-lag5/weighted by atomic masses (*MATSm5*)

38. Moran autocorrelation-lag6/weighted by atomic masses (*MATSm6*)

39. Moran autocorrelation-lag7/weighted by atomic masses (*MATSm7*)

40. Moran autocorrelation-lag 8/weighted by atomic masses (*MATSm8*)

41. Moran autocorrelation-lag1/weighted by atomic van der Waals volumes (*MATSv1*)

42. Moran autocorrelation-lag2/weighted by atomic van der Waals volumes (*MATSv2*)

43. Moran autocorrelation-lag3/weighted by atomic van der Waals volumes (*MATSv3*)

44. Moran autocorrelation-lag4/weighted by atomic van der Waals volumes (*MATSv4*)

45. Moran autocorrelation-lag5/weighted by atomic van der Waals volumes (*MATSv5*)

46. Moran autocorrelation-lag6/weighted by atomic van der Waals volumes (*MATSv6*)

47. Moran autocorrelation-lag7/weighted by atomic van der Waals volumes (*MATSv7*)

48. Moran autocorrelation-lag8/weighted by atomic van der Waals volumes (*MATSv8*)

49. Moran autocorrelation-lag1/weighted by atomic Sanderson electronegativities (*MATSe1*)

50. Moran autocorrelation-lag2/weighted by atomic Sanderson electronegativities (*MATSe2*)

51. Moran autocorrelation-lag3/weighted by atomic Sanderson electronegativities (*MATSe3*)

52. Moran autocorrelation-lag4/weighted by atomic Sanderson electronegativities (*MATSe4*)

53. Moran autocorrelation-lag5/weighted by atomic Sanderson electronegativities (*MATSe5*)

54. Moran autocorrelation-lag6/weighted by atomic Sanderson electronegativities (*MATSe6*)

55. Moran autocorrelation-lag7/weighted by atomic Sanderson electronegativities (*MATSe7*)

56. Moran autocorrelation-lag8/weighted by atomic Sanderson electronegativities (*MATSe8*)

57. Moran autocorrelation-lag1/weighted by atomic polarizabilities (*MATSp1*)

58. Moran autocorrelation-lag2/weighted by atomic polarizabilities (*MATSp2*)

59. Moran autocorrelation-lag3/weighted by atomic polarizabilities (*MATSp3*)

60. Moran autocorrelation-lag4/weighted by atomic polarizabilities (*MATSp4*)

61. Moran autocorrelation-lag5/weighted by atomic polarizabilities (*MATSp5*)

62. Moran autocorrelation-lag6/weighted by atomic polarizabilities (*MATSp6*)

63. Moran autocorrelation-lag7/weighted by atomic polarizabilities (*MATSp7*)

64. Moran autocorrelation-lag8/weighted by atomic polarizabilities (*MATSp8*)

## 1.6.3 Geary autocorrelation descriptors

65. Geary autocorrelation-lag1/weighted by atomic masses (*GATSm1*)

66. Geary autocorrelation-lag2/weighted by atomic masses (*GATSm2*)

67. Geary autocorrelation-lag3/weighted by atomic masses (*GATSm3*)

68. Geary autocorrelation-lag4/weighted by atomic masses (*GATSm4*)

69. Geary autocorrelation-lag5/weighted by atomic masses (*GATSm5*)

70. Geary autocorrelation-lag6/weighted by atomic masses (*GATSm6*)

71. Geary autocorrelation-lag7/weighted by atomic masses (*GATSm7*)

72. Geary autocorrelation-lag8/weighted by atomic masses (*GATSm8*)
73. Geary autocorrelation-lag1/weighted by atomic van der Waals volumes (*GATSv1*)
74. Geary autocorrelation-lag2/weighted by atomic van der Waals volumes (*GATSv2*)
75. Geary autocorrelation-lag3/weighted by atomic van der Waals volumes (*GATSv3*)
76. Geary autocorrelation-lag4/weighted by atomic van der Waals volumes (*GATSv4*)
77. Geary autocorrelation-lag5/weighted by atomic van der Waals volumes (*GATSv5*)
78. Geary autocorrelation-lag6/weighted by atomic van der Waals volumes (*GATSv6*)
79. Geary autocorrelation-lag7/weighted by atomic van der Waals volumes (*GATSv7*)
80. Geary autocorrelation-lag8/weighted by atomic van der Waals volumes (*GATSv8*)
81. Geary autocorrelation-lag1/weighted by atomic Sanderson electronegativities (*GATSe1*)
82. Geary autocorrelation-lag2/weighted by atomic Sanderson electronegativities (*GATSe2*)
83. Gearyautocorrelation-lag3/weighted by atomic Sanderson electronegativities (*GATSe3*)
84. Geary autocorrelation-lag4/weighted by atomic Sanderson electronegativities (*GATSe4*)
85. Geary autocorrelation-lag5/weighted by atomic Sanderson electronegativities (*GATSe5*)
86. Geary autocorrelation-lag6/weighted by atomic Sanderson electronegativities (*GATSe6*)
87. Geary autocorrelation-lag7/weighted by atomic Sanderson electronegativities (*GATSe7*)
88. Geary autocorrelation-lag8/weighted by atomic Sanderson electronegativities (*GATSe8*)
89. Geary autocorrelation-lag1/weighted by atomic polarizabilities (*GATSp1*)
90. Geary autocorrelation-lag2/weighted by atomic polarizabilities (*GATSp2*)
91. Geary autocorrelation-lag3/weighted by atomic polarizabilities (*GATSp3*)
92. Geary autocorrelation-lag4/weighted by atomic polarizabilities (*GATSp4*)
93. Geary autocorrelation-lag5/weighted by atomic polarizabilities (*GATSp5*)
94. Geary autocorrelation-lag6/weighted by atomic polarizabilities (*GATSp6*)
95. Geary autocorrelation-lag7/weighted by atomic polarizabilities (*GATSp7*)
96. Geary autocorrelation-lag8/weighted by atomic polarizabilities (*GATSp8*)

## 1.7 Charge descriptors

1. Most positive charge on H atoms ($Q_{Hmax}$)
2. Most positive charge on C atoms ($Q_{Cmax}$)
3. Most positive charge on N atoms ($Q_{Nmax}$)
4. Most positive charge on O atoms ($Q_{Omax}$)

5. Most negative charge on H atoms ($Q_{Hmin}$)
6. Most negative charge on C atoms ($\mathrm{Q_{Cmin}}$)
7. Most negative charge on N atoms ($\mathrm{Q_{Nmin}}$)
8. Most negative charge on O atoms ($\mathrm{Q_{Omin}}$)
9. Most positive charge in a molecule ($Q_{max}$)
10. Most negative charge in a molecule ($Q_{min}$)
11. Sum of squares of charges on H atoms ($Q_{HSS}$)
12. Sum of squares of charges on C atoms ($Q_{CSS}$)
13. Sum of squares of charges on N atoms ($Q_{NSS}$)
14. Sum of squares of charges on O atoms ($Q_{OSS}$)
15. Sum of squares of charges on all atoms ($Q_{aSS}$)
16. Mean of positive charges (*Mpc*)
17. Total of positive charges (*Tpc*)
18. Mean of negative charges (*Mnc*)
19. Total of negative charges (*Tnc*)
20. Mean of absolute charges (*Mac*)
21. Total of absolute charges (*Tac*)
22. Relative positive charge (*Rpc*)
23. Relative negative charge (*Rnc*)
24. Submolecular polarity parameter (*SPP*)
25. Local dipole index (*LDI*)

**Introduction:**

These are electronic descriptors defined in terms of atomic charges and used to describe electronic aspects of the whole molecule and of particular regions, such as atoms, bonds and molecular fragments. Charge descriptors are calculated by computational chemistry and therefore can be considered among quantum chemical descriptors.

Electrical charges in the molecule are the driving force of electrostatic interactions, and it is well known the local electron density or charge plays a fundamental role in many chemical reactions and physic-chemical properties.

Some most used charge descriptors are displayed here as followed:

(1) Most positive charge in a molecule (*$Q_{max}$*)

The maximum positive charge of the atoms in a molecule:

$$Q_{\max} = \max_a (q_a^+)$$

where $q^+$ are net atom positive charges

(2) Most negative charge in a molecule (*$Q_{min}$*)

The maximum negative charge of the atoms in a molecule:

$$Q_{\min} = \max_a (q_a^-)$$

where $q^-$ are net atom negative charges

(3) Total of positive charges (*Tpc*)

The sum of all of the positive charges of the atoms in a molecule:

$$Tpc = \sum_a (q_a^+)$$

where $q^+$ are net atom positive charges

(4) Total of negative charges (*Tnc*)

The sum of all of the negative charges of the atoms in a molecule:

$$Tnc = \sum_a (q_a^-)$$

where $q^-$ are net atom negative charges

## 1.8 molecular properties

1. Molar refractivity (*MREF*)
2. LogP value based on the Crippen method (*logP*)
3. Square of LogP value based on the Crippen method (*logP2*)
4. Topological polarity surface area (*TPSA*)
5. Unsaturation index (*UI*)
6. Hydrophilic index (*Hy*)

**Introduction:**

(1) Molar refractivity (*MREF*)

Molecular descriptor of a liquid which contains both information about molecular volume and polarizability, usually defined by the Lorenz-Lorentz equation:

$$MR = \frac{n^2 - 1}{n^2 + 2} \frac{MW}{\rho}$$

where MW is the molecular weight, $\rho$ is the liquid density, and n the refractive index of the liquid.

（2） LogP value based on the Crippen method (*logP*)

The Ghose-Crippen contribution method is based on hydrophobic atomic constants $a_k$ measuring the lipophilic contributions of atoms in the molecule, each described by its neighbouring atoms.

$$LogP = \sum_k a_k N_k$$

where $N_k$ is the occurrence of the *kth* atom type

（3） Topological polarity surface area (*TPSA*)

It is the sum of solvent-accessible surface areas of atoms with absolute value of partial charges greater than or equal to 0.2.

$$TPSA = \sum_a SA_a$$
$$|q_a| \geq 0.2$$

（4） Unsaturation index (*UI*)

The unsaturation index (*UI*) is defined as

$$UI = \log_2(1 + nDB + nTB + nAB)$$

where nDB=the number of double bonds, nTB=the number of triple bonds and nAB=the number of aromatic bonds. The unsaturation index is described in the user manual for Dragon.

(5) Hydrophilic index (*Hy*)

The hydrophilic index is given by

$$Hy = \frac{(1+N_{Hy})\log_2(1+N_{Hy}) + N_c(\frac{1}{A}\log_2\frac{1}{A}) + \sqrt{\frac{N_{Hy}}{A^2}}}{\log_2(1+A)}$$

where $N_{Hy}$ is the number of hydrophilic groups (or the total number of hydrogen attached to oxygen, sulfur and nitrogen atoms), $N_c$ is the number of carbon atoms, and $A$ is the number of non hydrogen atoms. The hydrophilic index is described in more detail on page 225 of the Handbook of Molecular Descriptors (Todeschini and Consonni 2000).

