The following claims concern proteomic technologies involving *in-silico* screening methods and the identified compounds thereof, as well as inventions involving the 3-D structural data of proteins *per se.* All these inventions are part of the rapidly evolving area of bioinformatics. *In-silico* screening consists of computerized simulations of the three-dimensional structure of a given polypeptide and was already introduced in Chapter II. The current availability of new information technologies enables scientists to compare a gross amounts of structural data. Therefore, approaches such as *in-silico* screening are increasingly replacing earlier *in-vivo*[579] and *in-vitro* methods.

The major goal of *in-silico* methods is to identify compounds which can bind to a computerized protein. In addition to applications for new *methods*, patent offices are confronted with an increasing number of patent applications related to the *results* from *in-silicio* screening. Specifically, we have seen in recent years the filing of applications involving the identification of candidate compounds which would theoretically form the most stable complex with the computerized 3-D models of proteins. The latter, again, are the subject of an increasing number of applications filed in recent years. Through methods such as NMR structure determination, X-ray crystallography and protein homologous-comparison, the speed of 3-D structure identification has increased steadily. Claims are often directly directed to *in-silicio* screening methods, since applications argue that the findings they put forth are a necessary precondition for compound identification.

Combined with a number of other influences, these new forms of research have resulted in the development of bioinformatics. Bioinformatics, in turn, refers to 'the application of quantitative analytical techniques to the modeling of biological systems'.[580] More specifically, the term describes the development and employment of computer-implemented algorithms and data processing methods directed to data analysis and interpretation.[581] The latter are then used in the design of new pharma-

579 Within a living organism or body. For example testing conducted on whole animals, such as mice.

580 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA - The Journal of Law and Technology 2003, 93-131, 94. Bioinformatics draws researchers from the fields of biology, computer science, statistical mathematics, and linguistics.

581 Rimmer, Matthew, Beyond Blue Gene: Intellectual Property and Bioinformatics, 34 IIC 31, 31 (2003) defines "bioinformatics" as "the art and science of using computer systems to store, manage and analyse biological information that brings together the diverse disciplines of mathematics, statistics, engineering, and computer science to map and model genes and proteins". The purpose of bioinformatics changes in relation to the improved organization of vast amounts and numerous types of biological information, and the clarification of the biological or medical significance of such information through its analyses. See also Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 85.

ceuticals.[582] The area of bioinformatics has not only attracted a large amount of venture capital in recent years.[583] It also poses a number of fascinating questions in the area of intellectual property rights protection. Among other things, it is closely related to the hotly debated issue of software implemented inventions, which has even been subject of an initiative of the European Commission.[584]

1. In-silico screening methods

One field which the patent offices had to consider were claims related to *in-silico* screening methods. As explained earlier, *in-silico* methods are computerized ways of searching for compounds, using the protein three-dimensional structural data regarding protein active sites.[585] The selection of compounds is achieved by evaluating their desirability in a computational model based on mathematical methods.[586] The method of *in-silico* screening therefore illustrates the major importance computerized techniques have for proteomic inventions. An increasing number of scientific studies are being carried out through the use of computers, a development that has come to be known as "*in-silico* biology".[587]

582 Krefft, Alexander Richard, Patente auf human-genomische Erfindungen: Rechtslage in Deutschland, Europa und den USA, München 2003, 35, who notes that bioinformatics is one of the most promising sectors of genomics. In particular, the ability to simulate entire cells in-silico ('e-cell simulation') is likely to have a large impact on life science in general. Against this background, the Human Genome Project can be understood as yet the greatest achievement of bioinformatics. Fernandez, Dennis/Chow, Mary, Intellectual Property Strategy in Bioinformatics and Biochips, Journal of Patent and Trademark Office Society, June 2003, 465, 465, provide another definition, stating that bioinformatics is understood as "the convergence of analytical and computational tools with the discipline of biological research".

583 The rapid growth of bioinformatics has created an environment of rigorous competitive efforts to create proprietary positions in areas of commercial interest. In the U.S., this development motivated increasing filings of patent applications for bioinformatics-based inventions. In 1999 alone, 289,448 such applications have been filed in the USPTO; see Hultquist, Steven J./Robert Harrison, and Yongzhi Yang, Patenting Bioinformatic Inventions: Emerging Trends in the United States, 20 Nature Biotechnology 2002, 743, 743.

584 Proposal for a Directive of the European Parlament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002. See also Chapter 3 B III 1 a cc i.

585 Chapter 2 E III 4.

586 Camebridge Healthtech Institute, in-silico & molecular modeling glossary available at: http://www.genomicglossaries.com/content/ molecular _modeling_gloss.asp, last checked on January 21, 2008.

587 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Science, 93 IDEA - The Journal of Law and Technology 2003, 93, 127 stresses that scientists already possessing the requisite computational ability are at a significant advantage, since they are able to accomplish the demands of various industries.

a) Claim 1

Claim 1 of the set of claims considered in this context reads:

> A method of identifying compounds that can bind to a protein P, comprising the steps of:
>
> a) The application of a 3-dimensional molecular modeling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
>
> b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P.[588]

aa) Background

Protein P was a known protein whose amino acid sequence was also established. The description indicated that the activity of protein P was known to result in lowering blood pressure. It provided the atomic coordinates of protein P, but did not include the position of its binding pocket. Instead, the specification provided general information on programs predicting the binding pocket of proteins and general information commonly used for in-silico screening programs. Prior art had demonstrated methods of peptide modeling and binding using rational drug design, but there was a clear technical difficulty in obtaining the claimed atomic coordinates of protein P. It was assumed in the specification that by using the binding pocket prediction program and *in-silico* screening program, the person skilled in the art could identify compounds binding to the given protein. The description provided no working examples of identifying compounds using the atomic coordinates of protein P. The specification contemplated that by using the binding pocket prediction program and *in-silico* screening program, the person skilled in the art could identify compounds binding to the given protein. The prior art did not include 3-D coordinates of protein P. It did not teach computer programs for prediction of the binding pocket of proteins. Several *in-silico* screening programs referring to predicted binding pockets of proteins are already established.[589]

588 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

589 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

bb) Patent Offices Analysis

The EPO concludes the *in-silico* claim to be a patentable invention under Art. 52(2) and 52(3) EPC, since it is directed to a method linked to a technical contribution through the use of technical data. Absent any working examples, however, the claimed method does not disclose sufficient information to comply with the disclosure and enablement requirements. The patentee only offers the filing of further technical information in the future. Presently, he does not provide sufficient evidence to ensure a correct prediction of binding-pockets positions.[590]

The USPTO considers the claims to constitute a patentable subject matter, referring to the *'State Street rationale*'.[591] In *State Street*, the court reasoned that to qualify as patent-eligible subject matter, an invention must accomplish a practical application.[592] With regard to the claim at issue, the method steps apply to a set of structural parameters and the result set provides a number of lead compounds with an increased probability of binding to the used protein. Hence, the method provides "a useful, concrete and tangible result" that can be used to guide further screening. Irrespective of the recitation of specific structural coordinates, the claims are directed to *in-silico* screening methods that have a practical application. Consequently, the methods must be considered statutory subject matter under the *State Street* rationale.[593]

The utility requirement of 35 U.S.C. § 101 depends on the utility of the candidate compounds identified by the screening methods. Utility is present if the specification discloses that the binding compounds may be used either to stimulate activity of protein P to reduce blood pressure or, in cases of hypertension, to inhibit the activity of protein P and thus cause an increase in blood pressure. An assertion of either or both of these uses for a protein P binding compound that is credible to one skilled in the art would be sufficient as a specific, substantial, and credible utility. Although

590 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

591 See State Street Bank & Trust Co. v. Signature Financial Group Inc., 149 F.3d 1368, 1373 (Fed. Cir. 1998). The 'useful result' aspect of the practical application test presupposes significant functionality. See Arrhythima Research Tech. v. Carazonix Gorp., 958 F.2d 1053, 1057 (Fed. Cir. 1992).

592 Managing Intellectual Property 2003, Issue 132, p. 38, In State Street the court overturned the long-accepted rule that business methods were not statutory subject matter. In favour of banks, software companies and the nascent internet industry, the court said that methods of doing business should be treated the same way as any other patentable invention. It thus extended the holding of the earlier decision, In re Alappat, 33 F.3d 1526 (Fed. Cir. 1994), which had affirmed the patentability of computer programs.

593 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 71.

the specification describes that protein P, when active, lowers blood pressure, there is no indication of a correlation between binding activity and activation. Absent of a known or disclosed correlation between binding and activation, the identification of compounds which bind to protein P lack a specific, substantial, and credible utility.[594]

The USPTO determines the principles of enablement by considering several factors. Enablement depends on the selection, with mere general guidance, from the specification, of one or more programs to identify the binding pocket of protein P. Further, identification of the binding pocket must be demonstrated to be valid. Finally, in order for the conditions of enablement to be fulfilled there must be an expectation of success in identifying compounds that bind to protein P, and the amount and nature of experimentation required to select candidate compounds must be clear.

