UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/124,826	03/03/2014	Julia Hoeng	4058.0020003	9814

155543 7590 09/24/2020

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER
HARWARD, SOREN T

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
09/24/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

e-office@sternekessler.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JULIA HOENG, FLORIAN MARTIN,
MANUEL CLAUDE PEITSCH, and ALAIN SEWER

Appeal 2020-000630
Application 14/124,826
Technology Center 1600

Before RICHARD M. LEBOVITZ, DEBORAH KATZ, and
JOHN A. EVANS, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review,[2] under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1, 4–23, and 26–28. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

---

[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as Phillip Morris Products S.A. (Appeal Br. 3.)

[2] We consider the Final Office Action issued June 28, 2018 ("Final Act."), the Appeal Brief filed July 29, 2019 ("Appeal Br."), the Examiner's Answer issued on September 4, 2019 ("Ans."), the Reply Brief filed November 4,

Appellant's Specification is directed to systems for studying the mechanisms by which biological systems respond to introduced agents. (Spec. ¶ 5.) Specifically, Appellant claims a computerized method for quantifying the perturbation of a biological system in response to an agent by making a model with nodes, representing biological entities, edges, representing the relationships between these entities, and direction values, representing the expected direction of change between control and treatment data and generating a set of hypotheses.

Appellant's claim 1 recites[3]:

> A computerized method for quantifying a perturbation of a biological system in response to an agent, comprising:
>
> [a] receiving, at at least one processor, a set of treatment data corresponding to a response of a biological system to an agent, wherein the biological system includes or comprises a plurality of biological entities, each biological entity interacting with at least one other of the biological entities;
>
> [b] receiving, at the at least one processor, a set of control data corresponding to the biological system not exposed to the agent;
>
> [c] providing, at the at least one processor, a network model that represents the biological system and includes or comprises:
>
> nodes representing the biological entities,
>
> edges representing relationships between the biological entities, and
>
> direction values, for the nodes, representing the expected direction of change between the control data and the treatment data;
>
> [d] generating, with the at least one processor, a set of mechanism hypotheses based on the network model, wherein each mechanism hypothesis in the set of mechanism hypotheses comprises

---

2019 ("Reply Br."), and the Specification as the publication of Appellant's International Application WO 2012/168483 A1.

[3] Bracketed numbers to identify claim elements have been added for reference.

> a set of causal paths from an upstream node in the network model to a set of downstream nodes in the network model;
>
> [e] calculating, with the at least one processor, activity measures for the set of downstream nodes of each mechanism hypothesis, wherein an activity measure represents a difference between the treatment data and the control data for each downstream node;
>
> [f] calculating, with the at least one processor, weight values for the set of downstream nodes of each mechanism hypothesis, wherein at least one weight value is different from at least one other weight value, and wherein the calculating the weight values comprises calculating a probability that the activity measures represent a departure from a null hypothesis of a zero difference;
>
> [g] generating, with the at least one processor, a scorable network model based on the set of mechanism hypotheses; and
>
> [h] generating, with the at least one processor, a score for the scorable network model representative of the perturbation of the biological system in response to the agent, wherein the perturbation of the biological system in response to the agent is unable to be measured directly, and the score is based on the direction values, the weight values, and the activity measures.

(Appeal Br. 41–42.) Appellant's claimed method results in a score for the network that represents perturbation of the system in response to an agent.

The Examiner rejects all of Appellant's pending claims as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. (*See* Final Act. 6–7.) The Examiner also rejects all of Appellant's pending claims under 35 U.S.C. § 101 because the claimed inventions are directed to non-statutory subject matter. (*See id.* at 7–9; *see* Ans. 4–7.) In addition, the Examiner makes rejections of Appellant's claims as being obvious under 35 U.S.C. § 103(a). (*See* Final Act. 11–21; *see* Ans. 7–15.) A rejection of claims 1–23 and 26–28 under 35 U.S.C. § 112, second

paragraph, was withdrawn in view of Appellants arguments in the Appeal Brief. (*See* Ans. 4.)

Appellant does not provide separate arguments for any of the rejected claims. Accordingly, we focus on claim 1 in our analysis.