## 1.9 MOE-type descriptors

1. topological polar surface area based on fragments (*TPSA*)
2. Labute's Approximate Surface Area (*LabuteASA*)
3. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA1*)
4. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA2*)
5. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA3*)
6. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA4*)
7. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA5*)
8. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA6*)
9. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA7*)
10. MOE-type descriptors using SLogP contributions and surface area contributions (*SLOGPVSA8*)
11. MOE-type descriptors using SLogP contributions and surface area contributions(*SLOGPVSA9*)
12. MOE-type descriptors using SLogP contributions and surface area contributions(*SLOGPVSA10*)
13. MOE-type descriptors using SLogP contributions and surface area contributions(*SLOGPVSA11*)
14. MOE-type descriptors using SLogP contributions and surface area contributions(*SLOGPVSA12*)
15. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA1*)
16. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA2*)
17. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA3*)
18. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA4*)
19. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA5*)

20. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA6*)

21. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA7*)

22. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA8*)

23. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA9*)

24. MOE-type descriptors using MR contributions and surface area contributions (*SMRVSA10*)

25. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA1*)

26. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA2*)

27. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA3*)

28. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA4*)

29. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA5*)

30. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA6*)

31. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA7*)

32. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA8*)

33. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA9*)

34. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA10*)

35. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA11*)

36. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA12*)

37. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA13*)

38. MOE-type descriptors using partial charges and surface area contributions (*PEOEVSA14*)

39. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA1*)

40. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA2*)

41. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA3*)

42. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA4*)

43. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA5*)

44. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA6*)

45. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA7*)

46. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA8*)

47. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA9*)

48. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA10*)

49. MOE-type descriptors using Estate indices and surface area contributions (*EstateVSA11*)

50. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate1*)

51. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate2*)

52. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate3*)

53. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate4*)

54. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate5*)

55. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate6*)

56. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate7*)

57. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate8*)

58. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate9*)

59. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate10*)

60. MOE-type descriptors using surface area contributions and Estate indices (*VSAEstate11*)

## 1.10 Molecular fingerprint

Molecular fingerprints are string representations of chemical structures designed to enhance the efficiency of chemical database searching and analysis. They can encode the 2D and/or 3D features of molecules as an array of binary values or counts. Therefore, molecular fingerprints consist of bins, each bin being a substructure descriptor associated with a specific molecular feature.

Molecular fingerprints directly encode molecular structure in a series of binary bits that represent the presence or absence of particular substructures in the molecule. Although it divides the whole molecule into a large number of fragments, it has the potential to keep overall complexity of drug molecules. Additionally, it does not need reasonable three-dimensional conformation of drug molecules and thereby does not lead to error accumulation from the description of molecular structures. Thus by means of such descriptors, each molecule can be described based on a set of fingerprints of structural keys, which is represented as a Boolean array. A SMARTS list of substructure patterns is first determined as a predefined dictionary. There is a one-to-one correspondence between each SMARTS pattern and bit in the fingerprint. For each SMARTS pattern, if its corresponding substructure is present in the given molecule, the corresponding bit in the fingerprint is set to 1; conversely, it is set to 0 if the substructure is absent in the molecule (see Figure 1). Note that different molecular fingerprint systems abstract and magnify different aspects of molecular topology.

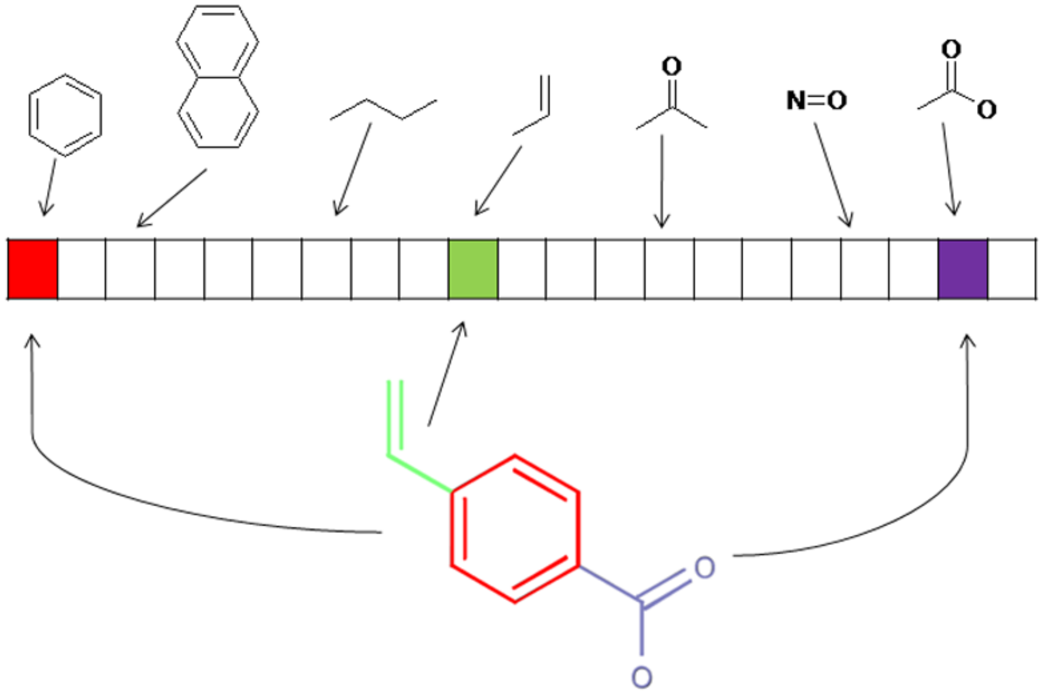

**Figure 1** Representation of a molecular substructure fingerprint with a substructure fingerprint dictionary of given substructure patterns. This molecule is represented in a series of binary bits that represent the presence or absence of particular substructures in the molecules.

### 1.10.1 Daylight-type fingerprint

The Daylight fingerprints (DFP) are hashed fingerprints encoding each atom type, all Augmented Atoms and all paths of length 2–7 atoms, giving a total string of 1024 bits [Daylight-James, Weininger et al., 1997].

### 1.10.2 MACCS keys and FP4 fingerprint

The FP4 and MACCS fingerprints are used to construct the substructure dictionaries, respectively. The dictionary of FP4 fingerprint contains 307 mostly common substructure patterns. It is originally written in an attempt to represent the classification of organic compounds from the viewpoint of an organic chemist. The MACCS fingerprint uses a dictionary of MDL keys, which contains a set of 166 mostly common substructure features. These are referred to as the MDL public MACCS keys. Both the definitions of FP4 and MACCS fingerprints are available from OpenBabel (version 2.3.0, http://openbabel.org/, accessed October, 2010). All calculations for these substructure fingerprints are performed in PyDPI package, developed by our group.

## 1.10.3 E-state fingerprint

Electrotopological State (E-state) fingerprints represent the presence/absence of 79 E-state substructures defined Kier and Hall in a molecule. The definition of 79 atom types can be found in section 1.5.

## 1.10.4 Atom pairs and topological torsions fingerprints

**Atom pairs fingerprint:**

Atom pairs are substructure descriptors defined in terms of any pair of atoms and bond types connecting them. An atom pair is composed of two non-hydrogen atoms and an interatomic separation:

$$\mathrm{AP} = \left\{ [i\text{th atom description}][\text{separation}][\,j\text{th atom description}] \right\}$$

The two considered atoms need not be directly connected and the separation can be the topological distance between them [Carhart, Smith et al., 1985]; these descriptors are usually called topological atom pairs being based on the topological representation of the molecules. Atom type is defined by the element itself, the number of heavy-atom connections and number of p electron pairs on each atom.

Unlike topological torsions, atom pairs are sensitive to long-range correlations between the atoms in molecules and therefore to small changes in one part of even large molecules. Atom pair descriptors usually are Boolean variables encoding the presence or absence of a particular atom pair in each molecule.

**Topological torsion fingerprint:**

The topological torsion descriptor (TT) is related to the 4-atom linear subfragment descriptor of Klopman because it is defined as a Boolean variable for the presence/absence of a linear sequence of four consecutively bonded non-hydrogen atoms *k*–*i*–*j*–*l*, each described by its atom type (TYPE), the number of *p* electrons (NPI) on each atom, and the number of non-hydrogen atoms (NBR) bonded to it [Nilakantan, Bauman et al., 1987]. Usually NBR does not include *k*–*i*–*j*–*l* atoms that go to make the torsion itself; therefore, it is -1 for k and l atoms and -2 for the two central atoms *i* and *j*. The torsion around the *i*-*j* bond and defined by the four indices *k*–*i*–*j*–*l* is represented by the following TT descriptor:

$$\mathrm{TT}=\{[\mathrm{NPI-TYPE-NBR}]_k[\mathrm{NPI-TYPE-NBR}]_i[\mathrm{NPI-TYPE-NBR}]_j[\mathrm{NPI-TYPE-NBR}]_l\}$$

The TT descriptor is a topological analogue of the 3D torsion angle, defined by four consecutively bonded atoms. The topological torsion is a short-range descriptor, that is, it is sensitive only to local changes in the molecule and is independent of the total number of atoms in the molecule.

The use of atom-centered fragments and related descriptors greatly increases the specific chemical information concerning different functional groups, but cannot discriminate between different arrangements of functional groups within a molecule.

### 1.10.5 Morgan fingerprint

This family of fingerprints, better known as circular fingerprints, is built by applying the Morgan algorithm to a set of user-supplied atom invariants. When generating Morgan fingerprints, the radius of the fingerprint need be provided. For detailed information about Morgan fingerprint, please refer to Ref. [19]. Note The default atom invariants use connectivity information similar to those used for the well known ECFP family of fingerprints. When comparing the ECFP/FCFP fingerprints and the Morgan fingerprints generated by the PyDPI, remember that the 4 in ECFP4 corresponds to the diameter of the atom environments considered, while the Morgan fingerprints take a radius parameter. So the examples above, with radius=2, are roughly equivalent to ECFP4 and FCFP4.

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## 2 Descriptors of protein and peptide

A protein or peptide sequence with *N* amino acid residues is expressed as: $R_1$, $R_2$, $R_3$, …, $R_N$, where $R_i$ represents the residue at the *i*-th position in the sequence. The labels *i* and *j* are used to index amino acid position in a sequence and r, s are used to index the amino acid type. The computed features are divided into 4 groups according to their known applications described in the literature.