The office alleges that enablement is likely to fail unless the binding pocket identification is known to be highly predictive. The amount of experimentation required to identify and confirm the binding pockets is likely to be undue, since the program would yield multiple possible binding pockets. Thus, a person skilled in the art would have to choose the most likely predicted binding pockets in order to verify the actual pocket. Since the binding pocket is not confirmed prior to screening, the sets of possible binding compounds could be completely devoid of compounds that bind to protein P. Moreover, even if the claimed methods identify compounds that bind to protein P, the specification does not demonstrate the use of these compounds without undue experimentation.[595]

The USPTO further states that the claimed methods satisfy the written description requirements of 35 U.S.C. § 112, first paragraph. The specification includes the elements that are necessary to carry out the claimed method, such that one skilled in the art would have recognized that the patentee indeed possessed the claimed invention. It also teaches prior art programs that can be used to identify the binding pocket and to screen for candidate binding compounds. In addition, the specification determines the structural coordinates of protein P required by the pocket prediction and screening programs.[596]

The USPTO further claims a lack of clarity under 35 U.S.C. § 112, second paragraph, because the claim is directed to a process, but does not set forth any particular

594 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 71.

595 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 72.

596 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 72.

steps involved in the process. Since the prior art did not disclose any 3-D coordinates, the U.S. office acknowledges novelty. However, prior art renders the invention obvious. The computer algorithm used to identify compounds that can potentially bind protein P is known and is unmodified. Consequently, the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on a machine. Data fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps is considered non-functional descriptive material, because there is no alteration of the process. Consequently, the claimed invention is directed to a method of using a known comparison in order to compare data sets. An invention does not become nonobvious merely because new data becomes available for analysis. Non-functional descriptive material cannot overcome nonobviousness of an invention that would have otherwise been obvious.[597]

cc) Discussion

i. The discussion on the patentability of computer-implemented inventions in Europe

For a better understanding of the EPO's decision to accept the patentability of the *in-silico* method (claim 1), it is beneficial to fully take into account the intense discussion surrounding the patentability of computer-implemented inventions taking place in Europe.[598] While the EPO has already granted large numbers of patents involving computer programs, two issues have exposed patentees and other groups to a significant risk. First, differences in national interpretations of the EPC have created a large amount of ambiguity related to the scope of protection for various classes of patents in different member states. Second, the fact that the EPC itself explicitly excludes "computer programs as such" from patentable subject matter has added to existing uncertainties. As to the latter, the EPO established its current practice to grant computer-implemented inventions by a number of decisions. In "*Computer program product/IBM*"[599] the Board of Appeals of the EPO acknowledged the patentability of computer-implemented inventions if any "further technical effect" is provided. The Board reasoned:

597 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 73.

598 Nack, Ralph, Neue Gedanken zur Patentierbarkeit von computerimplementierten Erfindungen - Bedenken gegen Softwarepatente - ein déjà vu?, GRUR Int. 2004, 771, 771; Nack, Ralph, Sind jetzt computerimplementierte Geschäftsmethoden patentfähig? GRUR Int. 2000, 853, 853 emphasizing that the discussion increasingly focuses on the question of whether the patent system as such should be criticized.

599 T 1173/97, Computer program product/IBM, OJ 1999, 609.

> "A computer program product is not excluded from patentability under Art. 52(2) and (3) EPC if, when it is run on a computer, it produces a *further* technical effect which goes beyond the "normal" physical interaction between program (software) and computer (hardware)."[600]

The decision of *Computer program product/IBM* thus specifies the meaning of Art. 52 EPC. According to Art. 52(2) EPC, computer programs shall not be regarded as inventions within the context of Art. 52(1) EPC and are therefore excluded from patentability. Art. 52(3) EPC, however, establishes an important limitation to the scope of this exclusion: the exclusion applies only to the extent to which a European patent application or a European patent relates to programs to computers "as such".[601] Since the technical character is generally accepted as an essential requirement for its patentability within the context of the application of the EPC (see Rules 27 and 29 EPC), the exclusion of computer programs as such from patentability would mean that such programs are considered mere abstract creations, lacking in technical character.[602] Computer programs cannot be considered as having technical character for the very reason that they are software programs. This technical character, however, can be exhibited by further effects derived from the execution of the instructions given by the computer program.[603] In "*Computer program product/IBM,* the court required a particular *further* technical effect such as a piece of software managing an "industrial process", "the working of a piece of machinery" or an "internal functioning" of a computer itself.[604]

In *Two Identities/COMVIK*[605], the Board further determined that the requirement of a technical character permits the invention „to have a mix of technical and "non-technical" features, even if the non-technical features should form a dominating part.""[606] An invention is patentable „even if the technical was not the dominating part of the invention. ""[607]

In the following cases, the Board of Appeals of the EPO appears to weaken the standards for computer related inventions by accepting claims for computer methods "using technical means". [608] In *Microsoft*, the invention involved "a method in a computer system having a clipboard for performing data transfer of data in a clipboard format."[609] The Board determined that the invention has "technical character"

600 T 1173/97, Computer program product/IBM, OJ 1999, 609, 628-623, see also T 208/84, OJ 1987, 14; T 26/86, N. Publ.(EPO 1989); T 209/91, N. Publ. (EPO 1991); T 6/83, OJ 1990, 5; T 158/88, OJ 1991, 566; T 769/92, OJ 1995, 525; T 59/93, N. Publ (EPO 1994).

601 Schulte/Moufang, PatG mit EPÜ, § 1 No. 156.

602 Vicom/X-ray Apparatus, OJ 1987, 14; Singer/Stauder, EPC, 3rd ed., Art. 52, Nos. 36-39.

603 Benkard/Melullis, EPC, Art. 52, 207, stating that the decision finally gave up the limits originally set forth by the EPC.

604 T 1173/97, Computer program product/IBM, OJ 1999, 609, 628.

605 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356-357.

606 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356.

607 T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356, see also T 935/97 Computer program product, RPC 1999, 861; T 931/95, Controlling pension benefits system, OJ 2001, 441.

608 T258/03, Auction method/Hitachi, OJ 2004, 575, 585; T 0411/03 GRUR Int. 2006, 851 – Microsoft (Board of Appeals 2006).

609 T 0411/03, GRUR Int. 2006, 851, 851 – Microsoft.

because it is "used independently of any cognitive content to enhance the internal operation of a computer" for "facilitating the exchange of data among various application programs."[610] By assisting "the user in transferring no-file data into files", the invention "solves a problem" by "technical means" and goes beyond the "elementary interaction of any hardware and software of data processing."[611]

The literature is generally consistent with the EPO's approach to accepting computer related inventions under certain circumstances.[612] *Benkard/Melullis*, however, emphasizes that the patentability standard should not be satisfied if a result or effect is merely "carried out" by a computer. Under this view, it is necessary that "a technical teaching" establishes the "technical effect" independently from the computer application.[613] *Busse/Keukenschrijver* agrees with *Benkard/Melullis*, but stresses that a technical effect cannot be caused by the mere application of software. Under this perspective it is, however, also not justified to use the fact that software is applied as an argument against a technical contribution.[614]

Once granted, however, a European patent becomes subject to the national patent laws of each country "in respect of which it is granted." (Art.64 I). According to Art. 64 III EPO, "any infringement of a European Patent shall be dealt with by national patent law. [615] The fact that a European patent to a computer-implemented invention might be challenged under the law of designated member states causes a high level of uncertainty for patent applicants and potential investors.[616] Although the basic national laws on patentability are in principle uniform as between themselves and the provisions of the European Patent Convention, the detailed interpretation is the task of the courts. In other words, they are not bound to follow the decisions of the EPO's appellate bodies and may, in the event of conflict, respect their own legal traditions.[617] With respect to the interpretation of computer-implemented inventions, this has lead to legal divergences. In contrast to the EPO case law, the U.K. jurisprudence considers computer program-related inventions which consist of a method for performing business to be not patentable, even if a technical contribution exists.[618] According to German case law, it had been assumed that the patentability of

