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(54) Title: MOTION OF A CHIRAL OBJECT

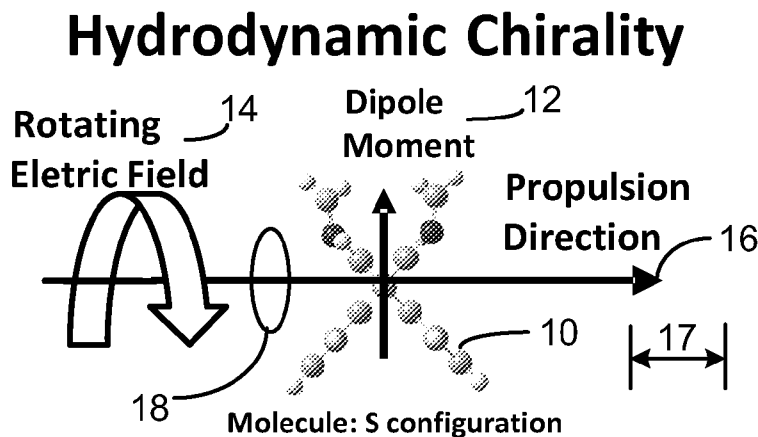


FIG. 3

(57) Abstract: Directional motion of chiral objects in a mixture is caused by rotation of the chiral objects produced by a field that is applied across, and rotates relative to, a chamber; and a computer-implemented step determines or uses, or determines and uses, in an application or process, a feature of a coupling between the rotational and the translational motion of the chiral objects.

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## MOTION OF A CHIRAL OBJECT

### BACKGROUND

This description relates to motion of a chiral object.

We use the term chiral object (or chiral system) very broadly to include, for example,  
5 any “original” object or system that differs from a mirror image of the original object  
such that a mirror image of the original cannot be superimposed on the original.

One kind of chiral object is a chiral molecule, also called an enantiomer. A common  
feature of a chiral molecule is its “handedness” (i.e., right-handed or left-handed).  
Enantiomers are a subset of chiral objects called stereoisomers.

10 As shown in figure 1, a stereoisomer is one of a set of isomeric molecules 2, 4.  
Different stereoisomers of the set share a similar connectivity of their atoms, but have  
different ways in which the atoms of the different stereoisomers are arranged in three-  
dimensional space (figure 2). A stereoisomer includes at least one stereocenter, which  
is any atom that bears groups such that an interchanging of any two groups leads to a  
15 different stereoisomer of the set. A stereoisomer may have more than one stereocenter.

Chirality is important in chemistry, especially for biological and drug applications.  
Natural bio-molecules are typically found in only one enantiomeric form (e.g., proteins,  
peptides, and amino acids in the human body are all left-handed, and sugars are all  
right-handed). The fields of drug discovery, development, and manufacturing are  
20 interested in samples of molecules that are enantiopure (i.e., contain only one  
enantiomeric form, all left-handed or all right-handed; we sometimes use the word  
“form” to refer to a “handedness”), because one form of enantiomer may work better *in*  
*vivo* while the opposite form may be toxic or may cause side effects.

Other chemistry-based fields would also benefit from enantiopure samples of  
25 molecules, including (for illustration purposes), but not limited to: flavors and  
fragrances, agrichemicals, fine chemicals, and others.

These applications may be categorized into two categories: analytical and preparative.  
For analytical purposes, one typically uses x-ray crystallography or vibrational circular  
dichroism (VCD) techniques to analyze and/or detect the presence or absence of

particular chiral objects in a mixture. And for preparative purposes, one typically uses high pressure liquid chromatography (HPLC) or asymmetric synthesis techniques to produce enantiopure and/or higher purity samples (we sometimes use the phrase “molecular separation techniques” to refer to ways to produce higher purity or enantiopure samples, among other things).

Some molecular separation techniques are not effective for chiral molecules, because two counterpart enantiomers generally share physical properties, including chemical composition, charge, size, electric and magnetic dipole moments  $\delta$ , and energy levels. Detection and separation of counterpart chiral molecules is typically done by interacting the molecules with a chiral medium (e.g., a chemical matrix). Enantiomers also can be identified by their interaction with a chiral (e.g., circularly polarized) electromagnetic field.

### SUMMARY

In general, in an aspect, directional motion of chiral objects in a mixture is caused by rotation of the chiral objects produced by a field that is applied across, and rotates relative to, a chamber; and a computer-implemented step determines or uses, or determines and uses, in an application or process, a feature of a coupling between the rotational and the translational motion of the chiral objects.

Implementations may include one or more of the following features. The feature of the coupling comprises a direction of the directional motion of the chiral objects for a given direction of the rotation of the field. The feature comprises a magnitude of the directional motion of the chiral objects for given parameters of the field, or of an apparatus that causes the directional motion, or of both. The feature comprises a distribution of directions or magnitudes or both of the directional motion of the chiral objects, over a set of configurations or structures of the chiral objects.