A protein sequence can be divided equally into segments and the methods, described as follows for the global sequence, can be applied to each segment.

## 2.1 Amino acid composition

The amino acid composition is the fraction of each amino acid type within a protein. The fractions of all 20 natural amino acids are calculated as:

$$f(r) = \frac{N_r}{N} \qquad r=1,2,3, ..., 20$$

Where $N_r$ is the number of the amino acid type *r* and *N* is the length of the sequence.

## 2.2 Dipeptide composition

The dipeptide composition gives 400 features, defined as:

$$f(r,s) = \frac{N_{rs}}{N-1} \qquad r, s=1,2,3, ..., 20$$

where $N_{rs}$ is the number of dipeptide represented by amino acid type *r* and *s*.

## 2.3 Tripeptide composition

The tripeptide composition gives 8000 features, defined as:

$$f(r,s,t)=\frac{N_{rst}}{N-2} \qquad r, s\text{=1,2,3, ..., 20}$$

where $N_{rst}$ is the number of tripeptide represented by amino acid type *r*, *s* and *t*.

## 2.4 Autocorrelation descriptors

Autocorrelation descriptors are defined based on the distribution of amino acid properties along the sequence. The amino acid properties used here are various types of amino acids index (http://www.genome.ad.jp/dbget/aaindex.html).Three type of autocorrelation descriptors are used here and are described as following.

All the amino acid indices are centralized and standardized before the calculation, i.e.

$$P_r=\frac{P_r-\overline{P}}{\sigma}$$

Where $\overline{P}$ is the average of the property of the 20 amino acids.

$$\overline{P}=\frac{\sum_{r=1}^{20}P_r}{20} \qquad \text{and} \qquad \sigma=\sqrt{\frac{1}{20}\sum_{r=1}^{20}(P_r-\overline{P})^2}$$

### 2.4.1 Normalized Moreau-Broto autocorrelation descriptors

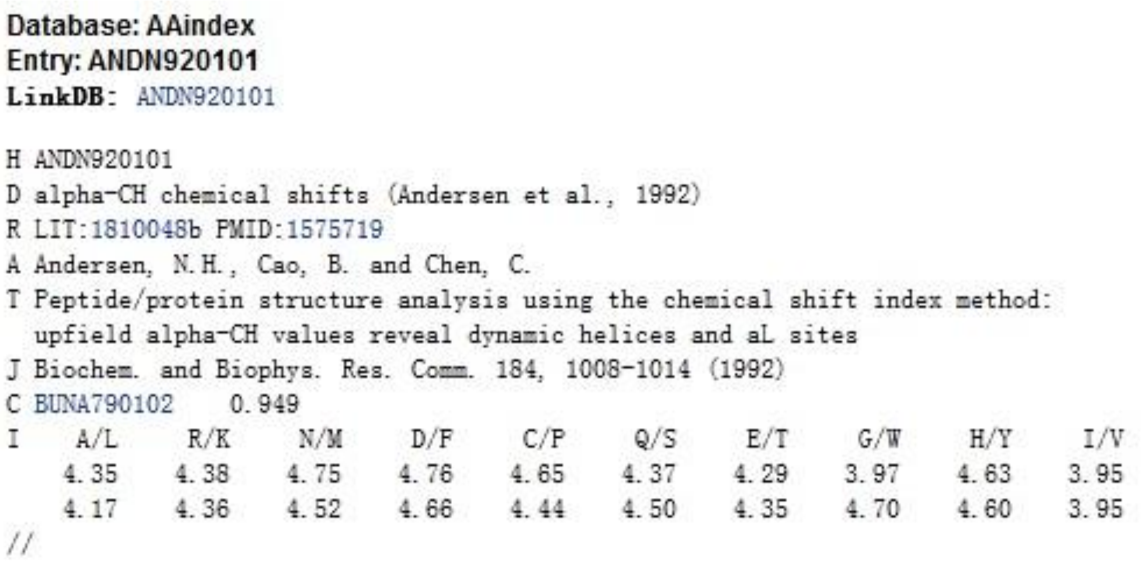
Moreau-Broto autocorrelation descriptors application to protein sequences may be defined as:

$$AC(d)=\sum_{i=1}^{N-d}P_iP_{i+d} \qquad d\text{=1,2,3, ..., nlag}$$

Where *d* is called the lag of the autocorrelation and $P_i$ and $P_{i+d}$ are the properties of the amino acids at position *i* and *i+d* , respectively. *nlag* is the maximum value of the lag.

The normalized Moreau-Broto autocorrelation descriptors are defined as:

$$ATS(d)=\frac{AC(d)}{N-d} \qquad d\text{=1,2,3, ..., }nlag$$



```
Database: AAindex
Entry: ANDN920101
LinkDB: ANDN920101

H ANDN920101
D alpha-CH chemical shifts (Andersen et al., 1992)
R LIT:1810048b PMID:1575719
A Andersen, N.H., Cao, B. and Chen, C.
T Peptide/protein structure analysis using the chemical shift index method:
  upfield alpha-CH values reveal dynamic helices and aL sites
J Biochem. and Biophys. Res. Comm. 184, 1008-1014 (1992)
C BUNA790102    0.949
I    A/L     R/K     N/M     D/F     C/P     Q/S     E/T     G/W     H/Y     I/V
    4.35    4.38    4.75    4.76    4.65    4.37    4.29    3.97    4.63    3.95
    4.17    4.36    4.52    4.66    4.44    4.50    4.35    4.70    4.60    3.95
//
```

**Figure 2** An illustrated example in the AAIndex database

## 2.4.2 Moran autocorrelation

Moran autocorrelation descriptors application to protein sequence may be defined as:

$$I(d)=\frac{\frac{1}{N-d}\sum_{i=1}^{N-d}(P_i-\overline{P})(P_{i+d}-\overline{P})}{\frac{1}{N}\sum_{i=1}^{N}(P_i-\overline{P})^2}\quad d=1,2,3,\ ...,\ 30.$$

Where $d$ and $P_i$ and $P_{i+d}$ are defined in the same way as in 2.2.1, and is the average of the considered property $P$ along the sequence, i.e.,

$$\overline{P}=\frac{\sum_{i=1}^{N}P_i}{N}$$

Where $d$, $\overline{P}$ , $P_i$ and $P_{i+d}$, *nlag* have the same meaning as in the above.

## 2.4.3 Geary autocorrelation Descriptors

Geary autocorrelation descriptors application to protein sequence may be defined as:

$$C(d)=\frac{\frac{1}{2(N-d)}\sum_{i=1}^{N-d}(P_i-P_{i+d})^2}{\frac{1}{N-1}\sum_{i=1}^{N}(P_i-\overline{P})^2} \qquad d\text{=1,2,3, ..., 30.}$$

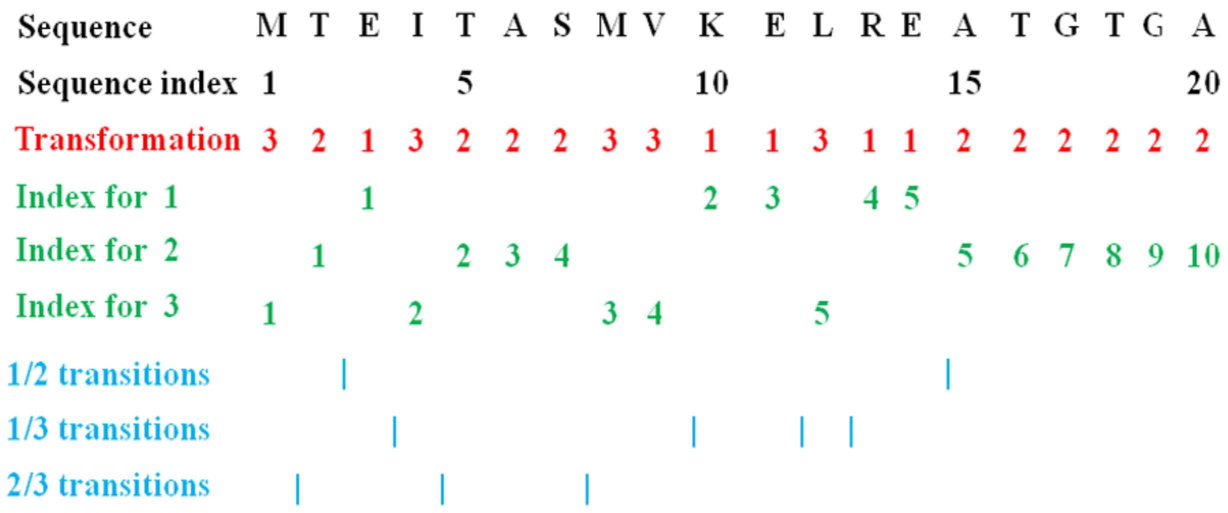
Where $d$, $\overline{P}$, $P_i$ and $P_{i+d}$ , *nlag* have the same meaning as in the above.

The amino acid indices used in these autocorrelation descriptors can be specified in file “input-param.dat” from “input-aaindexdb.dat”.

For each amino acid index, there will be 3 × *nlag* autocorrelation descriptors.

## 2.5 Composition, transition and distribution

These descriptors are developed by Dubchak, et.al.



| Sequence | M | T | E | I | T | A | S | M | V | K | E | L | R | E | A | T | G | T | G | A |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sequence index | 1 | | | | 5 | | | | | 10 | | | | | 15 | | | | | 20 |
| Transformation | 3 | 2 | 1 | 3 | 2 | 2 | 2 | 3 | 3 | 1 | 1 | 3 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| Index for 1 | | | 1 | | | | | | | 2 | 3 | | 4 | 5 | | | | | | |
| Index for 2 | | 1 | | | 2 | 3 | 4 | | | | | | | | 5 | 6 | 7 | 8 | 9 | 10 |
| Index for 3 | 1 | | | 2 | | | | 3 | 4 | | | 5 | | | | | | | | |

**Figure 3** The sequence of a hypothetic protein indicating the construction of composition, transition and distribution descriptors of a protein. Sequence index indicates the position of an amino acid in the sequence. The index for each type of amino acids in the sequence (‘1’ ‘2’ or ‘3’) indicates the position of the first, second, third, ... of that type of amino acid. 1/2 transition indicates the position of ‘12’ or ‘21’ pairs in the sequence (1/3 and 2/3 are defined in the same way.).

**Step1. Sequence encoding**

The amino acids are divided in three classes according to its attribute and each amino acid is encoded by one of the indices 1, 2, 3 according to which class it belonged. The attributes used here include hydrophobicity, normalized van der Waals volume polarity, and polarizability, as in the references. The corresponding division is in the table 1.