610 T 0411/03, GRUR Int. 2006, 851, 853 – Microsoft.
611 T 0411/03, GRUR Int. 2006, 851, 853 – Microsoft.
612 Schulte/Moufang, PatG mit EPÜ, § 1 No. 156.
613 Benkard/Melullis, EPC, Art. 52 No. 219.
614 Busse/Keukenschrijver, PatG, § 1 No. 75.
615 Benkard/Jestaedt, EPÜ, § 64 No. 29-43.; as for the German practice, see Schulte/Kühnen, PatG mit EPÜ, § 139 No. 6.
616 Krieger, Albrecht, Wann endlich kommt das europäische Gemeinschaftspatent? – Zwei Brüder als Kämpfer für den Schutz des geistigen Eigentums in Deutschland, in Europa und in der Welt, GRUR 1998, 256, 259.
617 Benkard/Jestaedt, EPÜ, § 64 No. 29.
618 Merrill Lynch [1989] RPC 561 (Court of Appeal). There also exists divergence with regard to the form of possible claims allowable. The U.K patent office and German court allow program product claims in the form approved in the EPO Board of Appeal decisions Computer program product I and II, see T1173/97, OJ 1999, 609 (EPO 1998) and T0935/97, N. Publ.(EPO 1999), where an additional "technical contribution" is required. The Netherlands

business methods having a technical aspect was allowable, even if the only technical contribution that exists is non-technical.[619] This is illustrated by the cases of "*Automatic Sales Control*"[620] and "*Speech Analysis Apparatus*"[621]. Although the German Federal Supreme Court later clarified its interpretation by determining that the adequate approach is the one followed by the EPO Board of Appeals, specifically that an inventive technical contribution is decisive for the requirement of the inventive step, the earlier decisions still serve as an example of how legal interpretation may result in major changes to the scope of patentability at the national level.[622] Addressing this situation, the European Commission presented a proposal in 2002 for a Directive on the Patentability of computer-implemented inventions.[623] The major goal of this proposal was to harmonize national patent laws with respect to the patentability of computer-implemented inventions by making the conditions of patentability more transparent. Any sudden change in the legal position, in particular any extension of patentability to computer programs "as such" should be avoided.[624] The draft provoked much criticism from opponents of extensive patent protection.[625] When the directive was voted on by the European Parliament on September 24, 2003 numerous amendments were introduced which reflected concerns from diverse backgrounds. Opponents of the directive claimed that the proposal would introduce U.S.-style regimes on behalf of large companies that were able to acquire unlimited software patents. Further, the directive would open the door to trivial patents after the

patent office, by contrast, allowed a claim to computer software without any additional contribution outside the computer, stating that already the download of software on the computer creates a technically distinct machine, see Netherland Patent Office CR 1986, 541; CR 1988, 29. This conclusion, however, is contrary to Art. 52 II EPC that prohibits the patentability of computer programs "as such", see Benkard/Melullis, PatG, § 52, No. 189.

619 Nack, Ralph, Sind jetzt computerimplementierte Geschäftsmethoden patentfähig?, GRUR Int. 2000, 853.

620 Federal Patent Court, 32 IIC 328 (2001) – Automatic Sales Control (Automatische Absatzsteuerung).

621 BGH, 33 IIC 343 (2002) – Speech Analysis Apparatus (Sprachanalyseeinrichtung).

622 BGH 33 IIC 232 (2002) – Logic Verification (Logikverifikation); Benkard/Melullis, EPÜ, Art. 52 No. 209.

623 Proposal for a Directive of the European Parliament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002; an overview is provided by Kraßer, Rudolf, Patentrecht: ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 166-171. See also Nack, Ralph, Die patentierbare Erfindung unter den sich wandelnden Bedingungen von Wissenschaft und Technologie, München 2002, 268.

624 Proposal for a Directive of the European Parliament and of the Council on the patentability of computer-implemented inventions, COM(2002) 92 final of 20.2.2002, 11.; Nack, Ralph, Die patentierbare Erfindung unter den sich wandelnden Bedingungen von Wissenschaft und Technologie, München 2002, 271 argues that the principles set forth by the Technical Board of Appeals of the European Patent Offices should be applied, but the prohibition to patent computer programs as such abolished.

625 The Foundation for a Free Information Infrastructure (FFII) is leading a campaign against the directive, claiming it would establish a 'situation comparable to the U.S.'.

U.S. example, such as Amazon's 'one-click' method.[626] On July 5, 2005, the European Parliament, however, finally rejected the initiative. As a response to the rejection, the European Commission declared that it would not attempt to submit any more proposals related to the issue.[627]

ii. Classification of *In-Silico* Screening Methods in Europe

As stated earlier, the EPO accepts the patentability of Claim 1[628] to the *in-silico* method, arguing that an algorithm for the simulation of a 3-D protein represents a technical contribution through the use of technical data. The reasoning, however, fails to explain why an algorithm is meant to be a technical contribution. Particularly in light of the fact that neither the statutory background, nor the existing case law provides an unambiguous definition of what is understood as technical contribution, it is beneficial to consider the EPO analysis more closely. This requires a more comprehensive analysis of the invention as such that goes beyond the aspects of computer-implementation. In addition, a more precise determination of patentability requirements is necessary. The questions that arise are the following: Why does the claim at issue in an *in-silico* method establish a technical contribution sufficient for patentability? Why is it considered more than "mere technical data" or "abstract ideas", both of which would be excluded from patentability under Art.52 II (a) EPC? To find an answer to these questions, the fact that an *in-silico* claim belongs to the field of bioinformatics is of major importance. As explained earlier, bioinformatics refers to the use of computing methods to study biological processes. An *in-silico* claim visualizes a biological process, namely the creation of a protein-ligand complex and thus is covered by this category.[629]

The EPO's analysis does not address the biological aspects that are included in the claim. It merely stresses that the claim includes the use of data for computerized compound libraries. Hence, the patent office only emphasizes the computer-related aspects of the claim, but does not take into account that the data relates to a molecular biological process. The latter, however, is a central characteristic of the invention. The question of whether the invention establishes a technical contribution can-

626 Schulte/Moufang, PatG mit EPÜ, § 1, No. 161.

627 FAZ of July, 6, 2005, S. 13 (Nr. 154); TAZ of July 7, 2005, S. 8 (No. 7709).

628 A method of identifying compounds that can bind to a protein P, comprising the steps:
a) The application of a 3-dimensional molecular modelling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P; see European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10.

629 Chapter 3 B III.

not be assessed without referring to the biotechnological nature of the claim. An *in-silico* screening method demonstrates the protein's ability to bind with certain compounds and thereby particularly refers to the protein's function. As explained in Chapter II, proteins perform a wide variety of functions, such as to provide catalytic activity or (in the case of receptor proteins) to detect chemical signals.[630] Since these functions define the characteristics of the biological binding process, they are critical elements of the *in-silico* method. Biological functions related to proteins typically control a wide range of processes in the living organism. The computer-based visualization of a biological function translates and transfers a biological mechanism (that is, a technical effect) into a virtual space, where the (*in vivo*) technical effect is reproduced *in silicio*. The biological function is performed independently from the computer software. The computerized protein of the claimed method *in-vivo* performs a particular biotechnological effect by binding compounds or regulating inhibitor activity. Hence, a significant effect is present outside the software-hardware relationship of the computer. Biological functions related to proteins thus must be considered "further technical effects which go beyond the normal physical interaction between software and hardware" as required under the standards developed by the EPO. [631]

Therefore, patent examiners and courts should examine bioinformatic claims, such as the one at issue directed to an *in-silico* method, in light of the simulated biological process. The patent law system should consider *in-silico* methods patentable subject matter, provided that the computerized molecule *in-vivo* performs a significant biological function. In summary, the author agrees with the EPO's decision to accept the patentability of *in-silico* methods (Claim 1). Rather than to exclusively focus on the question of whether the computerized data is used for the screening of other computerized databanks, the analysis of an *in-silico* claim should take into account the underlying biological process. If measurable biological effects exist, these should be considered adequate to establish patentability.[632]

630 Chapter 2 B.

631 T 1173/97, Computer program product/IBM, OJ 1999, 609, 618; also T 641/00, Two Identities/COMVIK, OJ 2003, 352, 356, see also T 935/97 Computer program product, RPC 1999, 861; T 931/95, Steuerung eines Pensionssystems, OJ 2001, 441; T 258/03, Auction method/Hitachi, OJ 2004, 575, 585; T 411/03 GRUR Int. 2006, 851 – Microsoft.

632 Masuoka, Kunishisa, Ways of Protecting New Technology Related Inventions in the Life Science Field, IIP Bulletin 2003, 28-34, 32. It is also suggested that the novelty of an in-silico screening process is assessed on grounds of the underlying information. Bearing technical significance, information on new tertiary protein structures should thus be considered positive element for the creation of novelty.

As for the USPTO's statement, the Office confirmed the patentable subject matter due to the *State Street*[633] rationale. Under this doctrine, an invention must comply with the technological arts. To the extent that the invention is nonobvious, technological contribution is not required. The mere fact that the invention uses a computer or software is sufficient to bring it within the technical art if it also provides a "useful, concrete and tangible result".[634] Thus, a particular technical contribution provided by the invention is not required. The case of *State Street Bank & Trust Co. v. Signature Financial Group Inc.* referred to a business method which was performed with the aid of a computer. [635] Concerning this matter, the court held that three categories of subject matter are not patentable: laws of nature, natural phenomena, and abstract ideas. Consequently, mathematical algorithms as mere abstract ideas are not patentable inventions. However, once an algorithm is applied, it becomes a patentable invention if it generates tangible results.[636] In *Diamond v. Diehr*[637], the Court had determined that "certain types of mathematical subject matter, standing alone, represent nothing more than abstract ideas until reduced to some type of practical application."[638] Hence, a mathematical algorithm must be applied in a "useful way". Applying *Diamond*, the court in *State Street* held that such a useful practical application of an abstract idea is achieved provided it produces "a useful, concrete and tangible result".[639] As to the claim at issue, it must be determined whether "the mathematical algorithm is directly or indirectly recited". If a mathematical algorithm is found, it must then be decided whether it is "applied in any manner to physical elements or process steps".