35 U.S.C. § 112, first paragraph – written description

The Examiner rejects all of Appellant's pending claims as lacking written description support, under 35 U.S.C. § 112, first paragraph, asserting that the claim phrase "the perturbation of the biological system in response to the agent is unable to be measured directly" when "generating ... a score for the computational causal network model representative of the perturbation of the biological system" recited in independent claims 1, 23, and 28 are not supported in the Specification. (*See* Ans. 4.) According to the Examiner, paragraph 50 of the Specification describes a situation in which "it is not necessary for the computerized method to receive data for all such measurable nodes," but does not describe a situation in which perturbation cannot be measured directly. (*See id.*)

Appellant persuades us that the Specification sufficiently describes generating a score for a network model wherein "the perturbation of the biological system in response to the agent is unable to be measured directly." (*See* Appeal Br. 14–18.) Appellant argues that the purpose of the claimed methods is to quantify the perturbation of a biological system in response to an agent, instead of measuring the perturbation itself. (*Id.* at 15–16, citing Spec. ¶¶ 4–5.) Appellant explains that the claimed method involves "the traversal of the causal networks" causing downstream effects to generate a

cumulative score, wherein the actual cause of the downstream effect cannot be measured. (*See* Appeal Br. 15.)

We find that Appellant's Specification supports Appellant's argument. Appellant's Specification explains that

> [t]he nodes in the graph can also represent relationships between nodes. Thus, it is possible to represent relationships between relationships, or relationships between a relationship and another type of biological entity represented in the graph. For example a relationship between two nodes that represent chemicals may represent a reaction. This reaction may be a node in a relationship between the reaction and a chemical that inhibits the reaction.

(Spec. ¶ 50; *see* Appeal Br. 17.) This portion of the Specification describes interrelationships that go beyond direct measurement of a cause and an effect. Appellant's Specification expressly describes "biological entities [that] are not necessarily limited to those biological entities for which treatment or control data are received or available" as being nodes of the claimed method. (Spec. ¶ 50.)

Furthermore, Appellant's Specification provides an example of the results of analyzing TNF treatment of NHBE cells to cause downstream gene activation by NF-κB and downstream gene activation, where TNF does not directly mediate transcription by NF-κB. (*See* Spec. ¶¶ 99–105; *see* Appeal Br. 15.) We are persuaded by Appellant's argument that this example demonstrates effects on an upstream biological entity where only raw RNA expression resulting from the perturbation, and not the perturbation itself, was measured directly. Thus, we are persuaded that the example provides a written description of generation of a score "wherein the perturbation of the biological system in response to the agent is unable to be

measured directly, and the score is based on the direction values, the weight values, and the activity measures," as recited in claim 1.

Accordingly, we reverse the Examiner's rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 103

The Examiner rejects Appellant's claims as being obvious under 35 U.S.C. § 103(a). Specifically, the Examiner rejects claims 1, 4–13, 15–21, 23, and 28 over Ladd,[4] Toyoshiba,[5] and Strimmer[6] (*see* Final Act. 11–18); claim 14 over Ladd, Toyoshiba, Strimmer, and Löfroth[7] (*see id.* at 18–19); claims 14, 26, and 27 over Ladd, Toyoshiba, Strimmer, and Sexton[8] (*see id.* at 19–20); and claim 22 over Ladd, Toyoshiba, Strimmer, and Friedman[9] (*see id.* at 20–21). Appellant does not raise any separate arguments against any of the claims or groups of claims in the separate rejections. (*See* Reply Br. 40.) Thus, we focus on claim 1. *See* 37 C.F.R. § 41.37(c)(1)(iv).

---

[4] Ladd and Elliston, U.S. Patent Application Publication 2009/0099784 A1, published April 16, 2009.
[5] Toyoshiba et al., "Gene Interaction Network Suggests Dioxin Induces a Significant Linkage between Aryl Hydrocarbon Receptor and Retinoic Acid Receptor Beta," *Environmental Health Perspectives*, 112:1217–24 (2004).
[6] Strimmer, "A unified approach to false discovery rate estimation," *BMC* BIOINFO*rmatics* 9:303 (2008).
[7] Löfroth and Rannug, "Ah receptor ligands in tobacco smoke," *Toxicology Letters*, 42: 131–36 (1988).
[8] Sexton et al., "Genomic biomarkers of pulmonary exposure to tobacco smoke components," *Pharmacogenetics and Genomics*, 18:853–60 (2008).
[9] Friedman et al., "Data Analysis with Bayesian Networks: A Bootstrap Approach," *Uncertaintly in Artificial Intelligence* 196–215 (1999).