The application or process comprises an analysis application or process. The analysis application or process comprises a determination of an absolute configuration or stereochemistry of the chiral objects. The analysis application or process comprises a determination of a presence or absence of the chiral objects. The analysis application or process comprises a purity analysis of the chiral objects. The application or process

comprises a preparative application or process. The preparative application or process comprises an isolation of the chiral objects. The preparative application or process comprises an enrichment of the chiral objects. The preparative application or process comprises a separation of the chiral objects.

- 5 The feature is provided for use in controlling, as feedback to, or as a result for use in, an apparatus, or for use in a combination of them. The feature is provided to a user as at least one of information, a result, or feedback. The user comprises a human or a machine or both.

10 In general, in an aspect, for use in connection with directional motion of chiral objects in a mixture—the directional motion being caused by rotation of the chiral objects produced by a field that is applied across, and rotates relative to, the chamber—a device is configured to determine or use, or to determine and use, in a step of an application or process, a feature of the coupling between the rotational and the translational motion of the chiral objects. In some implementations, the device comprises software (including  
15 computer implemented steps, for example) running on a computer, hardware, or a combination of them.

These aspects, features, and implementations, and combinations of them, can be expressed as methods, software products, apparatus, systems, components, methods of doing business, and in other ways.

20

## DESCRIPTION

Figure 1 is an illustration of molecules.

Figure 2 is an illustration of molecular structures.

Figure 3 is an illustration of hydrodynamic chirality and directional motion.

Figure 4 is a distribution profile of hydrodynamic chirality.

25 Figure 5 is a flow diagram.

Figure 6 is a flow diagram.

Figure 7 is a block diagram.

We have previously proposed a new technique, which we named “Chiral Separation by Propeller Motion” (HERO), that can be applied to analytical, preparative, or both types of applications, and other applications that are not analytical or preparative. See related United States patent applications 12/103,281, filed April 15, 2008; 60/912,309, filed  
5 April 17, 2007; 60/987,674, filed November 13, 2007; and 12/142,545, filed June 19, 2009, and all incorporated here by reference.

Here we propose and describe an approach to quantify and understand HERO and then apply it to analysis, preparation, and a wide variety of other applications for chiral objects. The approach that we discuss here can be applied, using hardware, software  
10 (including computer implemented steps, for example), or a combination of them, to determine or use, or determine and use, in an application or process, a feature of a coupling between the rotational and the translational motion of the chiral objects.

As we have described earlier, separation and manipulation of chiral objects can be achieved without using chiral media, instead by relying on the susceptibility of the  
15 objects to external influences (e.g., forces) and the handedness of the objects. For example, the dipole moment that characterizes chiral molecules is susceptible to being rotated by a rotating external electric field. And the left handedness or right handedness of counterpart enantiomers, for example, can be used to transform the rotational motion of the enantiomers into translational (i.e., directional) motion of each of the  
20 enantiomers in a direction or of the two counterpart enantiomers in opposite directions. The handedness of some molecules, for example, is similar to the opposite handedness of left-handed and right-handed macroscopic propellers, which (when rotated) can propel themselves and objects to which they are attached in respectively opposite directions through a medium.

The “propeller” of each molecule is characterized by a spatial configuration associated with its chiral features. As the propeller rotates, these spatial features act against fluid resistance of the mixture that holds the molecules, to force the propeller and the  
25 molecule to move in a direction. We sometimes refer to this transformation of rotational motion of the propeller into directional motion depending on the handedness  
30 of the propeller as the propeller effect.

In some examples, an external rotating electrical field is applied to a sample of chiral molecules. An electric dipole of each chiral molecule (which is an example of a feature of a molecule that is susceptible to an external influence) lines up with the external electric field and rotates with it causing rotation of the chiral molecules (this rotation being an example of motion of the molecule in response to the external influence). The handedness (i.e., chirality or chiral features) of the molecule (which can be viewed as a tiny propeller) transforms this rotation into a linear (i.e., directional or translational) motion (E. M. Purcell, "The efficiency of propulsion by a rotating flagellum," Proc. Natl. Acad. Sci. USA, Biophysics, v94, pp 11307-11311, Oct. 1997).

At a molecular level and in a fluid (characterized by very low Reynolds numbers), inertial forces on the chiral molecules are negligible. The motion of the molecule that results from its rotation is similar to a left-handed or right-handed corkscrew motion. For a particular force applied by the rotation of the molecules in the mixture, the S and R enantiomers will acquire the same velocities but in opposite directions. Concentration gradients for both enantiomers will be established based on the magnitudes of these velocities, compared to the inherent diffusive flux of the molecules in the mixture, which is characterized by the diffusion constant.

The magnitude and profile of the concentration gradient for each enantiomer, and thus, the enrichment achieved, will depend on the enantiomer's propeller efficiency (that is, the efficiency with which its spatial configuration converts the rotation induced by the external influence to a translational force on the molecule, which relates to the size, shape and orientation of the propeller, among other things), the effective length of the container that holds the mixture, how long the field is applied, the electric field strength, the frequency of rotation, and properties of the fluid in which the enantiomers are held in the mixture, among other things. We sometimes refer to the propeller efficiency as the propeller propulsion efficiency.