The claim at issue considers a method that involves a simulated protein. The polypeptide is based on algorithm data that determine the 3-D folding structure. Being an applied algorithm and producing a useful, concrete and tangible result, the *in-silico* method falls within the *State Street* doctrine and therefore constitutes a patentable subject matter.

The USPTO rejected the claim for lack of utility, because the description does not indicate whether there is a correlation between binding activity and activation of

633 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368 (Fed. Cir. 1998).

634 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1372.

635 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1373; In re Lowry, 32 F.3d 1579 (Fed. Cir. 1994) (claim to data structure stored on a computerreadable medium which increases the efficiency of the computer is held to be statutory subject matter), In re Warmerdam, 33 F.3d 1354 (Fed. Cir. 1994) (claim directed to data structure per se held nonstatutory subject matter if data structure did not cause functional change in computer)

636 State Street Bank & Trust Co. v. Signature Financial Group Inc, 149 F. 3d 1368, 1375.

637 Diamond v. Diehr, 450 U.S. 175, 182 (1981).

638 In re Alappat, 33 F.3d 1526, 1557 (Fed. Cir. 1994).

639 Diamond v. Diehr, 450 U.S. 175, 182.

protein P. Thus, the Office requires the indication of a pharmaceutical effect. The need for a particular pharmaceutical effect to comply with the utility requirement had already been established in the context of the patentability of *in vitro* screening methods. Certainly, the final drug design must be considered "useful". In the context of mass screening of expansive compound libraries – as the first step in discovering the lead compound for a new drug – the only demonstrated activity of the lead compound is a mere binding affinity to the *in vitro* or computerized receptor.[640] This binding activity is essential for the determination of a "practical use", i.e., the pharmaceutical effect of a screened compound.[641] In *Cross v. Lizuka*[642] the Court of Appeals for the Federal Circuit held that the mere inhibition of an enzyme by a compound was enough to establish a "practical use".[643] In *Cross*, however, the applicant provided exact experimental data regarding the inhibition process that included information subject to the correlation of binding activity and activation, which is essential for the binding process. The specification explained the following:

> "The imidazole derivatives … of this invention are novel compounds which are not described in literature, and which possess a strong inhibitory action for thromboxane synthetase from human or bovine platelet microsomes, and which exhibit a strong inhibitory action for biosynthesis or thromboxane A sub2 in mammalia including human. In general, a satisfactory inhibitory effect is found at a level of molar concentrations of 2.5 x 10-8, for example, 2-[p-(1-imidaoylmethyl) phenoxy]-acetic acid hydrochloride produce the about 50% inhibitory effect at the molar concentration of 2.5 x 10-8. Accordingly, the imidazole derivatives of this invention are extremely useful as therapeutical medicines for diseases caused by thromboxane A sub2, such as inflammation, hypertension, thrombus, cerebral apoplexy, asthma, etc."[644]

Based on this information, the court found that the screened compounds provided sufficient data to comply with the utility requirement.[645] The claim at issue, by contrast, lacks any experimental data and thus cannot provide any "practical use". The *in-silico* method itself, which is described by the claim language, only provides hypothetical information. The applicant had to provide additional *in vitro* testing in order to verify that the underlying technical problem of finding useful agents indeed had been solved.[646] The given specification does not disclose any working examples. It should provide more information pertaining to the actual screened compound and not only to the method itself.

As to enablement, the USPTO stated that the given claim does not satisfy the "how to make" prong of 35 U.S.C. § 112. The factors the USPTO considers with regard to enablement follow the principles the Federal Circuit developed in *In re*

640 Ducor, Phillippe, New drug discovery technologies and patents, 22 Rutgers Computer and Technology law journal (RUCTLJ) 1996, 369, 425.
641 Ducor, Phillippe, New drug discovery technologies and patents, 22 Rutgers Computer and Technology law journal (RUCTLJ) 1996, 369, 425.
642 Cross v. Lizuka 753 F.2d 1040 (Fed. Cir. 1985).
643 Cross v. Lizuka 753 F.2d 1040, 1046.
644 Cross v. Lizuka 753 F.2d 1040, 1044.
645 Cross v. Lizuka 753 F.2d 1040, 1049.
646 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 145.

Wands.[647] The enablement standard developed in *In re Wands* includes the quantity of experimentation necessary to practice the claimed invention, the amount of guidance presented in the specification, the presence or absence of working examples, and the predictability or unpredictability of the art.[648]

In addition, the Federal Circuit in *University of Rochester v. G.D. Searle & Co* established the principle that even if a three-dimensional structure of a protein is known it is not possible for an ordinary skilled person to predict a candidate compound for the binding pocket without undue experimentation.[649] The court stated that this could be different in a case based on the complementariness of a nucleic acid and a protein. In non-genetic situations, that correspondence could be less clear. In this context, the Federal Circuit reasoned:

> "Given the sequence of a single strand of DNA or RNA, it may therefore have become a routine matter to envision the precise sequence of a "complementary" strand that will bind to it. (…). Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them."[650]

Since the specification does not teach the use of potential candidate compounds which respond to the computerized screening method, the "how to use" prong of Section 112 is not satisfied, either. A strong correlation exists between the "how to use" prong of the enablement requirement and the requirement for a disclosure of practical utility found in 35 U.S.C. § 101. This principle has been confirmed in various decisions.[651]

The claim does not meet the threshold requirement of clarity and precision under 35 U.S.C. Section 112, second paragraph. Since the potential candidate compounds are not being included in the claim language, the application does not describe the particular subject matter of the invention. The scope of the invention sought to be patented is the finding of lead compounds as one step of the screening process. The claim only refers to the application of the algorithms in order to simulate the three-dimensional structure and to the potential screening of binding compounds. The ac-

647 In re Wands, 858 F.2d 731 (Fed. Cir. 1988).

648 In re Wands, 858 F.2d 731, 731.

649 University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 925 (Fed. Cir. 2004).

650 University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 925. Actually the court set its argument in the context of the written description factor. However, since there is a "significant overlap" between both requirements, the statement can also be applied with regard to enablement, University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916, 921 (citation omitted).

651 Process Control Corp. v. Hyd Reclaim Corp., 190 F.3d 1350, 1358 (Fed. Cir. 1999) ("If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement."); In re Brana, 51 F3d 1560, 1569 (Fed. Cir. 1995) (classifying practical utility as an implicit requirement of the enablement provision); Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) (clarifying that if the subject matter of a patent is inoperable, then the patent may fail to meet both the utility requirement and the enablement requirement).

tual binding process is not part of the claim language. In *In re Wiggins* the Federal Court concluded that

> "If the scope of the invention sought to be patented is unclear from the language of the claim, a rejection will lie under the second paragraph of 35 U.S.C. 112"[652]

The USPTO further rejects the claim for rendering the invention obvious under Section 103. The office applied the "Examination Guidelines for Computer-Related-Inventions" of February 28, 1996[653], which describe computerized data as falling between "functional descriptive material" and "non-functional descriptive material". The Guidelines define "functional descriptive material" as "data structures and computer programs, which impart functionality when encoded on a computer-readable medium." "Non-functional descriptive material, in contrast, "includes but is not limited to music, literary works and a compilation or mere arrangement of data". As to obviousness, the Guidelines state:

> "[A] rejection of the claim as a whole under § 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. Non-functional descriptive material cannot render non-obvious an invention that would have otherwise been obvious."[654]

The guidelines further provide:

> "[A] process that differs from the prior art only with respect to non-functional descriptive material that cannot alter how the process steps are to be performed is not sufficient to achieve the utility of the invention."[655]

The principles applied by the USPTO correspond with existing case law of the CAFC. In *In re Gulack,* the court stated that when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability.[656] In *Ex parte Carver,* by contrast*,* the court characterized the given material as "functionally-descriptive, because the signals at issue were used to actuate and control sound recording responsive device structure to produce the appellant's disclosed acoustic phenomena.[657]

From a comparative point of view, the USPTO maintains a stricter approach than the EPO. Although both the U.S. and the European patent offices classify the claim as computer-implemented invention, the USPTO concludes that the claim must be rejected for rendering the invention obvious. The Office argues that the 3-D protein data is fed to an algorithm that is already state of the art. Absent any alteration or modification of the algorithm, the office concludes that the invention is obvious.

652 In re Wiggins, 488 F.2d 538, 541 (C.C.P.A. 1973).
653 Examination Guidelines for Computer-Related-Inventions, [Federal Register: February 28, 1996 (Volume 61, Number 40) 7478-7492, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
654 Examination Guidelines for Computer-Related-Inventions, VI, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
655 Examination Guidelines for Computer-Related-Inventions, VI, available at: http://www.kuesterlaw.com/swguide.htm, last checked on January 21, 2008.
656 In re Gulack, 703 F.2d 1381, 1385 (Fed. Cir. 1983).
657 Ex parte Carver, 227 USPQ 465, 470 (Bd. Pat. App. & Int. 1985).

Given that there is no functional relationship between the data and the algorithm, the office considers the 3-D protein structure non-functional descriptive data.