Ladd teaches software assisted methods for identifying similarities and differences between biological states in a causal system model ("CSM") using nodes to represent the differences between two biological states and links between the nodes to indicate a causal directionality between the nodes. (*See* Ladd ¶ 25.) Ladd teaches that a researcher can conduct a series of experiments involving perturbations to the system to see which perturbations result in that outcome. The data from these experiments is mapped to a model that sums all of the upstream or downstream causal hypotheses explaining the outcome. (*See id.* ¶¶ 110, 111.) Ladd teaches, further, a method of "pruning" hypotheses by applying logic based criteria to each member of the set of models to reject paths or portions not likely to be representative of real biology and leaving a smaller number of remaining models to constitute new active causative relationships. (*See id.* ¶ 112.)

The Examiner's rejection of Appellant's claim 1 is based on the finding that Ladd teaches steps [a] through [e], [g], and [h] of claim 1, including receiving biochemical data, providing a network model with nodes and mapped relationships between the nodes, generating a set of mechanism hypotheses, calculating activity measures, and generating a scorable network model and a score for the model, which correspond to each step of the recited method, except step [f]. (*See* Ans. 7–9.)

The Examiner finds that Toyoshiba teaches an example of the ability to test hypotheses, for example to assess the health risks of compounds that affect genetic regulatory networks. (*See* Ans. 10, citing Toyoshiba 1217, 1223.) The Examiner finds further that Toyoshiba teaches a log-linear expression model that can be used to mathematically compare different models reflecting different mechanistic hypotheses (e.g., CSM). (*See* Ans.

10; *see* Toyoshiba 1218.) The Examiner bases the rejection of Appellant's claims on the finding that, whereas Ladd teaches using CSM to simulate biological behavior and then uses biological measurements and simulated behavior to evaluate the resulting mechanistic hypotheses, Toyoshiba teaches a mathematical procedure that can be used to compare different CSMs. (*See* Ans. 10; *see* Toyoshiba 1218 ("One of the simplest types of weighting function used to describe a gene expression network is the log-linear weighting function given by the following form . . . .").)

The Examiner finds further that Strimmer teaches a method of estimating the false (non-)discovery rate ("fndr") for a parameter and selecting a cutoff based on the fndr. (*See* Ans. 11, citing Strimmer 9 ("Selection of suitable truncation point using the false non-discovery rate").) The Examiner also finds that Strimmer teaches that "false discovery rate analysis is a key statistical innovation that has found widespread application in the study of high-dimensional data." (Ans. 11, citing Strimmer 13.) The Examiner points to the disclosure in Appellant's Specification:

> One value that may be advantageously used for weighting is the local false non-discovery rate $fndr_i$ (*i.e.*, the probability that a fold-change value β_i represents a departure from the underlying null hypothesis of a zero fold-change, in some cases, conditionally on the observed p-value) as described by Strimmer et al. in "A general modular framework for gene set enrichment analysis," BMC Bioinformatics 10:47, 2009 and by *Strimmer in "A unified approach to false discovery rate estimation," BMC Bioinformatics 9:303, 2008* [cited by the Examiner], each of which is incorporated by reference herein in its entirety.

(Spec. ¶ 72; *see* Ans. 11 (emphasis added).) Thus, According to the Examiner, the procedure of Strimmer distinguishes values that represent

statistically significant differences from zero, from values that represent statistically insignificant differences from zero and therefore provides a more rigorous way of identifying statistically insignificant β parameters in the model of Toyoshiba. (*See* Ans. 11.)

The Examiner finds that at the time of invention one of ordinary skill in the art would have found it obvious to have combined the teachings of Ladd and Toyoshiba because Toyoshiba teaches specific details of a mathematical procedure to evaluate mechanistic hypotheses based on CSMs. (*See* Ans. 13–14.) The Examiner finds further that a practitioner would have been motivated to modify the methods of Ladd and Toyoshiba to identify the β_is describing gene interactions as "substantial" or "insubstantial" using cutoff value for a parameter based on a local FNDR, as taught by Strimmer, because Strimmer teaches a more robust procedure for discriminating false positives and negatives that Toyoshiba. (*See id.* at 14.)

Appellant argues that the Examiner fails to articulate why Toyoshiba would be combined with Ladd. (*See* Appeal Br. 31–32.) According to Appellant, Ladd teaches a method that compares one causal system to another by searching for branch points and pruning those that are not likely representative of real biology. (*See id.* at 31, citing Ladd ¶ 21.) Appellant argues further that Ladd teaches "simulation tools [that] are used to probe the assembly" and teaches "suitable tools" as described in patent application 10/992,973 ("Chandra"). (*See* Appeal Br. 31, citing Ladd ¶ 103.) According to Appellant, because Ladd refers to suitable simulation tools, there is no apparent reason why the mathematical procedure of Toyoshiba should be used for performing the simulations of Ladd. (*See* Appeal Br. 31.) Appellant argues that Chandra, to which Ladd refers, discusses using a

mathematical procedure for simulations. (*See* Reply Br. 31, citing Chandra 14:66–15:21.)