Therefore to apply the propeller effect in a wide range of applications, it is useful to characterize, quantify, measure, and analyze the propeller efficiency for various different configurations of the molecule.

*Hydrodynamic Chirality and Propeller Efficiency*

The designation or categorization of a molecule to a form molecular chirality (for example S or R) is typically based on a predetermined set of rules that are arbitrary. Thus designated chirality of a molecule is not directly associated with any directly measurable physical property of the molecule (except its structure), because the

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chirality only defines a particular configuration of molecular structure. For example, different molecules of an enantiomer that have the same absolute configuration (e.g., S) can exhibit opposite directions of rotation of circularly polarized light or have opposite signatures in VCD spectra.

10

In order to establish a useful quantifiable link (or relationship or coupling) between chirality and translational propulsion properties of a rotating chiral molecule, we define a new physical property of a chiral molecule which we call hydrodynamic chirality. Hydrodynamic chirality characterizes both the direction and the magnitude of translational motion of a chiral molecule that has been forced into rotation by an external field.

15

As shown in figure 3, for example, when an S-form molecule having a dipole moment is subjected to a rotating electric field, the propeller effect causes motion of the molecule in a propulsion direction. The magnitude of the hydrodynamic chirality parameter specifies the propeller efficiency defined as a translational displacement of the chiral molecule in the propulsion direction that is caused by one complete (360 degrees) rotation/revolution of the molecule under the influence of the external field.

20

The direction of translational motion is expressed as a sign (e.g., plus or minus) of the propeller efficiency value for a specific direction of rotation. We define a standard direction of rotation of the external field to correspond to a motion of a right-hand screw. Positive and negative hydrodynamic chirality correspond to directions of motion along or against the direction of motion of a right-hand screw, respectively.

25

Thus, hydrodynamic chirality characterizes the coupling between rotational and translational degrees of freedom in chiral molecules, i.e., hydrodynamic chirality characterizes the ability and efficiency of chiral molecules to propel under the influence

30

of an external rotating field and is quantified through sign and magnitude of propeller efficiency. Hydrodynamic chirality can be characterized either with respect to a configuration of molecules of a particular 3-D structure for the enantiomer group to which the molecules belong, or (as shown in figure 4) with respect to a distribution profile 22, 24 of propeller efficiencies 26 for two or more of the different configurations or 3-D structures (along the x axis) of each of the enantiomers.

The opposite enantiomers of a chiral molecule have opposite signs for their hydrodynamic chirality, i.e., chiral molecules of S or R absolute configurations propel to opposite directions under the influence of a given external rotating field. Thus if direction of motion of a particular enantiomer can be experimentally obtained, then its absolute configuration (as between S and R) can be determined by comparing the determined direction of motion with the predicted sign of hydrodynamic chirality of that particular enantiomer.

Hydrodynamic chirality can be determined and then used in a wide variety of ways and for a broad range of practical applications.

#### *Method of Calculation*

We describe below how theoretical simulations can be used to associate a particular absolute configuration (e.g., S or R) of the chiral molecule or object with its hydrodynamic chirality and propeller efficiency (figure 5). In some examples, theoretical simulations consist of two main parts: 1) determination 50 of the 3D molecular structure, energy, and dipole moments of all thermally accessible conformations of a particular enantiomer, and 2) quantification of translational-rotational coupling for each conformation. The final value of propeller efficiency is obtained by Boltzmann averaging of propeller efficiency over all thermally accessible conformations; thus propeller efficiency can be a statistical quantity. Once the value of hydrodynamic chirality has been obtained, among other things, performance of a system can be predicted 54, and/or the absolute configuration of the molecule can be determined 56. The predicted performance, the determined absolute configuration, and/or other results can be used to control a process or instrument or to provide feedback to a user or both 58. And results can be presented to a user 60.

### *I. Structure and dipole moment determination*

3-D structure, energy and electrical dipole moment of the molecule can be determined using a number of existing standard molecular modeling techniques which include *ab initio*, density functional or molecular mechanics methods. Lowest energy structure and structures of all other thermally accessible conformations can be optimized and their energies (heat of formation) and dipole moments calculated.

### *II. Calculation of hydrodynamic chirality (propeller efficiency)*

Below we refer to a number of methods that can be used to determine hydrodynamic chirality. These are only examples.

#### *Molecular Dynamics with explicit solvent*

An enantiomer chiral molecule (solute) is put into a box filled with solvent molecules (in a simulation context) and a molecular dynamics (MD) simulation is performed in the presence of a simulated rotating electric field. Molecular dynamics takes into account all possible interactions between atoms in the combined solute-solvent system. MD enables assessment of the importance of specific interactions with the solvent and also estimates the effects of rotation of solvent molecules on the solute. During simulation the axial position of the center of mass of the molecule is recorded. After MD simulation is complete, the total axial displacement in the simulation is divided by the total number of revolutions of the molecule in the simulation to obtain the magnitude of the propeller efficiency, i.e., displacement per one revolution. The sign is obtained from the direction of displacement determined in the simulation.