Is such a classification, however, adequate for an obviousness standard in the field of bioinformatics? [658] Pursuant to 35 U.S.C. § 103, a patent claim is rejected "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains".[659] The statute clearly states that the invention must be considered "as a whole." The inventions at issue, however, do not only refer to the data itself. Rather, they include the simulation of a complex biological process, namely the emulation of a protein and of its binding ligands. They not only establish the descriptive data as such, but also the imitation of a biological operation performed by such data. One could argue that the USPTO fails to sufficiently take into account these biological features expressed by the data, and, consequently, does not consider the patented subject matter "as a whole."

For an evaluation of the entire invention, the key question must be whether a person skilled in the art is able to (a) predict the protein-ligand complex and (b) simulate it through the claimed *in-silico* method without involving inventive activity. In the claim at issue, the prior art does not include any similar *in-silico* screening method. In addition, the data necessary to simulate the protein by applying the algorithm must be obtained through extensive *in-vitro* testing. Consequently, neither part (a) nor part (b) of the above question can receive a positive answer, implying that the claim would not render the invention obvious. Against this background, it appears reasonable to argue that the claim should be accepted under the U.S. patent law system.

b) Claim 2

Claim 2 of the set of claims being directed to "*in-silico* screening methods" reads as follows:

> A method of identifying compounds which can bind to protein P by comparing the 3-D structure of candidate compounds with a specific 3-D molecular model which comprises the following steps:
>
> The given 3-D molecular model shows the positions of heteroatoms in the amino acids building out of the binding pockets of protein P (i.e., amino acids 223, 224, 227, 295, 343, 366, 370, 378, 384) wherein said hydrogen bonds can form hydrogen bonds with hydrogen bonding functional groups in a candidate compound.

658 Vorndran, Charles/Florence, Robert L., Bioinformatics: Patenting the Bridge between Information Technology and the Life Sciences, 93 IDEA - The Journal of Law and Technology 2003, 93, 121.

659 Chapter 3 A II 4 a.

Steps (1) through (n) describe a data processing method in which

(a) the coordinate data of the 3-D molecular model is input in a data structure such that the interatomic distances between the atoms of protein P are easily retrieved.

(b) the distances between hydrogen-bonding heteroatoms of different candidate compounds and the heteroatoms that form the binding pocket in the 3-D molecular model are compared thereby allowing the identification of those candidate compounds which would theoretically form the most stable complexes with the 3-D molecular model binding pockets of protein P, based on optimal hydrogen bonding between the two structures.[660]

aa) Background

Protein P is an established protein whose amino acid sequence is also clear. The description explains that the activity of protein P was previously known to result in lowering blood pressure. The description gives the atomic coordinates of protein P as a co-crystal with its natural ligand, and gives a logical explanation that the active residues in the binding pocket of protein P consists of specific and determined amino acids. The description demonstrates how the 3-D molecular model incorporates the 3-D structure of the binding pocket. It provides working examples of the claimed methods in which a number of compounds are identified. It also provides experimental data of the actual binding affinities of the compounds identified. Pursuant to that data, a skilled person would infer that the claimed method may be used to identify a number of compounds which bind sufficiently to protein P such that a biological effect results. No prior art suggested the 3-D coordinates of protein P. However, the prior art included *in-silico* screening programs that compare the 3-D structure of candidate compounds with the 3-D molecular model of the binding pocket of a protein of interest. Prior art also demonstrates the method of storing coordinates data to optimize the interatomic distance information.[661]

bb) Patent Offices' Analysis

The EPO states that the invention disclosed is patentable. The claim refers to a method having a link to a technical contribution that is characterized by technical features. This activity is not regarded as a presentation of information or as a pure mathematical method, excluded by Art. 52(2)(d) or (a) of the EPC, respectively, but rather as the use of the structural data. Because the description reports experimental

660 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10ff.

661 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 11ff.

data that includes information about identified compounds, the requirements of clarity, enablement and support are satisfied. Novelty, inventive step, and industrial application are present, since the prior art did not disclose or suggest the 3-D coordinates of protein P. The claimed method is considered to be novel, nonobvious and industrially applicable.[662]

The USPTO also agrees that a patentable subject matter is given. In addition, the utility requirement of the claimed methods is satisfied, since the utility of the candidate compounds identified through screening is also provided. With regard to the enablement factor, the USPTO differs from the EPO. The Office held that the specification adequately described and enabled one skilled in the art to make the claimed method of screening, by virtue of working examples that identified compounds that bind to protein P. The working examples provide sufficient guidance regarding the screening program. In addition, they show the effectiveness of the screening program in using the disclosed 3-D coordinates of protein P to identify ligands binding with sufficient affinity such that a biological effect would be expected by one skilled in the art. With respect to the "how-to-use-prong" of the enablement requirement, the specification demonstrates that protein P, when active, lowers blood pressure. However, there is no indication as to whether there is a correlation between binding activity and the modulation of blood pressure. The USPTO, nevertheless, states that if compounds binding protein P could be used to modulate blood pressure without undue experimentation, the claimed method would comply with the enablement requirement of 35 U.S.C. § 112.[663]

The Office further concluded that the claim can be considered novel. The claims are obvious with regard to the prior art if the claimed data-processing method used to identify compounds that can potentially bind protein P, i.e., steps (1) through (n), would have been obvious to one skilled in the art. Consequently, the claimed method would have been *prima facie* obvious over the prior art because steps (1) through (n) appear in the prior art methods.[664]

662 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

663 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 73.

664 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 74f.

cc) Discussion

The *in-silico* methods of Claim 2 differ from the prior *in-silico* related invention (Claim 1) in two ways. First, the language of Claim 2 includes information related to identified compounds which are defined by size and shape. Second, the description provides particular working examples that report the specific binding process. Thus, the differences are all related to compounds that respond to the screening process. Both offices treat the claim slightly differently than Claim 1. The EPO accepts the claim due to the working examples that are reported in the description. Sufficient disclosure (Art. 83 EPC) and support (Art. 84) requirements are thus met. The USPTO concurs with the EPO regarding the written description and enablement requirement, but maintains its divergent view regarding the definition of algorithms data as non-functional data. Therefore, the USPTO rejects the claim due to obviousness.

Yet, the results being developed by both offices must be reconsidered. The question of whether the applicant is allowed to claim protection for the compounds that can be identified by a screening process has been the subject of various discussions, in particular in the context of "reach-through" claiming. Reach-through claiming refers to claim language which is broad enough to dominate future compound discoveries that can be used for rational drug design.[665] With regards to the claim at issue, it remains to be established whether it fulfills the currently required measurements of case law. A series of decisions in biotechnology cases developed a very demanding written description requirement and a high standard for enablement. The claim at issue cannot be considered a typical reach-through claim. The applicant does not simply claim all molecules performing the function of binding the receptor, without providing any information regarding the structure of the ligand. By contrast, the claim provides theoretical information about the size and shape of binding sites of the computerized method and of responding compounds, which are based on protein analysis techniques such as protein crystallization. Thus, the claim reports a description of the structure necessary to complete the entire screening. The strategy followed by the patent claimer certainly succeeds in overcoming reach-through claiming problems. Nevertheless, recent decisions of the Federal Circuit as well as of the Technical Board of Appeal have taken a very severe approach toward claim scope. In addition, it was previously demonstrated that one panel at the Federal Circuit Court ruled in favor of a demanding written description requirement. The currently required high standards for enablement establish high demands for developers of *in-silico* methods, regardless of whether the illustrated dispute can be decided on behalf of such a separate obligation. Thus, the drafting method of the claim at issue is fraught with a number of scientific and legal hazards. Even though the applicant provides working examples which prove that his speculations regarding the structure of functional ligands are correct, the prior art may bear surprises rendering the patent

665 OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

invalid. A broad claim to a set of compounds lacks novelty even if a single member of the genus was reported in the prior art. This principle applies even if the properties of the prior art compound causing it to fall within the scope of the claim were merely inherent, and not reported. Provided only one prior art ligand bears the shape and size demonstrated by the claim, and therefore responds to the *in-silico* protein, the patent is invalid. Many molecules have been reported by prior art, but relatively few have been defined by size and shape. Straight-forward searches are rarely able to identify compounds falling within the scope of claims that are defined in terms of fit within a reported binding pocket.[666]

Finally, it must be stressed that patentability on *in-silico* screening methods can only succeed in relation to the patentability of the target used in the method. The entire screening method is not completed until the compound is identified. The discovery of a new receptor, however, is the key ingredient of the screening method; the other steps are merely routine.[667]

2. Structural Data of proteins per se

a) Claims and Claim Background

Another method of drafting claims in proteomics is to refer to the 3-D structural data of the protein *per se.* The claims of the trilateral study WM4 concerning 3-D structural data of the protein *per se* read as follows.

> Claim 1:
>
> A computer model of protein P generated with the atomic coordinates listed in a specific figure.
>
> Claim 2:
>
> A data array comprising the atomic coordinates of protein P as set forth in Fig. 1 which, when acted upon by a protein modeling algorithm, yields a representation of the 3-D structure of protein P.
>
> Claim 3:
>
> A computer-readable storage medium encoded with the atomic coordinates of protein P as shown in Fig. 1.