**Table 1** Amino acid attributes and the division of the amino acids into three groups for each attribute

| | **Group 1** | **Group 2** | **Group 3** |
|---|---|---|---|
| hydrophobicity | Polar<br>R,K,E,D,Q,N | Neutral<br>G, A, S,T,P,H,Y | Hydrophobicity<br>C,L,V,I,M,F,W |
| normalized van der Waals volume | 0-2.78<br>G,A,S,T,P,D | 2.95-4.0<br>N,V,E,Q,I,L | 4.03-8.08<br>M,H,K,F,R,Y,W |
| polarity | 4.9-6.2<br>L,I,F,W,C,M,V,Y | 8.0-9.2<br>P,A,T,G,S | 10.4-13.0<br>H,Q,R,K,N,E,D |
| polarizability | 0-1.08<br>G,A,S,D,T | 0.128-0.186<br>C,P,N,V,E,Q,I,L | 0.219-0.409<br>K,M,H,F,R,Y,W |
| charge | Positive<br>K,R | Neutral<br>A,N,C,Q,G,H,I,L,M,F,P,S,T,W,Y,V | Negative<br>D,E |
| secondary structure | Helix<br>E,A,L,M,Q,K,R,H | Strand<br>V,I,Y,C,W,F,T | Coil<br>G,N,P,S,D |
| solvent accessibility | Buried<br>A,L,F,C,G,I,V,W | Exposed<br>R,K,Q,E,N,D | Intermediate<br>M,S P,T,H,Y |

For example, for a given sequence “MTEITAAMVKELRESTGAGA”, it will be encoded as “32132223311311222222” according to its hydrophobicity division.

**Step 2: Composition, Transition and Distribution descriptors**

Three descriptors, “Composition (C)”, “Transition (T)”, and “Distribution (D)” were calculated for a given attribute as follows:

**Composition:** It is the global percent for each encoded class in the sequence. In the above example using hydrophobicity division, the numbers for encoded classes “1”, “2”, “3” are 5, 10, 5 respectively, so the compositions for them are 5/20=25%, 10/20=10%, and 5/20=25% respectively, where 20 is the length of the protein sequence. Composition can be defined as:

$$C_r = \frac{n_r}{n} \qquad r=1,2,3.$$

Where $n_r$ is the number of $r$ in the encoded sequence and $N$ is the length of the sequence.

**Transition:** A transition from class 1 to 2 is the percent frequency with which 1 is followed by 2 or 2 is followed by 1 in the encoded sequence. Transition descriptor can be calculated as:

$$T_{rs} = \frac{n_{rs} + n_{sr}}{N-1} \qquad rs=\text{"12", "13", "23".}$$

Where $n_{rs}$, $n_{sr}$ is the numbers of dipeptide encoded as "*rs*" and "*sr*" respectively in the sequence and $N$ is the length of the sequence.

**Distribution:** The "distribution" descriptor describes the distribution of each attribute in the sequence. There are five "distribution" descriptors for each attribute and they are the position percents in the whole sequence for the first residue, 25% residues, 50% residues, 75% residues and 100% residues , respectively, for a specified encoded class. For example, there are10 residues encoded as "2" in the above example, the positions for the first residue "2", the 2th residue "2" (25%*10=2), the 5th "2" residue (50%*10=5), the 7th "2" (75%*10=7) and the10th residue "2" (100%*10) in the encoded sequence are 2, 5, 15, 17, 20 respectively, so the distribution descriptors for "2" are: 10.0 (2/20*100), 25.0 (5/20*100), 75.0 (15/20*100), 85.0 (17/20*100) , 100.0 (20/20*100), respectively.

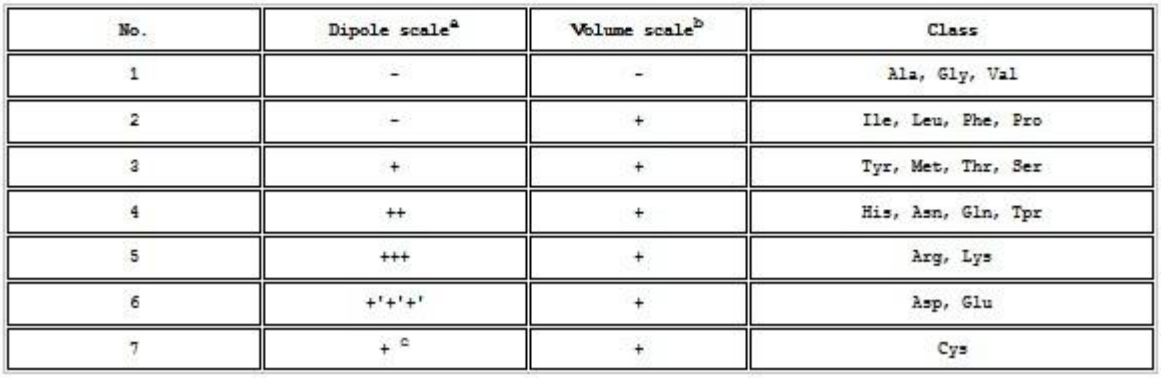
## 2.6 Conjoint Triad Descriptors

Conjoint triad descriptors are proposed by J.W. Shen et.al. These conjoint triad features abstracts the features of protein pairs based on the classification of amino acids. In this approach, each protein sequence is represented by a vector space consisting of features of amino acids. To reduce the dimensions of vector space, the 20 amino acids were clustered into several classes according to their dipoles and volumes of the side chains. The conjoint triad features are calculated as follows:

**Step 1: classification of amino acids**

Electrostatic and hydrophobic interactions dominate protein-protein interactions. These two kinds of interactions may be reflected by the dipoles and volumes of the side chains of amino acids, respectively. Accordingly, these two parameters were calculated, respectively, by using the density-functional theory method B3LYP/6-31G and molecular modeling approach. Based on the dipoles and volumes of the side chains, the 20 amino acids could be clustered into seven classes (See Table 2). Amino acids within the same class likely involve synonymous mutations because of their similar characteristics.

**Table** 2 Classification of amino acids based on dipoles and volumes of the side chains



| No. | Dipole scale[a] | Volume scale[b] | Class |
|---|---|---|---|
| 1 | - | - | Ala, Gly, Val |
| 2 | - | + | Ile, Leu, Phe, Pro |
| 3 | + | + | Tyr, Met, Thr, Ser |
| 4 | ++ | + | His, Asn, Gln, Tpr |
| 5 | +++ | + | Arg, Lys |
| 6 | +'+'+' | + | Asp, Glu |
| 7 | + [c] | + | Cys |

[a] Dipole scale (Debye): -, Dipole<1.0; +, 1.0<Dipole<2.0; ++, 2.0<Dipole<3.0; +++, Dipole>3.0; +'+'+', Dipole>3.0 with opposite orientation. [b] Volume scale (Å$^3$): -, Volume<50; +, Volume> 50. [c] Cys is separated from class 3 because of its ability to form disulfide bonds.

### Step 2: Conjoint triad calculation

The conjoint triad descriptors considered the properties of one amino acid and its vicinal amino acids and regarded any three continuous amino acids as a unit. Thus, the triads can be differentiated according to the classes of amino acids, i.e., triads composed by three amino acids belonging to the same classes, such as ART and VKS, could be treated identically. To conveniently represent a protein, we first use a binary space (**V**, **F**) to represent a protein sequence. Here, **V** is the vector space of the sequence features, and each feature $v_i$ represents a sort of triad type; **F** is the frequency vector corresponding to **V**, and the value of the *i*th dimension of **F** ($f_i$) is the frequency of type $v_i$ appearing in the protein sequence. For the amino acids that have been catalogued into seven classes, the size of **V** should be 7×7×7; thus $i$ = 1,2, ..., 343. The detailed description for (**V**, **F**) is illustrated in Figure 3. Clearly, each protein correlates to the length (number of amino acids) of protein. In general, a long protein would have a large value of $f_i$, which complicates the comparison between two heterogeneous proteins. Thus, we defined a new parameter, $d_i$, by normalizing $f_i$ with the following equation.

$$d_i = (f_i - \min\{f_1, f_2, f_3, ..., f_{343}\}) / \max\{f_1, f_2, f_3, ..., f_{343}\}$$

The numerical value of $d_i$ of each protein ranges from 0 to 1, which thereby enables the comparison between proteins. Accordingly, we obtain another vector space (designated **D**) consisting of $d_i$ to represent protein

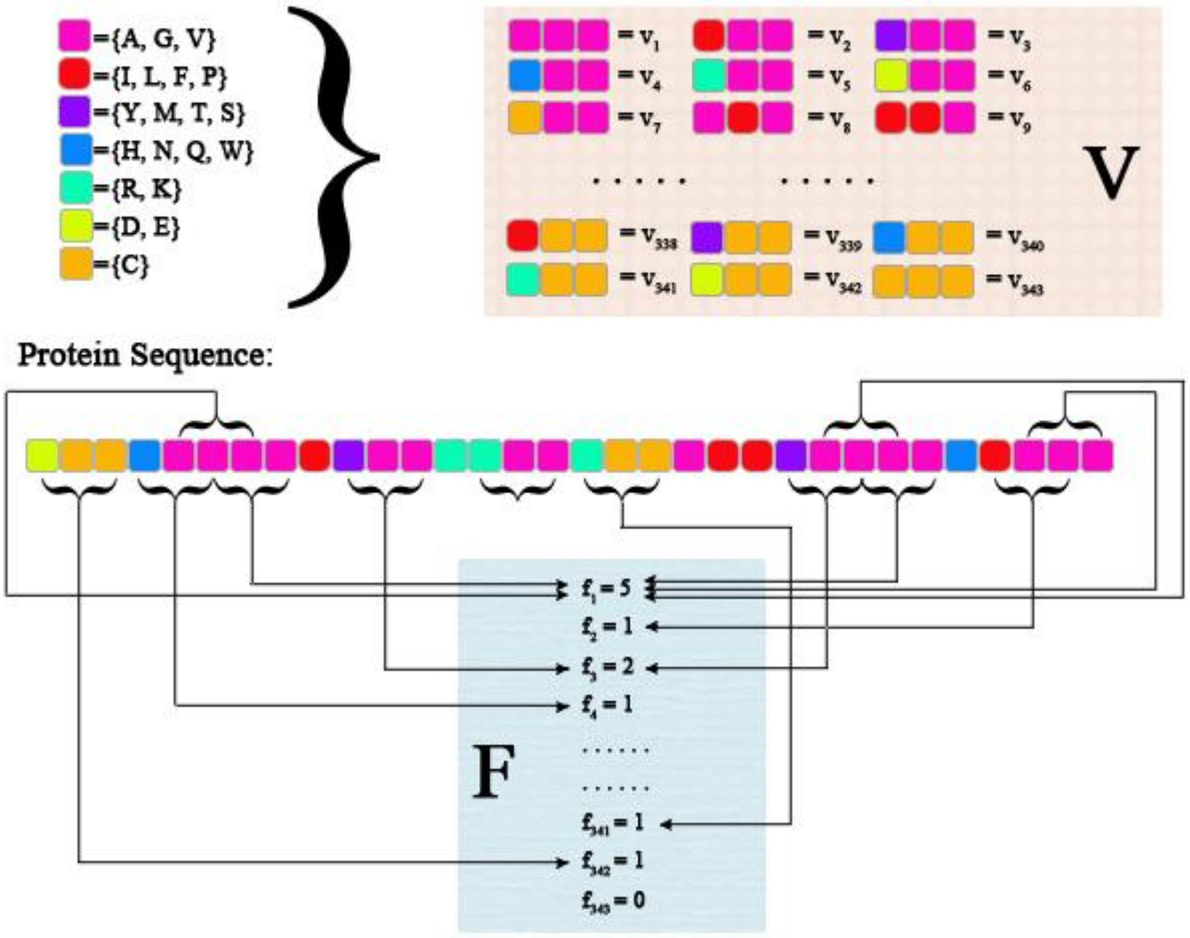


**Figure 3** Schematic diagram for constructing the vector space (V, F) of protein sequence. V is the vector space of the sequence features; each feature ($v_i$) represents a triad composed of three consecutive amino acids; F is the frequency vector corresponding to V, and the value of the *i*th dimension of F($f_i$) is the frequency that $\mathbf{v}_i$ triad appeared in the protein sequence.