#### *Molecular Dynamics based on the Hard Ball Model*

By eliminating a large number of degrees of freedom (e.g., internal vibrations) this method significantly reduces calculation times. Implementation can be based on solving equations of motion with Langevin damping terms, elastic collision model and step-like radial distribution function (interaction potential). The method is fast because trajectories of the particles can be calculated exactly. The shapes of the molecule can be determined from *ab initio* (density functional) calculation of total charge isodensity surface or van der Waals surfaces.

*Molecular Dynamics based on the Lennard-Jones Fluid model*

This approach is similar to the hard ball model, but more realistic interaction potentials are used in order to more reliably account for fluid viscosity effects.

*Full Hydrodynamics Model*

- 5 This approach solves Stokes equations (low Reynolds number) for a solute molecule with molecular shape determined by the total charge isodensity surface (from an initio or semiempirical simulations) or van der Waals surface and using stick/slip surface conditions. Quantitative results are possible especially when solute molecule is significantly larger than the solvent molecules.

10 *Angular Momentum Integration (for absolute configuration)*

This method provides an approximate estimate of the sign of propeller effect based on integration of angular momentum of the solute due to multiple interactions with randomly impinging solvent molecules. This approach could be suitable for quick qualitative determination of absolute configuration.

15 *Coupled Bead Method and the Shell model*

- A solute molecule can be modeled as a collection of spheres where interactions between spheres are included via the Oseen-Burgers hydrodynamic interaction tensor. In a shell model molecules with complicated shapes can be modeled by covering their isodensity surface with infinitely small spheres. This method has been used
- 20 successfully for calculation of both translational and rotational friction coefficients of various molecules.

Below we provide some example references to the above mentioned methods and models:

25 *Ab Initio, Density Functional*

I. N. Levine, Quantum Chemistry, 6th Edition Prentice Hall, (2008).

C. J. Cramer, Essentials of Computational Chemistry: Theories and Models, Wiley, 2nd edition (2004).

*Molecular Dynamics*

5 A. Leach, *Molecular Modelling: Principles and Applications*, Prentice Hall; 2nd edition (2001).

D. C. Rapaport, *The Art of Molecular Dynamics Simulation*, Cambridge University Press; 2nd edition (2004).

D. Frenkel, B. Smit *Understanding Molecular Simulation*, Academic Press; 2 edition (2001)

10 *Hydrodynamics*

J. Happel, H. Brenner, *Low Reynolds Number Hydrodynamics*, Kluwer, (1983)

*Coupled Bead Method and the Shell model*

I.N. Serdyuk, N. R. Zaccai, J. Zaccai, *Methods in Molecular Biophysics*, Cambridge University Press, 2007.

15 *Using Hydrodynamic Chirality*

We can then use a feature of the calculated hydrodynamic chirality 52 in an application or process (figure 6). For example, it can be used to predict performance 54 (e.g. propulsion velocity, separation time, purity level, throughput, and others such as power, heating, convection, solvent, chiral labels). To this end, we use methods based on  
20 analytical and numerical solutions of Fokker-Planck equation. And hydrodynamic chirality can also be used in a particular application, e.g. comparing direction of the translational motion of chiral objects in an apparatus with the predicted direction from simulations to determine absolute stereochemistry.

As also shown in figure 6, the particular application or process that makes use of the  
25 hydrodynamic chirality may be an analysis application or process (e.g. determination of absolute configuration or stereochemistry, determination of absence or presence, or purity analysis of the chiral objects); or it may be a preparative application or process (e.g. isolation, enrichment, or separation of the chiral objects) 82. Every possible application can be considered one or the other of analysis and preparation, and the only

distinction between the two of those is that in analysis, the chiral molecules or objects are not used at the end of an analysis application, but they are collected and used in a subsequent step in a preparation application.

*Interaction with Apparatus and/or User*

5 Our proposed computer-implemented step also includes interacting with an apparatus and/or a user 84, 86 (figures 6 and 7).

An interaction with an apparatus may comprise controlling the apparatus, providing feedback to it, using a result towards the operation or functionality of the apparatus, or a combination of them.

10 Similarly, the interaction may be with a user (e.g. a human, or a computer), to provide the user with information about the apparatus and/or the processes run with that apparatus, with a result or outcome, with feedback, or with a combination of them.

The above descriptions and examples also apply to an apparatus, as well as a device that comprises software (including computer-implemented steps) running on a  
15 computer, hardware, or a combination of them.

Other implementations are also within the scope of the following claims.