We are not persuaded by Appellant's argument because even if Ladd refers to a way to simulate biological networks quantitatively, other means of doing so may still have been obvious. As explained below, Appellant is mistaken that the Examiner erred by not giving a reason "why the use of such a model would be preferable over the simulation tools that are already referenced in Ladd." (*See* Appeal Br. 31; *see also* Reply Br. 35 ("the Examiner provides no rationale as to why the logical simulation of Toyoshiba, which is directed to a specific application of TCDD needs to be applied instead of the logic criteria of Change to Ladd for hypothesis prunning.").)

We are persuaded there would have been a reason to use the method of Toyoshiba because the Examiner finds that Ladd can use simulations tools other than those taught in Chandra and finds that the quantitative simulation of Toyoshiba provides more detail about the characteristics of a biological network, using a Bayesian approach to parameterizing that is advantageous by giving an estimate of the uncertainty in the quantitative estimates. (*See* Ans. 23, 26.) Appellant argues that the Examiner does not show that an estimate of uncertainty is quantitative estimates is "uniquely advantageous when provided by a Bayesian approach." (Reply Br. 36.) But the method of Toyoshiba need not be preferred or the most desirable for there to have been a reason to combine the references and render Appellant's claimed method obvious. A particular combination of prior art need not be preferred or the most desirable in order to provide motivation for the current invention, rather the question is whether there is something to suggest the

desirability of making the combination. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (rejecting Appellant's argument that because hexagonal patterns on shoe soles were not found to be preferred over other alternatives disclosed in the prior art, Appellant's claims were not obvious); *see also Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) ("After reviewing the prior art, the district court found that a person of ordinary skill 'would have been motivated to pursue everolimus as one of several potential treatment options for advanced solid tumors, including advanced RCC.' This finding should have affirmatively answered whether there would have been a motivation to combine. . . . It is thus improper to require West-Ward to prove that a person of ordinary skill would have selected everolimus over other prior art treatment methods.") (internal citations omitted).

Appellant does not argue that the method of Toyoshiba would not have any advantages, rather, Appellant argues that it would not be preferred over the disclosure of Chandra.

> In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 419 (2007).

Appellant argues further that modification of the method of Ladd with the method of Toyoshiba would render Ladd inoperable. (*See* Appeal Br. 32–33; Reply Br. 32–33.) Appellant argues that Toyoshiba is specifically

directed to a log-linear network for the response of one type of cell to one agent without any mention of assembling a simulation involving the "increases or decreases in the quantity or activity of nodes within the assembly . . . result[ing] in generation of a large number of branching paths" as required in Ladd. (*See* Appeal Br. 33, quoting Ladd ¶¶ 76, 103.) Appellant argues that it is not clear how the log-linear network for "defining a Bayesian network to derive the posterior distribution for the parameters of interest" would generate the large number of branching patterns or how these branches would be pruned or scored as taught in Ladd. (*See* Appeal Br. 33, citing Ladd ¶ 133.)

We are persuaded by the Examiner's explanation that a log-linear network, as in the simulation of Toyoshiba, does not refer to any particular network structure and imposes no limits on the structure of the network. The Examiner finds that a log-linear network can have as many or as few branches as desired and that scoring is based on the result of the simulation mathematics. Thus, according to the Examiner, the details of the simulation have no effect on the scoring. (*See* Ans. 24–25.)

Appellant argues that the Examiner is wrong about the effects on scoring because the score directly informs the pruning of hypotheses in Ladd, which in turn informs the score of Ladd. (*See* Reply Br. 35–36.) Although we understand that the ultimate score is directly impacted by the mathematical details of the simulation, because Appellant does not claim a method that produces a specific score, we are not persuaded that different mathematical details cannot be used in the method of Ladd and still fall within the claimed method. That is, Appellant does not direct us to evidence that the claimed method is limited to a particular simulation or mathematical

details to produce a certain result. Appellant's argument does not persuade us that the mathematical details taught in Toyoshiba are not encompassed by the claimed method.

Appellant argues that the combination of the Ladd and Toyoshiba would fail to operate as recited in the claimed method because the combination does not provide a step of calculating activity and weight values for the downstream nodes of each mechanism hypothesis and subsequently generating a score for the network model based on direction values of an expected direction of change, weight values, and activity measures as required in claim 1. (*See* Appeal Br. 35–38.)