## 2.7 Quasi-sequence-order Descriptors

The quasi-sequence-order descriptors are proposed by K.C. Chou, et.al. They are derived from the distance matrix between the 20 amino acids.

### 2.7.1 Sequence-order-coupling numbers

The dth-rank sequence-order-coupling number is defined as:

$$\tau_d = \sum_{i=1}^{N-d} (d_{i,i+d})^2 \qquad d=1,2,3,\ ...,\ maxlag$$

Where $d_{i,i+d}$ is the distance between the two amino acids at position $i$ and $i+d$.

**Note:** *maxlag* is the maximum lag and the length of the protein must be not less than *maxlag*.

## 2.7.2 Quasi-sequence-order (QSO) descriptors

For each amino acid type, a quasi-sequence-order descriptor can be defined as:

$$X_r = \frac{f_r}{\sum_{r=1}^{20} f_r + w \sum_{d=1}^{maxlag} \tau_d} \qquad r=1,2,3,\ ...,\ 20$$

Where $f_r$ is the normalized occurrence for amino acid type $i$ and $w$ is a weighting factor ($w$=0.1). These are the first 20 quasi-sequence-order descriptors. The other 30 quasi-sequence-order are defined as:

$$X_r = \frac{w\tau_{d-20}}{\sum_{r=1}^{20} f_r + w \sum_{d=1}^{maxlag} \tau_d} \qquad d=21,22,23,\ ...,\ 20+maxlag$$

In addition to Schneider-Wrede physicochemical distance matrix used by Chou et al, another chemical distance matrix by Grantham is also used here.

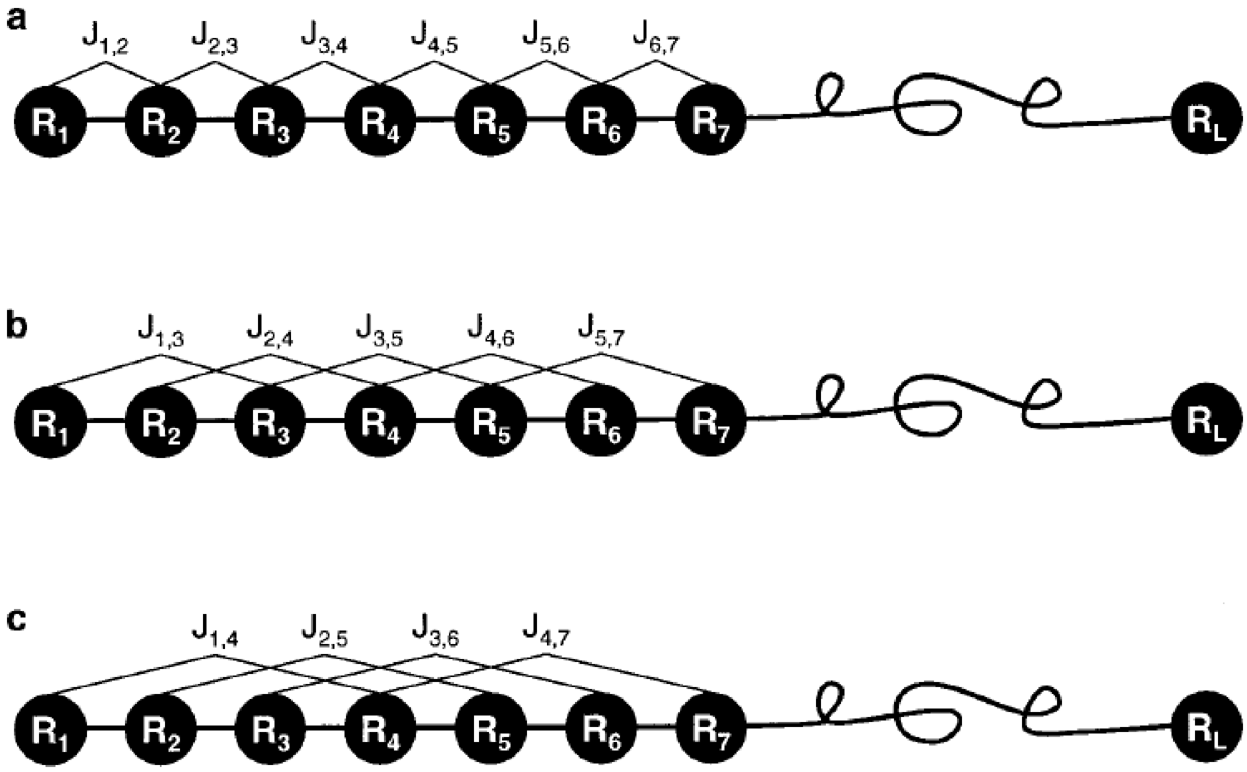


**Figure 4** A schematic drawing to show (a) the 1st-rank, (b) the 2nd-rank, and (3) the 3rd-rank sequence-order-coupling mode along a protein sequence. (a) Reflects the coupling mode between all the most contiguous residues, (b) that between all the 2nd most contiguous residues, and (c) that between all the 3rd most contiguous residues.

## 2.8 pseudo-amino acid composition (PAAC)

This groups of descriptors are proposed by Kuo-chen Chou. PAAC descriptors (http://www.csbio.sjtu.edu.cn/bioinf/PseAAC/type1.htm) are also called the type 1 pseudo-amino acid composition. Let $H_1^o(i), H_2^o(i), M^o(i)$ ($i$=1,2,3, ..., 20) be the original hydrophobicity values, the original hydrophilicity values and the original side chain masses of the 20 natural amino acids, respectively. They are converted to following qualities by a standard conversion:

$$H_1(i)=\frac{H_1^o(i)-\frac{1}{20}\sum_{i=1}^{20}H_1^o(i)}{\sqrt{\frac{\sum_{i=1}^{20}[H_1^o(i)-\frac{1}{20}\sum_{i=1}^{20}H_1^o(i)]^2}{20}}}$$

$H_2^o(i)$ and $M^o(i)$ are normalized as $H_2(i)$ and $M(i)$ in the same way.

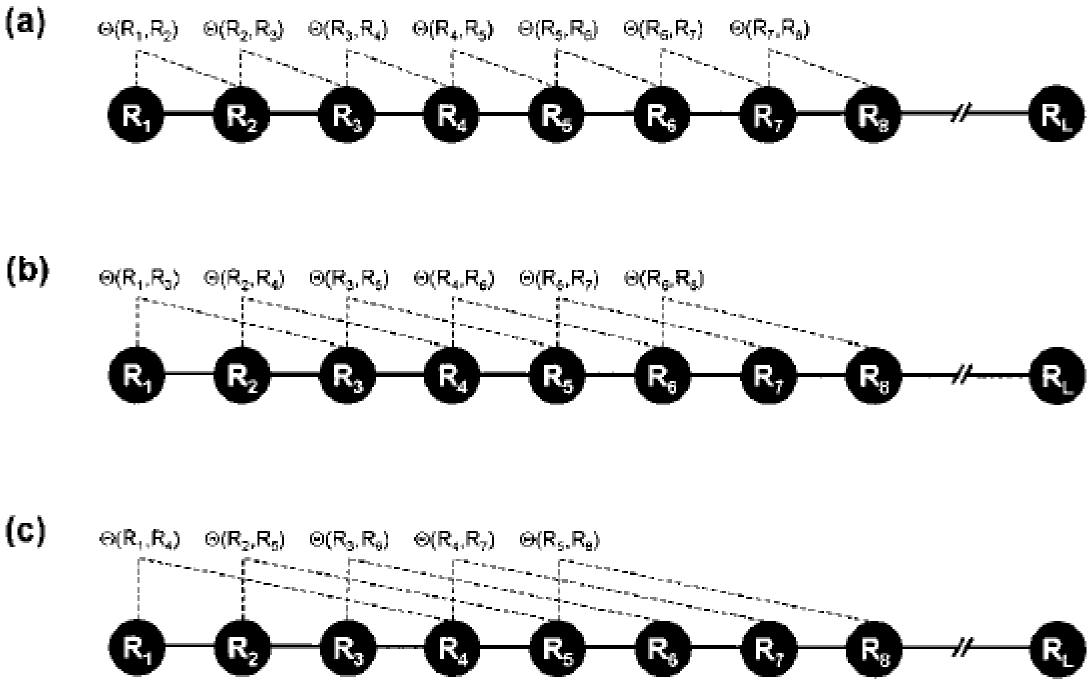


**Figure 5** A schematic drawing to show (a) the first-tier, (b) the second-tier, and (3) the third-tier

sequence order correlation mode along a protein sequence. Panel (**a**) reflects the correlation mode between all the most contiguous residues, panel (**b**) that between all the second-most contiguous residues, and panel (**c**) that between all the third-most contiguous residues.

Then, a correlation function can be defines as:

$$\Theta(R_i,R_j)=\frac{1}{3}\left\{\left[H_1(R_i)-H_1(R_j)\right]^2+\left[H_2(R_i)-H_2(R_j)\right]^2+\left[M(R_i)-M(R_j)\right]^2\right\}$$

This correlation function is actually an averaged value for the three amino acid properties: hydrophobicity value, hydrophilicity value and side chain mass. Therefore we can extend this definition of correlation function for one amino acid property or for a set of n amino acid properties. For one amino acid property, the correlation can be defined as:

$$\Theta(R_i,R_j)=\left[H_1(R_i)-H_1(R_j)\right]^2$$

where $H(R_{i)}$ is the amino acid property of amino acid $R_i$ after standardization.