## CLAIMS

1. A method for use in connection with directional motion of chiral objects in a mixture in a chamber, the directional motion being caused by rotation of the chiral objects produced by a field that is applied across, and rotates relative to, the chamber,  
5 the method comprising
- a computer-implemented step, that determines or uses, or determines and uses, in an application or process, a feature of a coupling between the rotational and the translational motion of the chiral objects.
2. The method of claim 1 in which the feature comprises a direction of the  
10 directional motion of the chiral objects for a given direction of the rotation of the field.
3. The method of claim 1 in which the feature comprises a magnitude of the directional motion of the chiral objects for given parameters of the field, or of an apparatus that causes the directional motion, or of both.
4. The method of claim 1 in which the feature comprises a distribution of  
15 directions or magnitudes or both of the directional motion of the chiral objects, over a set of configurations or structures of the chiral objects.
5. The method of claim 1 in which the application or process comprises an analysis application or process.
6. The method of claim 5 in which the analysis application or process comprises a  
20 determination of an absolute configuration or stereochemistry of the chiral objects.
7. The method of claim 5 in which the analysis application or process comprises a determination of a presence or absence of the chiral objects.
8. The method of claim 5 in which the analysis application or process comprises a purity analysis of the chiral objects.
9. The method of claim 1 in which the application or process comprises a  
25 preparative application or process.

10. The method of claim 9 in which the preparative application or process comprises an isolation of the chiral objects.
11. The method of claim 9 in which the preparative application or process comprises an enrichment of the chiral objects.
- 5 12. The method of claim 9 in which the preparative application or process comprises a separation of the chiral objects.
13. The method of claim 1 also comprising providing the feature for use in controlling, as feedback to, or as a result for use in, an apparatus, or for use in a combination of them.
- 10 14. The method of claim 1 also comprising providing the feature to a user as at least one of information, a result, or feedback.
15. The method of claim 14 in which the user comprises a human or a machine or both.
- 15 16. An apparatus for use in connection with directional motion of chiral objects in a mixture in a chamber, the directional motion being caused by rotation of the chiral objects produced by a field that is applied across, and rotates relative to, the chamber, the apparatus comprising
- 20 a device configured to determine or use, or to determine and use, in a step of an application or process, a feature of the coupling between the rotational and the translational motion of the chiral objects.
17. The apparatus of claim 16 in which the device comprises software running on a computer, hardware, or a combination of them.