Appellant argues further that the Examiner does not consider the claimed method as a whole because the Examiner "disregards that the scoring of the model in Ladd is based on the simulation performed, and the subsequent pruning that occurs." (Appeal Br. 34; *see* Reply Br. 34.) Appellant focuses first on the claim limitation "providing direction values, for the nodes, representing the expected direction of change between the control data and the treatment data." (*See* Appeal Br. 35–36.) According to Appellant, the teaching in Ladd of a causal system model that includes nodes representing differences in a first biological state and a second biological state does not include a teaching of an "expected direction of change." (*See id.*) Appellant argues that such expected directions are not taught in Toyoshiba or Strimmer either. (*See id.* at 36, 38.)

The Examiner refutes Appellant's argument, explaining that Toyoshiba teaches a factor, I_{ji}, to indicate stimulation, inhibition, or no change, thus indicating whether two nodes are expected to change in the same direction (stimulation) or different directions (inhibition), as described

in Appellant's Specification. (*See* Ans. 25, citing Toyoshiba 1218 ("I_{ji} is an indicator variable describing the direction of the change denoted by β_{ji}, where $I_{Ji;}$ = 1 for stimulation, $I_{Ji;}$ = - 1 for inhibition, and $I_{Ji;}$ = 0 for no effect."); Spec. ¶ 5.) Appellant argues that "the provision of direction values, as well as the inclusion of said provided direction values in such a score generation step, has not been shown in any of Ladd, Toyoshiba, or Strimmer." (Reply Br. 37–38.) The teaching of Toyoshiba provides direction values, thus, we are persuaded that determining values for nodes, representing an expected direction of change, when developing a network model was known in the art.

Appellant argues further that the Examiner has not shown how calculating the activity measures and weight values for the set of downstream nodes of each mechanism hypothesis are met by the prior art. (*See* Appeal Br. 36–37.) This argument reiterates Appellant's argument that there would have been no motivation to use the mathematical procedures of Toyoshiba with the method of Ladd because Ladd refers to Chandra for simulation tools. (*See id.*) As explained above, we are not persuaded by this argument.

Appellant argues further that the Examiner inappropriately equates the teaching in Strimmer of a false non-discovery rate fndr with the claim step of "calculating the weight values comprises calculating a probability that the activity measures represent a departure from the null hypothesis of a zero difference." (*See* Appeal Br. 37.) Appellant acknowledges that Strimmer teaches the fndr probability may be useful for weighting, but argues that there is no weighting taught in Toyoshiba to which Strimmer may be applied. (*See id.*) In particular, Appellant argues that Strimmer teaches that

fndr probability is conditioned on the observed p-value, but the p-values are not calculated in the methods of Toyoshiba. (*See id.*) Appellant argues further that Strimmer does not teach a calculation of weight values and that the Examiner does not show why weight values should be part of the overall network score. (*See id.* at 38.)

The Examiner responds that Toyoshiba teaches computation of weight values in its score simulation by teaching inclusion of weight parameters β_{ji} when scoring a network model by computing the likelihood of the model. (*See* Ans. 26.) The Examiner explains that Strimmer teaches a specific procedure for determining when the values of particular β_{ji} parameters are statistically significant and for zeroing statistically insignificant weight parameters. (*See id.* at 26–27.) Thus, we are not persuaded that the Examiner erred in combining Strimmer with Toyoshiba, and Ladd, to teach computation of weighting values.

Appellant also argues that the Examiner has not shown that the prior art teaches the claim step of generating a score for the network based on direction values, weight values, and activity measures, as recited in claim 1. (*See* Appeal Br. 38.) Appellant reiterates the argument that the prior art fails to teach including direction values in a score and argues further that Strimmer does not teach calculating weight values or why they should be included as part of an overall network score. (*See id.*)

Appellant argues there is no teaching in Toyoshiba of calculating a network score, rather Toyoshiba teaches only calculating a conditional likelihood of data in the form of an equation for deriving the posterior distribution of a Bayesian network. (*See* Appeal Br. 38.) The Examiner explains that the likelihood function of Toyoshiba incorporates an observed

activity measure (χ_j), weight value (β_{ij}), and direction value (I_{ij}) in calculating the conditional density, which is used to determine the likelihood of a data point or an entire dataset. (*See* Ans. 27, citing Toyoshiba 1218–19.) Toyoshiba supports the Examiner's findings by providing that χ_j is the "observed level of expression," β_{ij} is the "magnitude by which a change in one log unit of gene X_j will affect the level of expression of gene X_{ij}," and I_{ji} is "an indicator variable describing the direction of the change denoted by β_{ij}." (Toyoshiba 1218.)