For a set of n amino acid properties, it can be defined as: where $H_k(R_i)$ is the *k*th property in the amino acid property set for amino acid $R_i$.

$$\Theta(R_i,R_j)=\frac{1}{n}\sum_{k=1}^{n}\left[H_k(R_i)-H_k(R_j)\right]^2$$

where Hk(Ri) is the kth property in the amino acid property set for amino acid Ri.

A set of descriptors called sequence order-correlated factors are defined as:

$$\theta_1=\frac{1}{N-1}\sum_{i=1}^{N-1}\Theta(R_i,R_{i+1})$$

$$\theta_2=\frac{1}{N-2}\sum_{i=1}^{N-2}\Theta(R_i,R_{i+2})$$

$$\theta_3=\frac{1}{N-3}\sum_{i=1}^{N-3}\Theta(R_i,R_{i+3})$$

$$\cdots$$

$$\theta_\lambda=\frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda}\Theta(R_i,R_{i+\lambda})$$

$\lambda$ (<L) is a parameter to be chosen. Let $f_i$ is the normalized occurrence frequency of the 20 amino acids in the protein sequence, a set of 20+$\lambda$ descriptors called the pseudo-amino acid composition for a protein sequence can be defines as:

$$Xc = \frac{f_c}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{\lambda}\theta_j} \qquad (1<c<20)$$

$$Xc = \frac{w\theta_{c-20}}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{\lambda}\theta_j} \qquad (21<c<20+\lambda)$$

where *w* is the weighting factor for the sequence-order effect and is set as *w*=0.05 in PyDPI as suggested by Chou KC.

Note: the original hydrophobicity values for amino acids in PyDPI are different from the values by Chou KC. In this updated version, the default values of amino acid properties are the values of Chou KC. However, in the work of Chou KC, the definition for "normalized occurrence frequency" is not given and in this work we define it as the occurrence frequency of amino acid in the sequence normalized to 100% and hence our calculated values are not the same as values by them.

## 2.9 Amphiphilic pseudo-amino acid composition (APAAC)

APAAC (http://www.csbio.sjtu.edu.cn/bioinf/PseAAC/type2.htm) are also called type 2 pseudo-amino acid composition. The definitions of these qualities are similar to the above PAAC descriptors. From $H_1$($_i$) and $H_2(j)$ defined in eq. 16 and eq. 17, the hydrophobicity and hydrophilicity correlation functions are defined respectively as:

$$H_{i,j}^1 = H_1(i)H_1(j)$$

$$H_{i,j}^2 = H_2(i)H_2(j)$$

From these qualities, sequence order factors can be defines as:

$$\tau_1 = \frac{1}{N-1}\sum_{i=1}^{N-1} H_{i,i+1}^1$$

$$\tau_2 = \frac{1}{N-1}\sum_{i=1}^{N-1} H_{i,i+1}^2$$

$$\tau_3 = \frac{1}{N-2}\sum_{i=1}^{N-2} H_{i,i+2}^1$$

$$\tau_4 = \frac{1}{N-2}\sum_{i=1}^{N-2} H_{i,i+2}^2$$

...

$$\tau_{2\lambda-1} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H^1_{i,i+\lambda}$$

$$\tau_{2\lambda} = \frac{1}{N-\lambda}\sum_{i=1}^{N-\lambda} H^2_{i,i+\lambda}$$

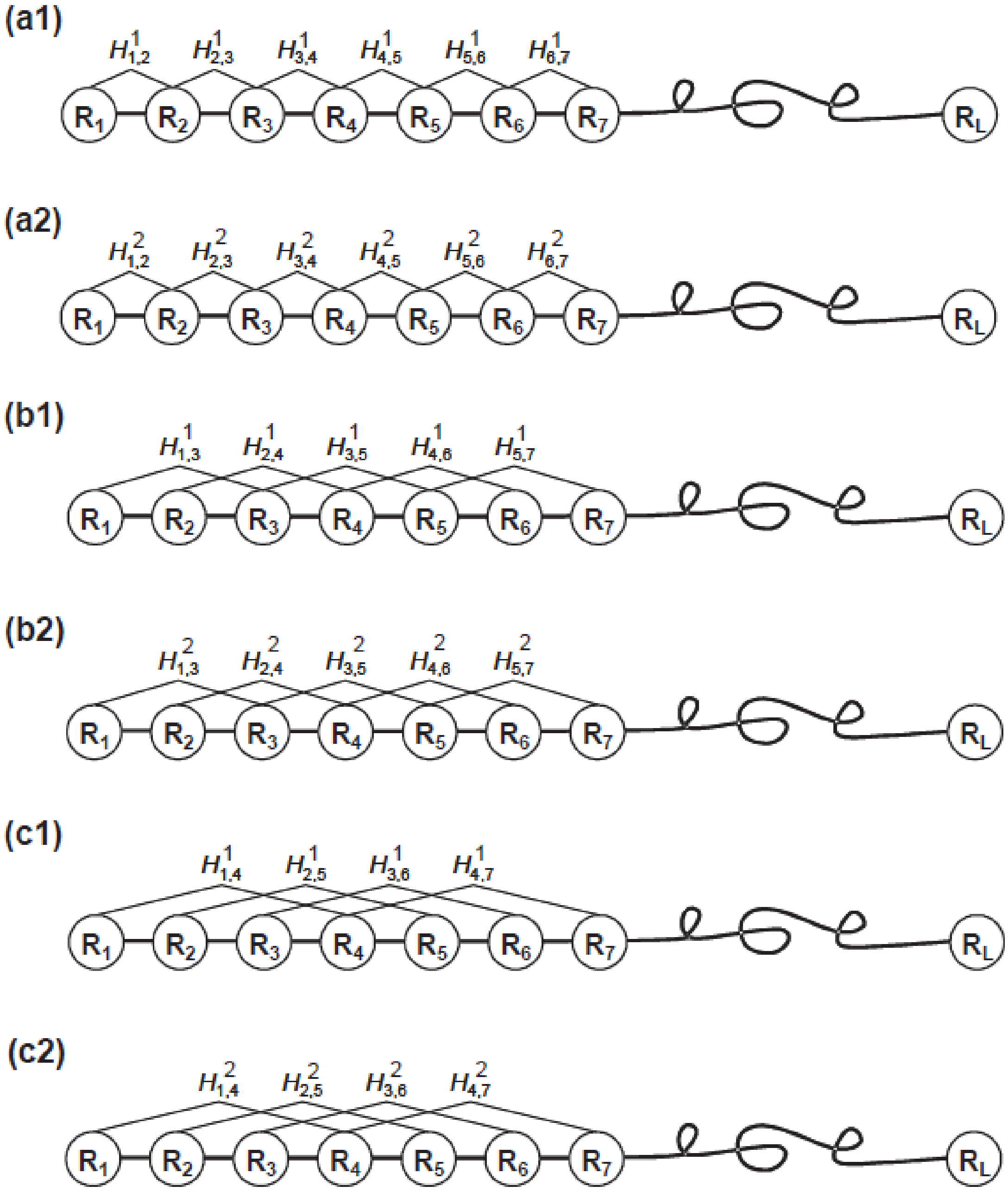

(a1)
$H^1_{1,2}$ $H^1_{2,3}$ $H^1_{3,4}$ $H^1_{4,5}$ $H^1_{5,6}$ $H^1_{6,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$
(a2)
$H^2_{1,2}$ $H^2_{2,3}$ $H^2_{3,4}$ $H^2_{4,5}$ $H^2_{5,6}$ $H^2_{6,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$
(b1)
$H^1_{1,3}$ $H^1_{2,4}$ $H^1_{3,5}$ $H^1_{4,6}$ $H^1_{5,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$
(b2)
$H^2_{1,3}$ $H^2_{2,4}$ $H^2_{3,5}$ $H^2_{4,6}$ $H^2_{5,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$
(c1)
$H^1_{1,4}$ $H^1_{2,5}$ $H^1_{3,6}$ $H^1_{4,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$
(c2)
$H^2_{1,4}$ $H^2_{2,5}$ $H^2_{3,6}$ $H^2_{4,7}$
$R_1$ $R_2$ $R_3$ $R_4$ $R_5$ $R_6$ $R_7$ $R_L$

**Figure 6** A schematic diagram to show (**a1**/**a2**) the first-rank, (**b1**/**b2**) the second-rank and (**c1**/**c2**) the third-rank sequence-order-coupling mode along a protein sequence through a hydrophobicity/hydrophilicity correlation function, where $H1$ $i,j$ and $H2$ $i,j$ are given by Equation (3).

Panel (a1/a2) reflects the coupling mode between all the most contiguous residues, panel (b1/b2) that between all the second-most contiguous residues and panel (c1/c2) that between all the third-most contiguous residues.

Then a set of descriptors called “Amphiphilic pseudo amino acid composition” (APAAC) are defined as:

$$Pc = \frac{f_c}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{2\lambda}\tau_j} \qquad 1<c<20$$

$$Pc = \frac{w\tau_u}{\sum_{r=1}^{20} f_r + w\sum_{j=1}^{2\lambda}\tau_j} \qquad 21<u<20+2\lambda$$

Where *w* is the weighting factor and is taken as *w*=0.5 in PyDPI as in the work of Chou KC.

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## 3 Protein-protein interaction descriptors

Let **Fa**={**Fa**(i),i=1,2,…,n} and **Fb**={**Fb**(i),i=1,2,…,n} are the two descriptor vectors for interaction protein A and protein B, respectively, then there are 3 methods to construct the descriptor vector **F** for A and B:

**(1)** Two vectors **F**ab and **F**ba with dimension of 2n are constructed: **F**ab=(**F**a,**F**b) for interaction between protein A and protein B and **F**ba=(**F**b,**F**a) for interaction between protein B and protein A.

**(2)** One vector **F** with dimension of 2n is constructed: **F**={**F**a(i)+**F**b(i), **F**a(i) ×**F**b(i), i=1,2, …, n}.

**(3)** One vector **F** with dimension of $n^2$ is constructed by the tensor product: **F**={**F**(k)=**F**a(i) ×**F**b(j), i=1, 2, …, n, j=1, 2 ,… , n, k=(i-1) ×n+j}.

## 4 Protein-ligand interaction descriptors

There are two methods for construction of descriptor vector **F** for protein-ligand interaction from the protein descriptor vector $\mathbf{F}_p$ ($F_p$(i), i=1,$n_p$) and ligand descriptor vector $\mathbf{F}_l$($\mathbf{F}_l$(i), i=1,$n_l$)**:**

**(1)** One vector V with dimension of np+nl are constructed : **F=(**$\mathbf{F}_p$**,**$\mathbf{F}_l$) for interaction between protein P and ligand L.