**Example Molecule**

(S)-(-)-1,1'-Binaphthyl-2,2'-diamine (R)-(+)-1,1'-Binaphthyl-2,2'-diamine

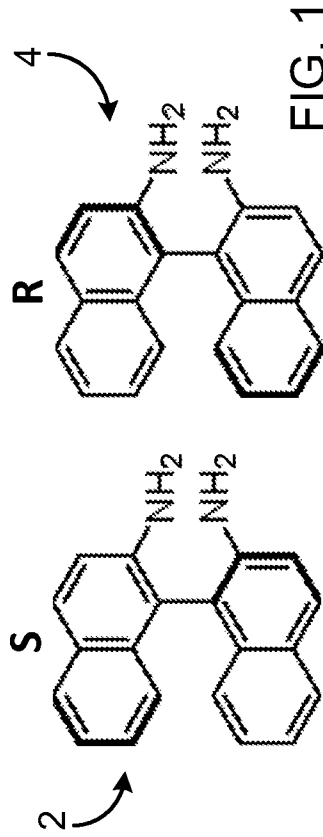


FIG. 1

**3D Molecular Structure**

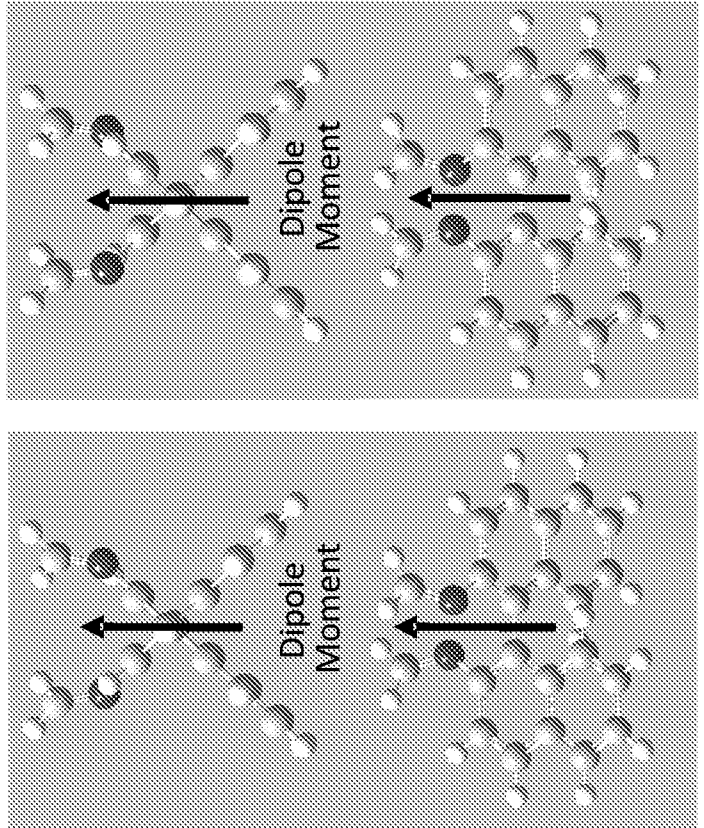


FIG. 2

**Hydrodynamic Chirality**

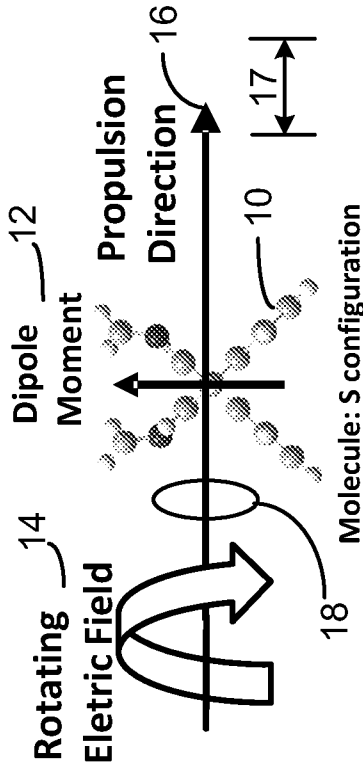