Appellant refutes this explanation, arguing that $I_{ij,}$ $\beta_{ij,}$ and χ_j are not equivalent to the direction value, weight value, and activity measure recited in claim 1 because there "is not a *necessary* correspondence of an observed level of expression of a gene X_j with an activity measure as claimed" because claim 1 requires the activity measure "represents a difference between the treatment data and the control data for each downstream node." (Reply Br. 39 (emphasis added).) Appellant points to the Specification, which provides that the activity measure *may* include "a logarithm of the difference between the treatment data and the control data." (*See* Reply Br. 39, quoting Spec. ¶ 5.) Appellant argues further that

> the magnitude by which a change in one log unit of gene X_j will affect the level of expression of gene X_i is not *necessarily* a weight value, where in fact this mode of calculation of weight values as asserted by the examiner does not "comprise calculating a probability that the activity measures [for a downstream node] represents a departure from a null hypothesis of a zero difference" as required by claim 1, but rather represents the magnitude by which the change in level of one gene affects the level of expression of another gene.

(Reply Br. 39–40 (emphasis added).) These arguments are not persuasive because although Appellant argues that the Examiner's findings regarding $I_{ij,}$ $\beta_{ij,}$ and χ_j may not *necessarily* be the elements of claim 1, Appellant fails to direct us to evidence they are not. Instead, Toyoshiba seems to support the Examiner's findings that the network could be scored as taught in Ladd "based on multiple criteria indicative of how close a given hypothesis/branching path approaches explanation of the operational data." (Ans. 24, quoting Ladd ¶ 23.) We agree with the Examiner that the likelihood function of Toyoshiba is a score with the characteristics needed by the method of Ladd because it is a statistical measure "indicative of how close a given hypothesis/branching path [*i.e.* genetic network model] approaches explanation of the operational data." (Ans. 25.)

Appellant does not persuade us that the Examiner erred in rejecting claim 1 as being obvious. Appellant fails to present separate arguments for the rejection of any other of the pending claims. Accordingly, we sustain each of the rejections under 35 U.S.C. § 103.

35 U.S.C. § 101

The Examiner rejects Appellant's claim 1 as being drawn to ineligible subject matter under 35 U.S.C. § 101, finding that the claims do not recite significantly more than the abstract idea of "quantifying the perturbation of a biological system in response to an agent" on a generic computer and that this abstract idea is not integrated into a practical application. (*See* Ans. 4–7.)

Although 35 U.S.C. § 101 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may

obtain a patent therefor . . . ," the Supreme Court has determined that there are exceptions to what is patentable. Specifically, "laws of nature, natural phenomena, and abstract ideas" are not eligible subject matter. *See Diamond v. Diehr*, 450 U.S. 175, 185 (1981). To determine if claimed subject matter is statutorily eligible in light of these judicial exceptions the Supreme Court has articulated a two-step framework in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), and later cases. Specifically,

> [f]irst, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat else is there in the claims before us?" To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application.

Alice Corp. v. CLS Bank Int'l, 573 U.S. 208, 217 (2014) (quoting *Mayo*, 566 U.S. at 78) (internal citations omitted). Thus, we must determine whether the claim is directed to a judicially determined patent-ineligible concept and, if so, then ask if there is anything in the claim that transforms it into patent-eligible subject matter.

The USPTO issued revised guidance on the application of § 101. *See* 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50–57 (2019) ("2019 Guidelines"). After determining that claimed subject matter falls within one of the four categories of patentable subject matter identified in 35 U.S.C. § 101, the 2019 Guidelines provides a "revised step 2A." which corresponds to the first step of the *Alice/Mayo* test articulated above, to determine whether a claim is directed to a judicial exception. (*See*

2019 Guidelines, 84 Fed. Reg. 50, 53–54.) In a first prong of revised step 2A, the Examiner must determine whether the claim recites a judicial exception. (*See id.* at 54.) If a judicial exception is identified, the second prong requires a determination of whether the judicial exception is integrated into a practical application. (*See id.*) If so, the inquiry ends and the claim is determined to be directed to eligible subject matter under the 2019 Guidelines. (*See id.* at 54 ("When the exception is so integrated [into a practical application], then the claim is not directed to a judicial exception (Step 2A: NO) and is eligible. This concludes the eligibility analysis.").) If not, the analysis continues to determine if the claim provides an inventive concept. (*See id.* at 56.)