**(2)** One vector V with dimension of $n_p$×$n_l$ is constructed by the tensor product: **F**={f(k)=$\mathbf{F}_p$(i) ×$\mathbf{F}_l$(j), i=1,2, …, np, j=1,2,…,$n_l$, k=(i-1) ×np+j}.

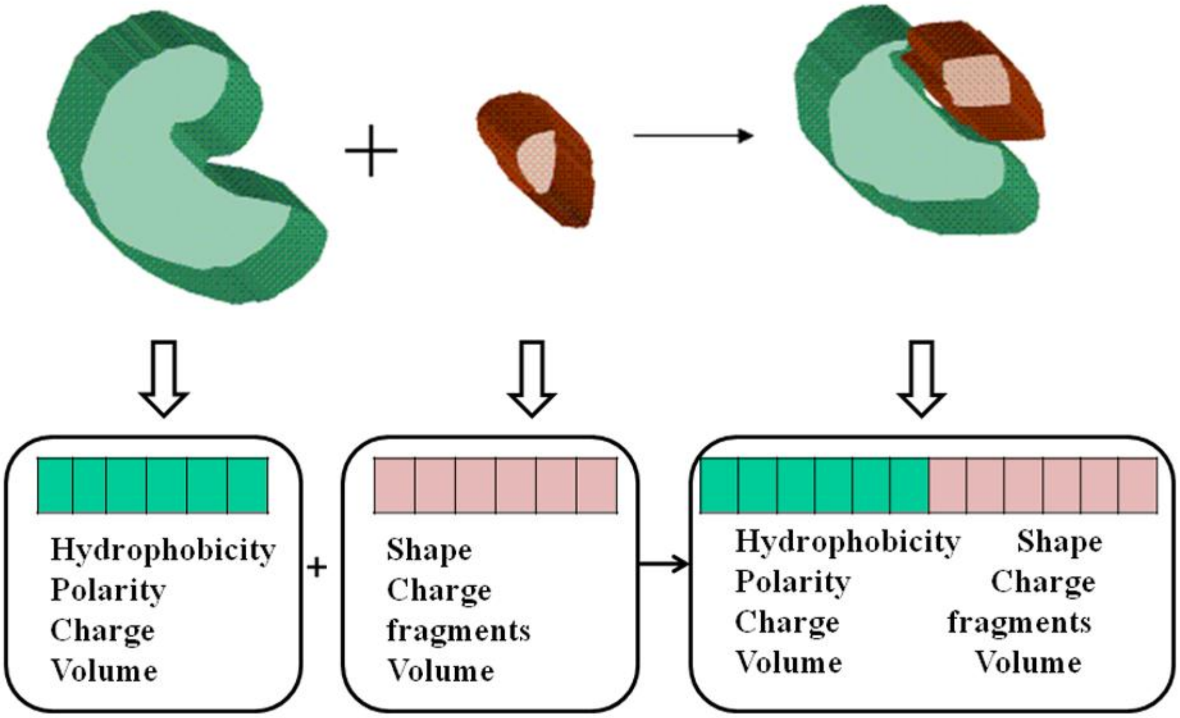

**Figure 7** The schematic diagram dealing with the drug-target interaction by using the chemogenomics approach. This interaction can be considered as an event triggered by many factors influencing the binding between this drug and this protein. Therefore it can be efficiently represented by

simultaneously considering the structure content from this drug and this protein under a common chemogenomics representation framework.

## References:

[1] Large-scale prediction

[2]

[3]

[4]

[5]

# Appendix:

**Table S1** List of PyDPI computed features for protein sequences

| Feature group | Features | Number of descriptors |
|---|---|---|
| Amino acid composition | Amino acid composition | 20 |
| | Dipeptide composition | 400 |
| | Tripeptide composition | 8000 |
| Autocorrelation | Normalized Moreau-Broto autocorrelation | 240[a] |
| | Moran autocorrelation | 240 [a] |
| | Geary autocorrelation | 240 [a] |
| CTD | Composition | 21 |
| | Transition | 21 |
| | Distribution | 105 |
| Conjoint Triad | Conjoint Triad | 343 |
| Quasi-sequence order | Sequence order coupling number | 60 |
| | Quasi-sequence order descriptors | 100 |
| Pseudo amino acid composition | Pseudo amino acid composition | 50 [b] |
| | Amphiphilic pseudo amino acid composition | 50[c] |

[a] The number depends on the choice of the number of properties of amino acid and the choice of the maximum values of the *lag*. The default is use eight types of properties and *lag* = 30.

[b] The number depends on the choice of the number of the set of amino acid properties and the choice of the *lamda* value. The default is use three types of properties proposed by Chou et al and *lamda* = 30.

[c] The number depends on the choice of the *lamda* vlaue. The default is that *lamda* = 30.

**Table S2** List of PyDPI computed descriptors for small molecules

| **Molecular descriptors** | | |
|---|---|---|
| | **Constitutional descriptors** | |
| 1 | Weight | Molecular weight |
| 2 | nhyd | Count of hydrogen atoms |
| 3 | nhal | Count of halogen atoms |
| 4 | nhet | Count of hetero atoms |
| 5 | nhev | Count of heavy atoms |
| 6 | ncof | Count of F atoms |
| 7 | ncocl | Count of Cl atoms |
| 8 | ncobr | Count of Br atoms |
| 9 | ncoi | Count of I atoms |
| 10 | ncarb | Count of C atoms |
| 11 | nphos | Count of P atoms |
| 12 | nsulph | Count of S atoms |
| 13 | noxy | Count of O atoms |
| 14 | nnitro | Count of N atoms |
| 15 | nring | Number of rings |
| 16 | nrot | Number of rotatable bonds |
| 17 | ndonr | Number of H-bond donors |
| 18 | naccr | Number of H-bond acceptors |

| | | |
|---|---|---|
| 19 | nsb | Number of single bonds |
| 20 | ndb | Number of double bonds |
| 21 | ntb | Number of triple bonds |
| 22 | naro | Number of aromatic bonds |
| 23 | nta | Number of all atoms |
| 24 | AWeight | Average molecular weight |
| 25-30 | PC1<br>PC2<br>PC3<br>PC4<br>PC5<br>PC6 | Molecular path counts of length 1-6 |
| | **Topological descriptors** | |
| 1 | W | Weiner index |
| 2 | AW | Average Wiener index |
| 3 | J | Balaban’s J index |
| 4 | $T_{hara}$ | Harary number |
| 5 | $T_{sch}$ | Schiultz index |
| 6 | Tigdi | Graph distance index |
| 7 | Platt | Platt number |
| 8 | Xu | Xu index |
| 9 | Pol | Polarity number |
| 10 | Dz | Pogliani index |

| | | |
|---|---|---|
| 11 | Ipc | Ipc index |
| 12 | BertzCT | BertzCT |
| 13 | GMTI | Gutman molecular topological index based on simple vertex degree |
| 14-15 | ZM1<br>ZM2 | Zagreb index with order 1-2 |
| 16-17 | MZM1<br>MZM2 | Modified Zagreb index with order 1-2 |
| 18 | Qindex | Quadratic index |
| 19 | diametert | Largest value in the distance matrix |
| 20 | radiust | radius based on topology |
| 21 | petitjeant | Petitjean based on topology |
| 22 | Sito | the logarithm of the simple topological index by Narumi |
| 23 | Hato | harmonic topological index proposed by Narumi |
| 24 | Geto | Geometric topological index by Narumi |
| 25 | Arto | Arithmetic topological index by Narumi |
| | | |
| | **Connectivity descriptors** | |
| 1-11 | ${}^{0}\chi^{v}$<br>${}^{1}\chi^{v}$<br>${}^{2}\chi^{v}$<br>${}^{3}\chi_{p}^{v}$<br>${}^{4}\chi_{p}^{v}$<br>${}^{5}\chi_{p}^{v}$<br>${}^{6}\chi_{p}^{v}$<br>${}^{7}\chi_{p}^{v}$ | Valence molecular connectivity Chi index for path order 0-10 |

| | | |
|---|---|---|
| | ${}^{8}\chi_{p}^{v}$<br>${}^{9}\chi_{p}^{v}$<br>${}^{10}\chi_{p}^{v}$ | |
| 12 | ${}^{3}\chi^{v}_{c}$ | Valence molecular connectivity Chi index for three cluster |
| 13 | ${}^{4}\chi^{v}_{c}$ | Valence molecular connectivity Chi index for four cluster |
| 14 | ${}^{4}\chi^{v}_{pc}$ | Valence molecular connectivity Chi index for path/cluster |
| 15-18 | ${}^{3}\chi^{v}_{CH}$<br>${}^{4}\chi^{v}_{CH}$<br>${}^{5}\chi^{v}_{CH}$<br>${}^{6}\chi^{v}_{CH}$ | Valence molecular connectivity Chi index for cycles of 3-6 |
| 19-29 | ${}^{0}\chi$<br>${}^{1}\chi$<br>${}^{2}\chi$<br>${}^{3}\chi_{p}$<br>${}^{4}\chi_{p}$<br>${}^{5}\chi_{p}$<br>${}^{6}\chi_{p}$<br>${}^{7}\chi_{p}$<br>${}^{8}\chi_{p}$<br>${}^{9}\chi_{p}$<br>${}^{10}\chi_{p}$ | Simple molecular connectivity Chi indices for path order 0-10 |
| 30 | ${}^{3}\chi_{c}$ | Simple molecular connectivity Chi indices for three cluster |
| 31 | ${}^{4}\chi_{c}$ | Simple molecular connectivity Chi indices for four cluster |
| 32 | ${}^{4}\chi_{pc}$ | Simple molecular connectivity Chi indices for path/cluster |
| 33-36 | ${}^{3}\chi_{CH}$<br>${}^{4}\chi_{CH}$<br>${}^{5}\chi_{CH}$ | Simple molecular connectivity Chi indices for cycles of 3-6 |