FIG. 3

**Hydrodynamic Chirality: Distribution Profile**

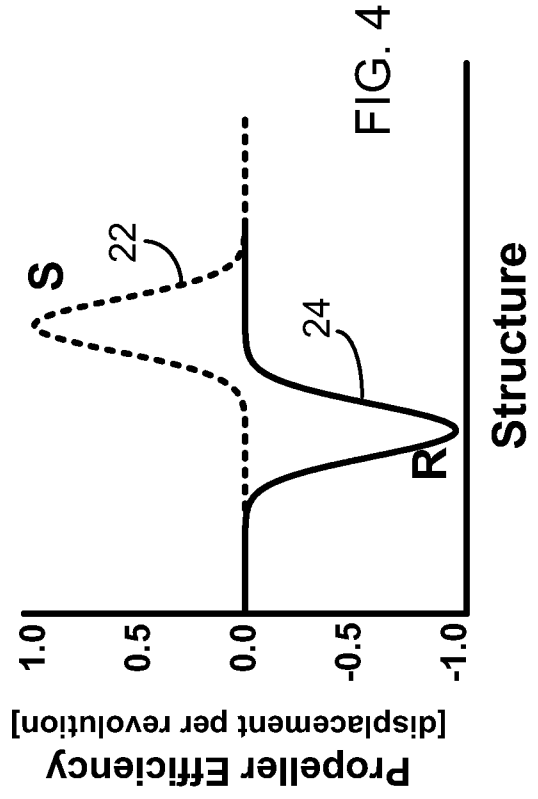


FIG. 4

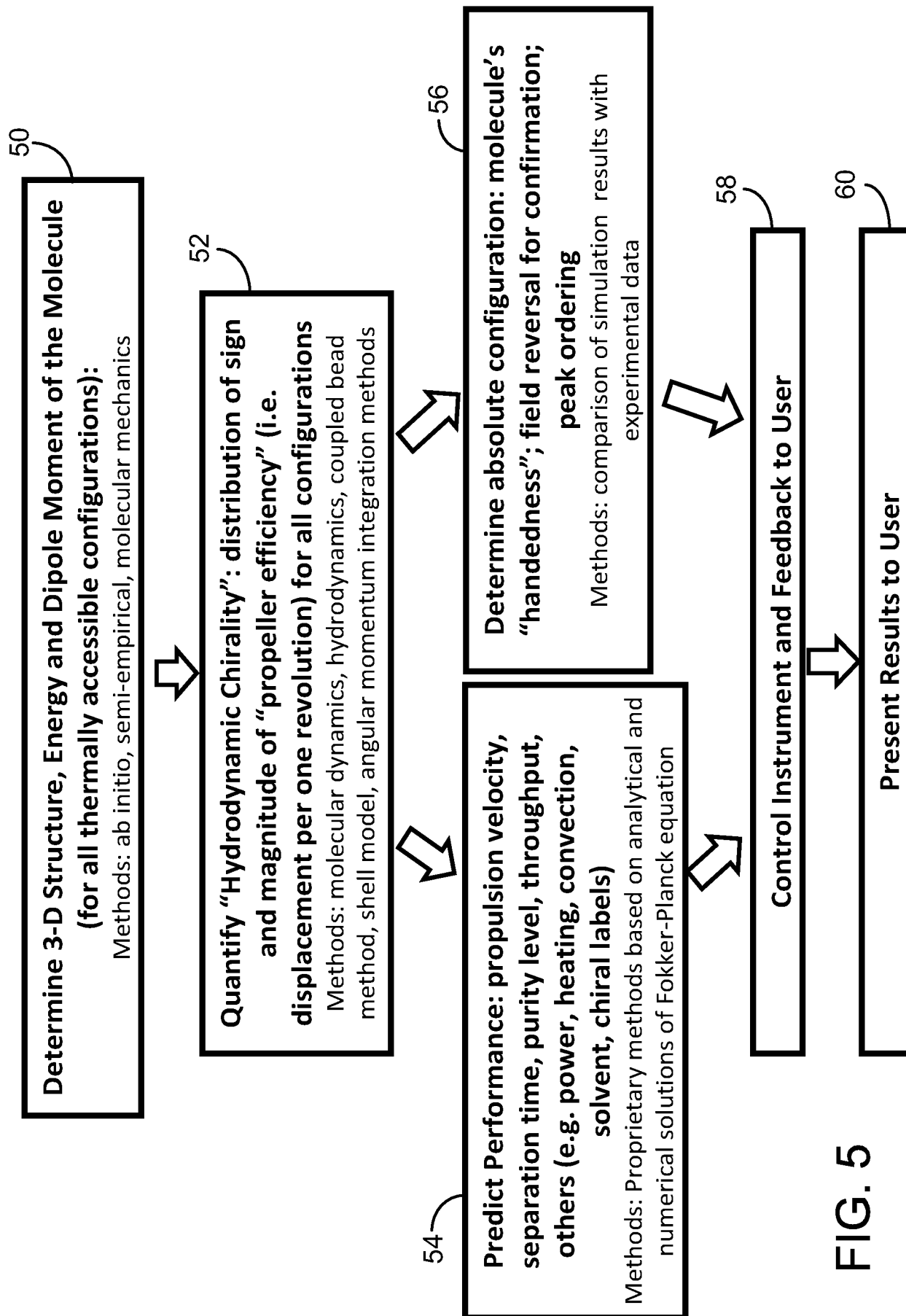


FIG. 5

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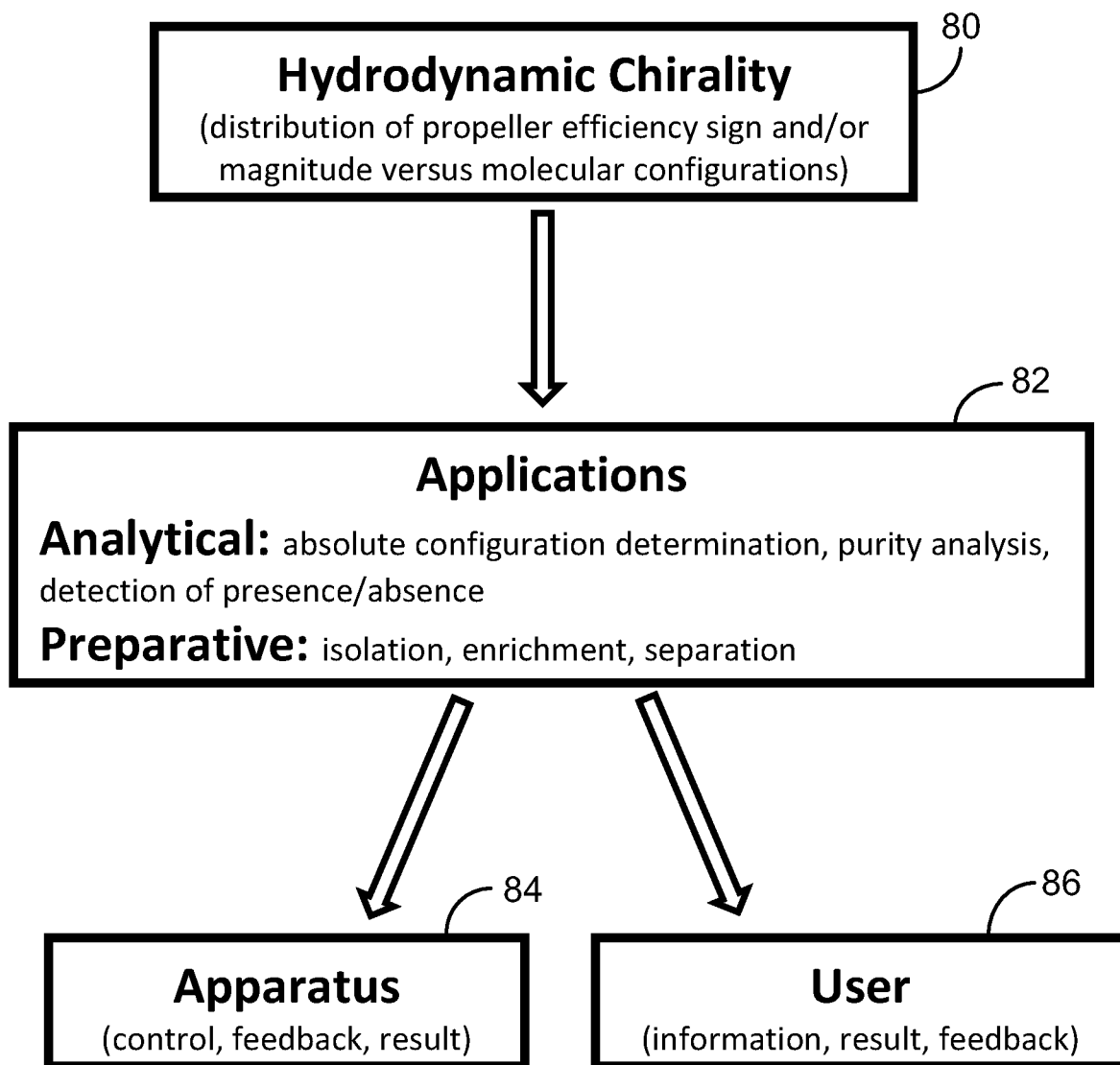