The specification classifies protein P as novel. Experimental data is provided and it is explained that the protein, when active, lowers blood pressure. The pro-

666 Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225.

667 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 144.

tein modeling algorithms are well known in the prior art. The description provides the atomic coordinates of protein P, and asserts that the coordinates can be used for *in-silico* screening methods. The prior art does not include any reference that teaches or suggests protein P.[668]

b) Patent Offices' Analysis

As for claim 1, the EPO reasons that a computer model is not considered to be a patentable invention, since it merely presents the atomic coordinates of a single protein molecule as such. The model does not offer any technical problem solution and does not provide any further technical effect. Consequently, the claim at issue does not meet the requirements of a patent-eligible subject matter under Art. 52(2)(d) EPC, which excludes presentations of information from patentability. Further, the EPO states that the claimed invention does not provide sufficient information for an adequate prior art search. Consequently, a search cannot be carried out under Art. 54 EPC. Hence, it is not necessary to examine whether such a prior art search would identify any references that demonstrate or suggest protein P.[669]

With regard to Claim 2, the EPO states that the claimed invention cannot be considered as a patentable subject matter, since a data array is a mere presentation of information and excluded under Art. 52(2)(d) EPC.[670]

As for Claim 3, the EPO states that a storage medium does not qualify for a patent-eligible subject matter pursuant to Art. 52(2)(d), because it only determines the atomic coordinates of a single protein molecule in space, without providing a particular technical character. The data merely includes cognitive content in a generalized manner.[671] The EPO notes that the claim is distinct from cases in which the Technical Board of Appeals had acknowledged computer storage to be patentable. In con-

668 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 7.

669 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 34.

670 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 34.

671 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 35.

trast to the claim at issue, the particular data referred to a computer program with a further technical effect.[672]

The USPTO holds that Claim 1 is not tangibly embodied and thus must be considered as non-functional descriptive material *per se*. Since descriptive material is considered as an abstract idea, the claim at issue cannot be acknowledged as patentable subject matter pursuant 35 U.S.C. § 101.

As to Claim 2, the USPTO states that it is directed to a mere compilation or arrangement of data. With the 3-D coordinates consisting of non-functional descriptive material without physical structure, they must be interpreted as abstract ideas which do not qualify as patentable subject matter. See *In re Warmerdam*[673], where the court stated that descriptive material *per se* is not patent-eligible subject matter. As to the specification, the decisive element is that the atomic coordinates of protein P can be used for *in-silico* screening methods. Presupposing that the identified compounds can provide a specific, substantial, and credible utility, the claim at issue meets the utility requirement. However, such a specific, substantial, and credible utility cannot be acknowledged when the correlation between binding activation and compounds binding protein P are not disclosed. The specification only determines that protein P, when active, lowers blood pressure. It fails to provide any detailed information regarding binding activity or inhibitor regulation. A sufficient disclosure must include information about how the compounds can be used. Their use could either be directed to a stimulation of proteins P's activity to reduce blood pressure, or, in cases of hypotension, to an inhibition of the activity of protein P causing an increased blood pressure. Absent of any of these assertions, a specific, substantial, and credible utility is not acceptable.[674] The enablement requirement is satisfied. Based on the disclosure that protein modeling algorithms are well known in the art, and the complete description of the atomic coordinates of protein P, claims 1 and 2 are enabled for how to make the claimed method and are adequately described.

The how-to-use prong is not satisfied by the disclosure, unless the patent specification provides information regarding the binding activity or inhibitory regulation amounting to a specific, substantial, and credible utility. Regarding enablement, the patent description must teach one skilled in the art to use the claimed invention without undue experimentation.[675]

672 T 1173/97, OJ 1999, 609, the EPO applied its guidelines, see Guidelines for Examination in the EPO, Part C-IV.2

673 In re Warmerdam; 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1760 (Fed. Cir. 1994).

674 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 63.

675 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 63.

With regard to Claim 3, the USPTO maintains that the structural data of protein must be considered non-functional descriptive material because the claimed invention only refers to protein data stored on a computer-readable medium. It is merely stored so as to be read by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes carried out by the computer. Thus, the 3-D coordinates do not impart functionality to either the data or the computer. With non-functional descriptive material being stored in a computer-readable medium as an abstract idea, it cannot be defined/classified as patent eligible subject matter pursuant to 35 U.S.C. § 101.[676] As mentioned above, the specification does not include any functionality related to either the data or the computer, and therefore must be understood as non-functional descriptive material. Descriptive material that is not functionally related to the substrate does not distinguish the invention from the prior art for patentability purposes.[677]

c) Discussion

In contrast to the treatment of *in-silico* methods, the EPO rejects the claims for lack of a further technical effect. The USPTO again classifies the claims as merely including non-functional descriptive material and rejects the claims due to obviousness. Applying the reasoning established in *In re Warmerdam*, the USPTO concludes that no patentable subject matter is established. The question in *In re Warmerdam* is whether the claim directed to a specific data process goes beyond the simple manipulation of abstract ideas. Absent any such effect, no patentable subject matter could be acknowledged.[678]

The approach taken by both patent offices is consequent in light of their general practices regarding the treatment of databases.[679] Nevertheless, scientists could ar-

676 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64.

677 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 64.

678 In re Warmerdam , 33 F.3d 1354, 1361.

679 In Europe, investment in the compilation of the data might be protected under sui generis rights. The use of a considerable amount of data will only be allowed with the permission of the database owner. In practice, access to these databases will be subject to payment of a licensing fee. Due to a lack of originality, the data as such, i.e., the mere sequence as pieces of written information, are not protectable under copyright. Consequently, the information of the sequences may be used freely, see Bostyn, Sven J.R., Living in an (im)material world: bioinformatics and intellectual property protection, 01 Journal of International Biotechnology Law 2004, 2-10; 54-61, 59. For a precise and detailed overview of German and international approaches to database protection see further Nack, Ralph, Nationaler und internatio-

gue that the patent offices do not sufficiently take into account biophysical concepts, such as the importance of non-covalent bonds,[680] native vs. denatured states of proteins, etc. Patent offices allow patents on standard chemical formulae which are, in fact, merely 2-D coordinates of molecules combined together with some standard rules of chemical connectivity. 3-D coordinates of proteins, by contrast, are not deemed to be patentable, although they too demonstrate standard rules of chemical connectivity between the atoms. From a legal perspective, the offices distinguish between computer storable data and the established chemical practice to determine compounds by a chemical formula. From a scientists' perspective, however, it appears that the dimensionality (i.e., 1-D, 2-D, 3-D) in which the coordinates are represented determines the patentability of a molecule.[681]

3. Compounds identified by *in-silico* screening methods

Advances in proteomics resulted in the discovery of great numbers of new protein "targets". Due to new computerized methods, compound libraries could be increased in size. Progress in the development of screening assays, particularly "high-throughput screening" technologies (HTS)[682], enables scientists to screen such libraries for their potential protein targets and effects within a very short time.[683] The design and development of screening methods, which must be considered as research tools, is generally time-consuming and expensive.

Furthermore, economic value emerges only after years of investment and only in the case that the development of a new drug succeeds. The use of the screening target is usually made at a stage in which further steps of drug design are not yet foreseeable.[684] If the sale of the pharmaceutical is successful, however, high revenues

naler Rechtsschutz von Datenbanken (Q182), GRUR 2004, 227. The treatment of data through mechanism other than patent law is no major subject of this study.

680 Covalent bonds arise as a result of the sharing of one or more pairs of bonding electrons.

681 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 203.

682 A "high throughput screening" is a computerized technique of rapidly searching for molecules with desired biological effects from very large compound libraries (up to 60,000 per day), see Burke, Adrienne J., Blowing a Path for HTP Proteomics, Genome Technology 2003, 24, 24; Bader, Joel S./Chaudhuri, Amitabha/Rothberg, Jonathan M./Chant, John, Gaining confidence in high-throughput protein interaction networks, 22 Nature Biotechnology 2004, 78.

683 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen? Mitteilungen der deutschen Patentanwälte 2003, 57, 58.

684 See Figure 8 at Chapter 2 E III 3.

can be expected. It is thus understandable that the owners of research tools are interested in receiving a share of such profits.[685]

Inventors attempt to protect the products they develop with the help of their research tools, such as *in-silico* methods, by including the identified compounds in the claim language.

a) Claims

A claim involving the described method may be drafted as follows:

> Compounds[686] identified by
>
> A method of identifying compounds that can bind to a protein P, comprising the steps of:
>
> a) The application of a 3-dimensional molecular modeling algorithm to the atomic coordinates of protein P to determine the spatial coordinates of the binding pocket of protein P.
>
> b) The electronic screening of the stored spatial coordinates of a set of candidate compounds against the spatial coordinates of the protein P binding pocket with the goal of identifying compounds that can bind to protein P.[687]

b) Patent Offices' Analysis

The EPO holds that the claim meets the requirement of a patentable subject matter since it refers to identified compounds. When the claimed invention does not provide enablement over the entire range of claimed embodiments, the requirement of sufficient disclosure is not met. A prior art search is limited to the example provided by the description.[688] The invention cannot be considered novel, since the natural ligand is already state of the art and thus prejudicial to novelty.