The 2019 Guidelines provide that mental processes are a type of judicial exception. (*See* 2019 Guidelines, 84 Fed. Reg. at 52.) Mental processes are concepts performed in the human mind, including observation, evaluation, judgment, and opinion. (*See id.*) The Examiner finds that the claim steps of "receiving . . . a set of treatment data," "receiving . . . a set of control data," and "generating . . . a set of mechanism hypotheses . . ." are mental processes recited in Appellant's claim 1. (*See* Ans. 5.) We agree with the Examiner that receiving data, generating a set of hypotheses, and scoring the hypotheses are processes that can be performed by a human either mentally or with the aid of pen and paper. Specifically, we agree that receiving data (steps [a] and [b]) is an activity of observation. The recited steps of providing a network model representing the biological system (step [c]) and generating a mechanism hypothesis (step [d]) are activities of judgment and opinion, whereas calculating activity measures and weight values for the downstream biological entities (steps [e] and [f]), and

generating a scorable model and a score for the model (steps [g] and [h]), are activities of evaluation. We are persuaded that nothing would prevent one of ordinary skill in the field of the observation and evaluation of biological systems from performing each of these steps without a computer, for at least a small scale system.

Appellant argues that some of the data and activity values of the biological entities represented by nodes in the claimed process cannot be measured directly, but can be, instead, "inferred based on their interactions with other entities," for example by using measured data or activity values of other entities to infer data. (Appeal Br. 21, citing Spec. ¶¶ 49, 53, 57.) However, these inferences are based on observations and therefore could be performed in the human mind, as well. The Specification refers to methods for such inferences, including by "overrepresentation of functionally-related genes within the differentially expressed genes, Bayesian network analysis, a graphical Gaussian model technique or a gene relevance network technique, to identify a relevant biological network based on a set of experimental data (*e.g.,* gene expression, metabolite concentrations, cell response, *etc.*)." (Spec. ¶ 53.) The claims, however, do not require that any of these specific techniques be performed. Appellant fails to explain how inferences based on overrepresentation of related genes could not be performed in the human mind. Similarly, the Specification explains that "[t]he mechanism hypothesis can be used to make predictions, such as if the abundance of an entity represented by an upstream node increases, the downstream nodes linked by causal increase relationships would be inferred to be increase, and the downstream nodes linked by causal decrease relationships would be inferred to decrease." (Spec. ¶ 57.) Appellant argues that such predictions

and hypotheses are not based on formulaic approaches, but on causal relationships. (*See* Appeal Br. 22.) Appellants have not provide adequate evidence that such inferences, predictions, and hypotheses could not be performed in the human with the aid of paper and pen, particularly where they are not based on formulas.

In addition to agreeing with the Examiner that Appellant's claimed method recites a mental process, the steps of the method are also based on the natural relationship between treatment with an agent and the perturbation of the biological system in response. In *Mayo*, the steps of "(a) administering a drug providing 6–thioguanine to a subject having [an] immune-mediated gastrointestinal disorder; and (b) determining the level of 6–thioguanine in said subject having said immune-mediated gastrointestinal disorder" were found to set forth only the relationship between concentrations of certain metabolites in the blood and the likelihood that a dosage of a drug would prove ineffective or cause harm. *Mayo*, 566 U.S. at 74 (internal quotation omitted). This relationship was determined to be a law of nature. *See id.*

Similarly, the recitation in claim 1 of receiving data in response to an agent, generating a score for a model of the data by generating a hypothesis, and calculating activity measures and weights for downstream biological entities, merely sets forth the natural law of the effect of the agent on the downstream biological entities. In *Mayo*, "[t]he relation [between concentrations of metabolites in the blood and the likelihood that a dosage of the drug will be ineffective or cause harm] is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a

natural law." *Mayo*, 566 U.S. at 77. In Appellant's claim 1 the relation between the effect of the agent and a downstream biological entity is a consequence of the ways in which the agent acts on the biological system – also an entirely natural process.

Appellant argues that the steps of claim 1 cannot be performed practically in the human mind because they require a large-scale treatment data set to ensure that the variability of a vast amount of data is taken into account. (*See* Appeal Br. 23–24; *see* Reply Br. 12–13.) We are not persuaded by this argument because claim 1 does not recite a limitation on the size of the data set from which the treatment and control data is obtained. Nor does claim 1 recite any degree of certainty or confidence in determining a score representative of the perturbation of the biological system that would indicate how big the data set must be. Accordingly, claim 1 could encompass even small databases and limited biological systems.