FIG. 6

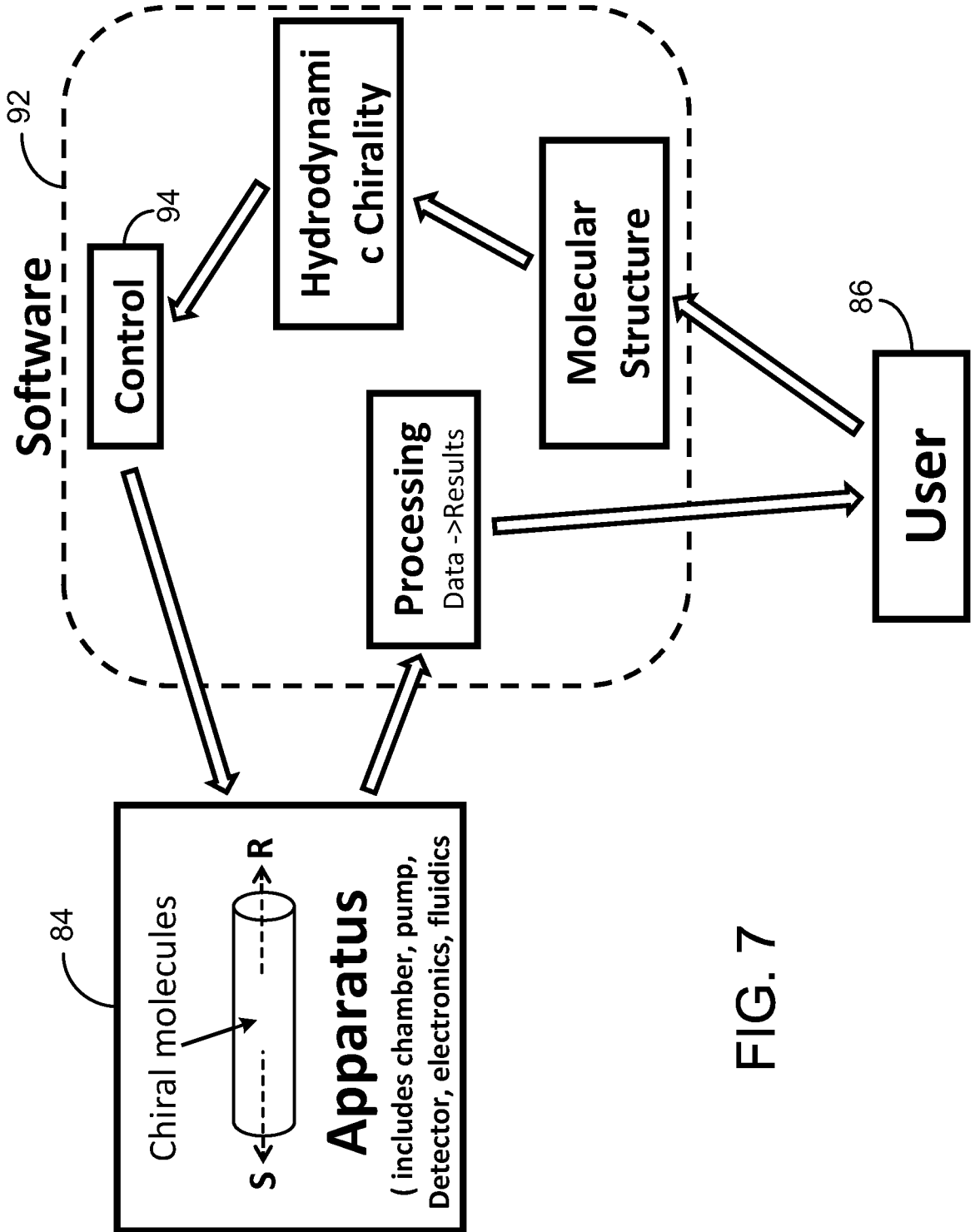


FIG. 7

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2010/053525

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - G01N 33/00 (2010.01) USPC - 436/71 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8) - C12N 1/00, 1/12, 1/20, 7/00, 7/01, 9/00, 13/00; G01N 33/00, 33/92 (2010.01) USPC - 435/173.1, 183, 235.1, 243, 252.1; 436/71, 86, 94 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) MicroPatent, Google Patent		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0274555 A1 (KIBAR et al) 06 November 2008 (06.11.2008) entire document	1-17
A	US 5,398,037 A (ENGHETA et al) 14 March 1995 (14.03.1995) entire document	1-17
A	US 2008/0262240 A1 (KIBAR et al) 23 October 2008 (23.10.2008) entire document	1-17
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