685 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 58.

686 Claim 2 of the same case.

687 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 10. Another U.S. patent No. 6,083,711 entitled "Proteases compositions capable of binding to said site, and methods of use thereof" covers compounds screened by 3-D in-silico structure defined by structural coordinates, see Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225.

688 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 37.

The USPTO concludes that Claim 2 refers to a statutory subject matter. The claim only satisfies the utility requirement of 35 U.S.C. § 101 if the specification teaches that the binding compounds may be used to either stimulate activity of protein P to reduce blood pressure, or in cases of hypotension, inhibit the activity of protein P to cause an increase in blood pressure. Nevertheless, the claim must be rejected, both due to a lack of enablement and of a sufficient description under the principles developed in *Regents of the University of California v. Eli Lilly*.[689] Since one skilled in the art would come to the conclusion that the inventors were not in possession of the claimed invention, the claim fails to comply with the written description requirement. It is not sufficient that the claim at issue is directed to a "compound identified by an in-silico method"; rather the claim language has to include specific structural or functional characteristics.[690]

The USPTO further determines that the claim does not comply with the enablement requirement for the "how-to-make" prong of 35 U.S.C. § 112, first paragraph. The patent lacks a disclosure of any particular structure for the claimed compound. The specification does not provide any guidance or working example in this unpredictable art. Thus, an artisan would not have been unable to make the claimed compound without undue experimentation. An assay for finding a product is not equivalent to a positive recitation of how to synthesize such a product. The USPTO maintains that the claimed invention does not comply with the "how to use" prong of 35 U.S.C. § 112, first paragraph. The specification does not show how to administer the claimed compound so as to effect a viable blood pressure treatment regimen. Treatment/administration protocols depend upon the nature of the compound being administered as well as the clinical condition of the patient. In the absence of additional information, a skilled person would not have been able to use the undisclosed compound(s) for treatment without undue experimentation.

As for novelty, Claim 2 is rejected as anticipated by the prior art compound, particularly if a search yielded one of the compounds tested experimentally in the specification. It would be rejected as being anticipated, or rendered *prima facie* obvious by the prior art under two conditions. First, the prior art demonstrates agonists or antagonists of protein P, and second, the examiner can provide evidence to support the judgment that prior art compounds inherently fall within the scope of the claim.[691]

With regard to the written description requirement, the USPTO holds that the claim at issue is directed to a genus of compounds identified by the method of Claim 2. Moreover, the specification discloses at least some examples of the structure of compounds within the scope of the claim. Nevertheless, there is no evidence of a

689 Regents of the University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997).

690 Regents of the University of California v. Eli Lilly, 119 F.3d 1559.

691 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 76.

structure/function relationship *per se* between the disclosed compounds and any others that might be found using the claimed method. Structurally identified characteristics of the genus members are not disclosed. Thus, the claimed invention is not supported by a sufficient written description. The rejection might be overcome with a demonstration of objective evidence. This evidence must support the proposition that the selected disclosed compounds are representative of the structure of the group of molecules identified by the claimed method.[692]

c) Discussion

aa) Reach-through-Claims

Both offices classify the claim as a reach-through claim.[693] Consequently, they treat it similarly to inventions involving identified compounds of *in-vitro* screening methods.[694] The question is whether such claims are patentable. Reach-through claims use a claim language broad enough to include future product discoveries without providing any information, such as structure coordinates or other elements.[695] The inventor does not only claim the structure of a protein, but also of compounds that bind to the protein, even though the latter is still unknown at the time the claims are drafted. In terms of *in-silico* methods, the applicant not only claims the computerized screening method, but also the compounds, which might be identified by such methods.[696] The topic of reach-through claims has been the subject of various discussions.[697] After an increasing number of applications contained claims drawn to

692 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002; Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 205.

693 As for reach-through claims, see Straus, Joseph, Reach-through claims and research tools as recent issues of patent law in: Estudios sobre propiedad industrial e intellectual y derecho de la competencia, Curell Suñol, M./et al. (Eds.): Grupo Español de la AIPPI, Barcelona, 2005, 921. The need of inventors to protect screened proteins emerged in the 'post-genomic' era where proteins capable of becoming the targets of drug development are identified rapidly and in large quantities. This is also emphasized in Masuoka, Kunihisa, Study on the Ways of Protection of Post-Genome Research Products, IIP Bulletin 2002, 84, 89.

694 As "in-vitro" is understood "outside the living body and in an artificial environment"; see at Medline Plus, Medical Dictionary, available at: http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=in%20vitro, last checked on January 21, 2008.

695 OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

696 Lonati, Milena, Patentability of receptors and screening methods: does in silico screening pose new legal problems?, Bioscience Law Report 2000/2001, 144, 145.

697 Eisenberg, Rebecca S., Reaching through the Genome, In: Perspectives on Properties of the Human Genome Project; Kieff, F. Scott Ed. Amsterdam, 2003; 209, 225 who argues that legal provision of reach-through rights should follow indications in the market that such allo-

include all potential pharmaceutical candidate compounds identified by assaying, the issue was examined in the course of a trilateral study in 2001.[698] In this case, the patent offices agreed not to accept claims reaching beyond that embodied by the patent. Applying those principles, the USPTO refused to grant the claim at issue. The hypothetical claim to compounds which bind to the receptor is rejected, since the applicant only discloses the function of the ligand without revealing information regarding its structure. Hence, the office is relatively tolerant with regard to the obviousness and utility criterion, but applies a particularly strict written description requirement. Relying on the principles developed in the *Regents' of California*[699] and *Enzo*[700] cases, the office supports a separate written description requirement.[701] The importance of the discussion, however, is attenuated by the fact that the claim at issue is also rejected due to a lack of enablement. When a skilled person is unable to make and use the invention without undue experimentation, the 'how-to-make' and 'how-to-use' prongs are not met. In sum, reach-through claims are subject to the same standards as all patent claims. An invigorated written description requirement generates a high threshold level to the granting of reach-through claims. With the USPTO also refusing to grant reach-through claims because of a lack of enablement, the dispute as to where to set the limits of a written description obligation is, however, not dispositive.

The EPO analysis is in accordance with German patent law developed in the field of chemicals. In the *Trioxan*[702] decision, the German Federal Supreme Court held that an unambiguous identification of the patented subject matter is the factual basis for not only the grant of the patent requirement but also for the start of the examination procedure made by the patent offices. The court discusses the first issue by analyzing how to reward the inventor appropriately on the one hand, and provide sufficient legal certainty on the other. Rewarding the inventor appropriately means, however, the court stated, that an inventor should only receive the advantages of a patent

cations are appropriate; also Kunin, Stephen G/ Nagumo, Mark/ Stanton, Brinaet al., Reach-through claims in the age of biotechnology, 51 American University Law Review April 2002, 609, provides a good overview how reach-through claims are treated by the USPTO applying the B3b Trilateral Study on reach-through claims undertaken by the Patent offices of Japan, the U.S. and Europe. Clark, Vici, Reach-through infringement: what are the limits? 6 Bio-Science Law Review 2000/2001, 249-252 who gives an overview about the legal situation in the U.K. For a comparative treatment, see OECD, Genetic Inventions, Intellectual Property Rights and Licensing Practices, Paris 2002, 63.

698 Trilateral Project B3b Comparative study on "reach-through claims", San Francisco, California, USA 2001.

699 Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997).

700 Enzo Biochem v. Gen-Probe, 323 F.3d 956 (Fed. Cir. 2002).

701 Rochester illustrated how courts treat reach-through claims that have already been issued by the USPTO. The patent involving reach-through claims was based on the identification of molecules and processes in Cox-2 pathway. The claims to unidentified COX-2 inhibitors such as Celebrex were held to be invalid; See University of Rochester v. G.D. Searle & Co.; Inc, 358 F.3d 916 (Fed. Cir. 2004).