| | | |
|---|---|---|
| | $^{6}\chi_{CH}$ | |
| 37 | mChi1 | mean chi1 (Randic) connectivity index |
| 38 | knotp | the difference between chi3c and chi4pc |
| 39 | dchi0 | the difference between chi0v and chi0 |
| 40 | dchi1 | the difference between chi1v and chi1 |
| 41 | dchi2 | the difference between chi2v and chi2 |
| 42 | dchi3 | the difference between chi3v and chi3 |
| 43 | dchi4 | the difference between chi4v and chi4 |
| 44 | knotpv | the difference between chiv3c and chiv4pc |
| | **Kappa descriptors** | |
| 1 | $^{1}\kappa_{\alpha}$ | Kappa alpha index for 1 bonded fragment |
| 2 | $^{2}\kappa_{\alpha}$ | Kappa alpha index for 2 bonded fragment |
| 3 | $^{3}\kappa_{\alpha}$ | Kappa alpha index for 3 bonded fragment |
| 4 | phi | Kier molecular flexibility index |
| 5 | $^{1}\kappa$ | Molecular shape Kappa index for 1 bonded fragment |
| 6 | $^{2}\kappa$ | Molecular shape Kappa index for 2 bonded fragment |
| 7 | $^{3}\kappa$ | Molecular shape Kappa index for 3 bonded fragment |
| | **E-state descriptors** | |
| 1 | S(1) | Sum of E-State of atom type: sLi |
| 2 | S(2) | Sum of E-State of atom type: ssBe |
| 3 | S(3) | Sum of E-State of atom type: ssssBe |
| 4 | S(4) | Sum of E-State of atom type: ssBH |

| | | |
|---|---|---|
| 5 | S(5) | Sum of E-State of atom type: sssB |
| 6 | S(6) | Sum of E-State of atom type: ssssB |
| 7 | S(7) | Sum of E-State of atom type: sCH3 |
| 8 | S(8) | Sum of E-State of atom type: dCH2 |
| 9 | S(9) | Sum of E-State of atom type: ssCH2 |
| 10 | S(10) | Sum of E-State of atom type: tCH |
| 11 | S(11) | Sum of E-State of atom type: dsCH |
| 12 | S(12) | Sum of E-State of atom type: aaCH |
| 13 | S(13) | Sum of E-State of atom type: sssCH |
| 14 | S(14) | Sum of E-State of atom type: ddC |
| 15 | S(15) | Sum of E-State of atom type: tsC |
| 16 | S(16) | Sum of E-State of atom type: dssC |
| 17 | S(17) | Sum of E-State of atom type: aasC |
| 18 | S(18) | Sum of E-State of atom type: aaaC |
| 19 | S(19) | Sum of E-State of atom type: ssssC |
| 20 | S(20) | Sum of E-State of atom type: sNH3 |
| 21 | S(21) | Sum of E-State of atom type: sNH2 |
| 22 | S(22) | Sum of E-State of atom type: ssNH2 |
| 23 | S(23) | Sum of E-State of atom type: dNH |
| 24 | S(24) | Sum of E-State of atom type: ssNH |
| 25 | S(25) | Sum of E-State of atom type: aaNH |
| 26 | S(26) | Sum of E-State of atom type: tN |

| | | |
|---|---|---|
| 27 | S(27) | Sum of E-State of atom type: sssNH |
| 28 | S(28) | Sum of E-State of atom type: dsN |
| 29 | S(29) | Sum of E-State of atom type: aaN |
| 30 | S(30) | Sum of E-State of atom type: sssN |
| 31 | S(31) | Sum of E-State of atom type: ddsN |
| 32 | S(32) | Sum of E-State of atom type: aasN |
| 33 | S(33) | Sum of E-State of atom type: ssssN |
| 34 | S(34) | Sum of E-State of atom type: sOH |
| 35 | S(35) | Sum of E-State of atom type: dO |
| 36 | S(36) | Sum of E-State of atom type: ssO |
| 37 | S(37) | Sum of E-State of atom type: aaO |
| 38 | S(38) | Sum of E-State of atom type: sF |
| 39 | S(39) | Sum of E-State of atom type: sSiH3 |
| 40 | S(40) | Sum of E-State of atom type: ssSiH2 |
| 41 | S(41) | Sum of E-State of atom type: sssSiH |
| 42 | S(42) | Sum of E-State of atom type: ssssSi |
| 43 | S(43) | Sum of E-State of atom type: sPH2 |
| 44 | S(44) | Sum of E-State of atom type: ssPH |
| 45 | S(45) | Sum of E-State of atom type: sssP |
| 46 | S(46) | Sum of E-State of atom type: dsssP |
| 47 | S(47) | Sum of E-State of atom type: sssssP |
| 48 | S(48) | Sum of E-State of atom type: sSH |

| | | |
|---|---|---|
| 49 | S(49) | Sum of E-State of atom type: dS |
| 50 | S(50) | Sum of E-State of atom type: ssS |
| 51 | S(51) | Sum of E-State of atom type: aaS |
| 52 | S(52) | Sum of E-State of atom type: dssS |
| 53 | S(53) | Sum of E-State of atom type: ddssS |
| 54 | S(54) | Sum of E-State of atom type: sCl |
| 55 | S(55) | Sum of E-State of atom type: sGeH3 |
| 56 | S(56) | Sum of E-State of atom type: ssGeH2 |
| 57 | S(57) | Sum of E-State of atom type: sssGeH |
| 58 | S(58) | Sum of E-State of atom type: ssssGe |
| 59 | S(59) | Sum of E-State of atom type: sAsH2 |
| 60 | S(60) | Sum of E-State of atom type: ssAsH |
| 61 | S(61) | Sum of E-State of atom type: sssAs |
| 62 | S(62) | Sum of E-State of atom type: sssdAs |
| 63 | S(63) | Sum of E-State of atom type: sssssAs |
| 64 | S(64) | Sum of E-State of atom type: sSeH |
| 65 | S(65) | Sum of E-State of atom type: dSe |
| 66 | S(66) | Sum of E-State of atom type: ssSe |
| 67 | S(67) | Sum of E-State of atom type: aaSe |
| 68 | S(68) | Sum of E-State of atom type: dssSe |
| 69 | S(69) | Sum of E-State of atom type: ddssSe |
| 70 | S(70) | Sum of E-State of atom type: sBr |

| | | |
|---|---|---|
| 71 | S(71) | Sum of E-State of atom type: sSnH3 |
| 72 | S(72) | Sum of E-State of atom type: ssSnH2 |
| 73 | S(73) | Sum of E-State of atom type: sssSnH |
| 74 | S(74) | Sum of E-State of atom type: ssssSn |
| 75 | S(75) | Sum of E-State of atom type: sI |
| 76 | S(76) | Sum of E-State of atom type: sPbH3 |
| 77 | S(77) | Sum of E-State of atom type: ssPbH2 |
| 78 | S(78) | Sum of E-State of atom type: sssPbH |
| 79 | S(79) | Sum of E-State of atom type: ssssPb |
| 80-158 | Smax1-Smax79 | maxmum of E-State value of specified atom type |
| 159-237 | Smin1-Smin79 | minimum of E-State value of specified atom type |
| | **Autocorrelation descriptors** | |
| 1-8 | ATSm1-ATSm8 | Moreau-Broto autocorrelation descriptors based on atom mass |
| 9-16 | ATSv1-ATSv8 | Moreau-Broto autocorrelation descriptors based on atomic van der Waals volume |
| 17-24 | ATSe1-ATSe8 | Moreau-Broto autocorrelation descriptors based on atomic Sanderson electronegativity |
| 25-32 | ATSp1-ATSp8 | Moreau-Broto autocorrelation descriptors based on atomic polarizability |
| 33-40 | MATSm1-MATSm8 | Moran autocorrelation descriptors based on atom mass |
| 41-48 | MATSv1-MATSv8 | Moran autocorrelation descriptors based on atomic van der Waals volume |
| 49-56 | MATSe1-MATSe8 | Moran autocorrelation descriptors based on atomic Sanderson electronegativity |

| | | |
|---|---|---|
| 57-64 | MATSp1-MATSp8 | Moran autocorrelation descriptors based on atomic polarizability |
| 65-72 | GATSm1-GATSm8 | Geary autocorrelation descriptors based on atom mass |
| 73-80 | GATSv1-GATSv8 | Geary autocorrelation descriptors based on atomic van der Waals volume |
| 81-88 | GATSe1-GATSe8 | Geary autocorrelation descriptors based on atomic Sanderson electronegativity |
| 89-96 | GATSp1-GATSp8 | Geary autocorrelation descriptors based on atomic polarizability |
| | **Charge descriptors** | |
| 1-4 | $Q_{Hmax}$<br>$Q_{Cmax}$<br>$Q_{Nmax}$<br>$Q_{Omax}$ | Most positive charge on H,C,N,O atoms |
| 5-8 | $Q_{Hmin}$<br>$Q_{Cmin}$<br>$Q_{Nmin}$<br>$Q_{Omin}$ | Most negative charge on H,C,N,O atoms |
| 9-10 | $Q_{max}$<br>$Q_{min}$ | Most positive and negative charge in a molecule |
| 11-15 | $Q_{HSS}$<br>$Q_{CSS}$<br>$Q_{NSS}$<br>$Q_{OSS}$<br>Qass | Sum of squares of charges on H,C,N,O and all toms |
| 16-17 | Mpc<br>Tpc | Mean and total of positive charges |
| 18-19 | Mnc<br>Tnc | Mean and total of negative charges |

| | | |
|---|---|---|
| 20-21 | Mac<br>Tac | Mean and total of absolute charges |
| 22 | Rpc | Relative positive charge |
| 23 | Rnc | Relative negative charge |
| 24 | SPP | Submolecular polarity parameter |
| 25 | LDI | Local dipole index |
| | **Molecular property descriptors** | |
| 1 | MREF | Molar refractivity |
| 2 | logP | LogP value based on the Crippen method |
| 3 | logP2 | Square of LogP value based on the Crippen method |
| 4 | TPSA | Topological polarity surface area |
| 5 | UI | Unsaturation index |
| 6 | Hy | Hydrophilic index |
| | **MOE-type descriptors** | |
| 1 | TPSA | topological polar surface area based on fragments |
| 2 | LabuteASA | Labute's Approximate Surface Area |
| 3-14 | SLOGPVSA | MOE-type descriptors using SLogP contributions and surface area contributions |
| 15-24 | SMRVSA | MOE-type descriptors using MR contributions and surface area contributions |
| 25-38 | PEOEVSA | MOE-type descriptors using partial charges and surface area contributions |
| 39-49 | EstateVSA | MOE-type descriptors using Estate indices and surface area |

| | | |
|---|---|---|
| | | contributions |
| 50-60 | VSAEstate | MOE-type descriptors using surface area contributions and Estate indices |
| | **Fragment/Fingerprint-based descriptors** | |
| 1 | FP2 | (Topological fingerprint) A Daylight-like fingerprint based on hashing molecular subgraphs |
| 2 | MACCS | (MACCS keys)Using the 166 public keys implemented as SMARTS |
| 3 | E-state | 79 E-state fingerprints or fragments |
| 4 | FP4 | 307 FP4 fingerprints |
| 5 | Atom Paris | Atom Paris fingerprints |
| 6 | Torsions | Topological torsion fingerprints |
| 7 | Morgan/Circular | Fingerprints based on the Morgan algorithm |