702 BGH, 3 IIC 226 (1972) – Trioxane.

if he discloses a new technical teaching to the public. The teaching of a substance invention under German law consists of making a substance available and providing at least one way to prepare it. Applying these principles to the claim at issue, the claim to the identified compounds of an *in-silico* method lacks both requirements and thus no "reward" can be provided to the inventor. With regard to unambiguous identification, the court in *Trioxane* emphasized that a claim must be drafted so precisely that it clearly demonstrates which substances are included in the claim language. Patent offices must be enabled to determine whether a substance already belongs to the prior art or not. Again, the principles established in *Trioxane* apply: if a substance is not described by its structural formula, any parameter that enables a clear distinction is sufficient for description. Claim language as "identified through …" does not provide such a distinction. Thus, it does not meet the standards for patentability.[703]

bb) Reach-through licensing

Another approach to protecting pharmaceutical inventions, instead of by broad reach-through claims is by reach-through licensing. The basic idea of this contract strategy is that the patent holder restricts access to his patented screening technology to those who agree to share future drug sales with him in the form of royalties. The specific characteristics of such royalties may violate existing anti-trust laws. The question of whether they are allowed influences the drafting of licensing contracts but also the amount of damage awards that can be claimed in the course of the infringement process. On the one hand, critics may claim that reach-through practices excessively reward those who rest on their laurels at the expense of those who carry research forward. On the other hand, it may be seen as a valuable way to allow early innovators to realize that their discoveries contribute to subsequent research. Whether the statutory background and existing case law is allowing the practice of reach-through licensing, will be discussed below.

i. Statutory background in Germany

A patent establishes a monopoly position that is authorized by legislation. If the patentee extends such a position by drafting personal licensing agreements that go beyond what is allowed by patent law, existing antitrust law rules may be violated. In order to prevent the monopoly right provided for the patentee from being extended beyond its legislative limitations by licensing contracts, the German competi-

703 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through Licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 60; BGH, 3 IIC 226 (1972) – Trioxane.

tion law restricts the freedom of contract. Sections 17 and 18 of the Act of restraints of competition (ARC)[704] state that licensing agreements for the sale or use of certain intellectual property rights shall only contain such restrictions on the licensee that are covered by the scope of the intellectual property right as such. According to Section 17 para 1 sentence 2 ARC, only restrictions pertaining to the nature, extent, field of use, quantity, territory or duration of the right of use are allowed. The share of future profits is not addressed by this provision, which is why reach-through royalties are not covered. Reach-through royalties may, however, qualify for an exemption under Section 17 para 3 ARC if the licensee's economic freedom of movement or the market competition is "not unfairly restricted and if competition on the market is not substantially impaired because of the extent of the restrictions." In the event that research tools are used for identifying substances, the licensee will typically apply for a patent in order to protect such substances. During the duration of the patent, the substances are excluded from market competition. If no competition exists, an agreement regarding reach-through royalties does not thereby establish any restraint on the market. Furthermore, if the freedom of movement of the licensee is not restricted, an exemption will be granted. This is typically the case when parties agree upon moderate royalties. The exemption is considered to be granted if the cartel office does not reject the application within a period of three months.[705]

Another approach for protecting pharmaceutical inventions is through "milestone payments". In order to save the share of future profits, the parties agree upon payments triggered by contractual achievements. Typically, they are directed to major project events such as the beginning of pre-clinical or clinical trials or the achievement of drug approval. Milestone payments can be understood as escrows[706] and thus are acceptable under antitrust laws.[707]

ii. Legal situation under U.S. law

In the U.S., the topic of reach-through licensing is subject to heated discussion. The National Institutes of Health (NIH) rejects the idea of reach-through royalties due to policy reasons. It is claimed that they restraint research and the distribution of research tools. Only in exceptional cases are receivers of NIH subsidies allowed to conclude reach-through-licensing agreements.[708]

704 "Gesetz gegen Wettbewerbsbeschränkungen"

705 Kraßer, Rudolf, Patentrecht: Ein Lehr- und Handbuch zum deutschen Patent- und Gebrauchsmusterrecht, europäischen und internationalen Patentrecht, 5. Aufl., München 2004, 981.

706 "Aufschiebend bedingte Verpflichtung zur Zahlung einer Pauschallizenzgebühr für die Benutzung des Research tools"

707 Wolfram, Markus, 'Reach-Through Claims' and 'Reach-Through licensing' - Wie weit kann Patentschutz auf biotechnologische Research Tools reichen?, Mitteilungen der deutschen Patentanwälte 2003, 57, 63.

708 Department of Health and Human Services/National Institutions of Health: "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Dissemi-

Licenses providing reach-through royalties may give rise to antitrust issues under the patent misuse doctrine.[709] The doctrine requires that the alleged infringer demonstrate that the patent owner has unlawfully broadened the scope of the patent with a resulting anti-competitive effect. In *Zenith Radio Corp. v. Hazeltine Research, Inc.*, the Court of Appeals held that patent misuse is established if the grant of a patent license is conditioned upon payment of royalties on products, which do not involve the teaching of the patent.[710] The patentee "extend(s) the monopoly of his patent to derive a benefit not attributable to use of the patent's teachings" if "the leverage of a patent" is used to "garner as royalties a percentage share of the licensee's receipts from sales of other products.[711] Patent misuse thus must be assessed if the patentee's actions affect competition in unpatented goods or otherwise extends the economic effect beyond the scope of the patent grant.[712] There are several cases which deal with the question of whether reach-through royalties are considered to be patent misuse.

In *Sibia Neuroscience, Inc. v. Cadus Pharm. Corp.,* the infringing activity consisted of the use of a patented screening method to detect antagonists[713] and agonists[714] of proteins. The district court for the Southern District of California assessed damages, based on the calculation of a "reasonable royalty" of $18 million. The amount was calculated with the assumption that the parties had agreed upon reach-through royalties. With the subsequent invalidation of the patent by the CAFC due to obviousness in the light of the prior art[715], this type of damage assessment was not further examined. In *Ajinomoto Co. v. Archer Daniels Midland*, the claim was directed to methods of producing bacteria to make amino acids. The district court assessed damage awards by determining a royalty of $1.23/kg of amino acid sold. With the parties not disputing this calculation, it was not subject to any further discussion.[716] In addition, the decision of *Bayer v. Housey* assists in dealing with the details of patent misuse. In the district court decision, the court found that the plaintiffs sufficiently stated a claim of patent misuse reasoning that

nating Biomedical Research Resources, Final Notice", U.S. Federal Register Notice 64 FR 72090, 23.12.1999, http://ott.od.nih.gov/pdfs/64FR28205.pdf, last checked on January 21, 2008.

709 For a comparative analyis of the patent misuse doctrine see Riziotis, Dimitrios, Patent Misuse als Schnittstelle zwischen Patentrecht und Kartellrecht, GRURInt. 2004, 367.

710 Zenith Radio Corp. V. Hazeltine Research, Inc., 395 U.S. 100, 135. (Fed. Cir. 1969).

711 Zenith Radio Corp. V. Hazeltine Research, Inc., 395 U.S. 100, 136.

712 See C.R. Bard, Inc. v. M3 Sys., Inc., 157 F.3d 1340, 1372 (Fed. Cir. 1998).

713 An antagonist is a substance that attenuates the effects of an agonist by binding to the agonist's binding sites. See glossary, available at http://www.adrenoceptor.com/abc.htm, last checked on January 21, 2008.

714 An agonist is a substance that binds to a receptor and activates it, producing a pharmacological response (such as contraction, relaxation, secretion, enzyme activation, etc.), see glossary, available at http://www.adrenoceptor.com/abc.htm, last checked on January 21, 2008.

715 Sibia Neuroscience, Inc. v. Cadus Pharm. Corp.225 F.3d 1349 (Fed. Cir. 2000).

716 The CAFC in Ajinomoto Co. v. ADM Co., 228 F.3d 1338 held that the claims at issue were valid and infringed by a commercial process using bacteria made by these methods.

> "Certain practices that do not equal *per se* patent misuse may constitute misuse if a court determines that such practices do not reasonably relate to the subject matter within the scope of the patent claims. If "the practice has the effect of extending the patentee's statutory rights and does so with an anti-competitive effect, ... the finder of fact must decide whether the questioned practice imposes an unreasonable restraint on competition".[717]

For the reasons set forth above, the legal treatment of reach-licensing agreements is yet not clear. Hence, it is advisable to handle such strategy with caution.

IV. Conclusion

Based on the study of the different approaches provided by the European and the U.S. patent offices, it can be concluded that both offices largely share the same views with respect to the patentability requirements of 3-D protein structures-related claims.[718] Yet, different approaches exist with regard to the patentability of *in-silico* screening methods. The European Patent office accepts the claim, assuming a patentable subject matter due to a further technical effect of the computerized invention. The USPTO, by contrast, rejects the claim, concluding there is obviousness due to the understanding that the algorithm is considered as non-functional descriptive material.

The study shows that an inventor seeking patent protection for 3-D protein structures should obey the following guidelines.[719] Generally, a patent applicant should provide accurate and precise information regarding the 3-D structural coordinates. Furthermore, a precise description of how the structural analysis was carried out should be provided in the patent specification. Isolated and determined 3-D protein structures establish novelty, if the inventor proves that the tertiary structure coordinates are a more unambiguous parameter than the amino acid sequence already disclosed in the prior art.

The further rule that novelty can be derived from physical morphology applies principles developed in the field of chemical inventions. The possibility of creating novelty through the principles of selection inventions are also in line with classical chemical patent principles. The question of dependency from the patent covering the whole protein is another key factor and will be discussed below.

717 Bayer v. Housey, 169 F.Supp.2d 328, 331 (District Court of Deleware 2001).

718 European Patent Office, Japan Patent Office, United States Patent and Trademark Office, Trilateral Project WM4, Comparative Studies in New Technologies (Biotechnology, Business Methods, etc.), Report on Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims, Vienna 2002, 32; also Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 206.

719 Vinarov, Sara D., Patent protection for structural genomics-related inventions, Journal of structural and functional genomics 2003, 191, 207, who emphasizes that understanding how patent offices will analyze structural genomics-based inventions is crucial for formulating strategies in patent prosecution and litigation.