We are also unpersuaded by Appellant's argument regarding the size of the data sets because simply reciting the use of a computer to perform complicated calculations or algorithms that could be performed by the human mind does not necessarily make a method patentable. *See CyberSource Corp. v. Retail Decisions, Inc.*, 654 F.3d 1366, 1375 (Fed. Cir. 2011) ("That purely mental processes can be unpatentable, even when performed by a computer, was precisely the holding of the Supreme Court in *Gottschalk v. Benson* [409 U.S. 63, 67 (1972)]."); *see Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1335 (Fed. Cir. 2015) ("Courts have examined claims that required the use of a computer and still found that the underlying, patent-ineligible invention could be performed via pen and paper or in a person's mind."). Therefore, although the claim may recite steps

which are accomplished on a computer, the computer-implementation does not confer patent-eligibility because the steps could still be performed by a human. *See Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1318 (Fed. Cir. 2016) ("Furthermore, with the exception of generic computer-implemented steps, there is nothing in the claims themselves that foreclose them from being performed by a human, mentally or with pen and paper.").

Appellant refers to the example in the Specification of TNF-treated NHBE cells, where a computational causal network model was formed out of a database repository with 1.5 million nodes and over 7.5 million edges. (*See* Appeal Br. 23, citing Spec. ¶ 100.) Although Appellant argues that scanning such a vast database could not possibly be performed in the human mind, we do not limit claim 1 to this example. "Claims, not the specification embodiments, define the scope of the protection." *American Permahedge, Inc. v. Barcana, Inc.*, 105 F.3d 1441, 1444 (Fed. Cir. 1997).

Appellant also argues that the method of claim 1 is not an abstract idea in light of Example 39 of the Subject Matter Eligibility Examples regarding abstract issued by the USPTO on January 7, 2019. (*See* Appeal Br. 20–24, citing https://www.uspto.gov/sites/default/files/documents/101_examples_37to42_20190107.pdf.) Appellant argues that, like the claim directed to a method for training a neural network in Example 39, Appellant's claims "do not recite any mathematical concepts including mathematical relationships, mathematical formulas or equations, or mathematical calculations." (Appeal Br. 21.) Appellant argues that instead, the pending claims are drawn to "using a computational causal network model to simulate interaction within

a biological system, taking into account edge and direction values which represent causal activation relationships between nodes which represent sets of biological entities . . . ." (*Id.*)

In Example 39, the steps were found to address the problem of false-positives encountered with prior methods by training a neural network. The claims were characterized as not invoking the mental process category of abstract ideas. The difference between Appellant's claims and the claim of the network is that the Examiner found that steps in the claims could be performed in the human mind, whereas the Example steps could not be practically performed in the mind. An improvement in the judicial exception, itself, cannot serve as the technological improvement upon which eligibility is based. Eligibility Guidelines 55 (fn. 24).

Appellant characterizes the claimed method as not being based on any mathematical formula or algorithm, but rather on dynamic comparisons and evaluations with respect to received data. (*See* Appeal Br. 22; *see* Reply Br. 7–11.) According to Appellant, "although a network model is based off of a mathematical concept, the model as recited is not itself a mathematical concept, wherein the network model itself is not a mathematical relationship, formula/equation, or calculation, as described in p. 3 of the USPTO update." (Reply Br. 19.) Appellant's Specification that a "network model of a biological system is a mathematical construct that is representative of a dynamic biological system and that is built by assembling quantitative information about various basic properties of the biological system." (Spec. ¶ 47; *see* Ans. 18–19.) The Specification also states that a score "is computed by using any of various mathematical and computational algorithms known in the art and according to the methods disclosed herein,

employing one or more datasets obtained from a sample or a subject." (Spec. ¶ 30.)

Even if we agree that Appellant's claims do not recite mathematical relationships, formulas, or calculations as determined in Example 39, the claim in Example 39 provides a trained neural network, a machine learning process that bases input on previously learned training processes to train the network to detect faces, whereas Appellant's claims merely generate a score. The Examiner notes further that Appellant's claims include "'calculating' steps" and steps to generate a score. (*See* Ans. 19.) Thus, even if Appellant's claims do not recite mathematical concepts as equations, we are not persuaded by Appellant's argument that they are not based on mathematical concepts based on at least this step of the claim. (*See* Ans. 18.)

Because we find that the Examiner did not err in determining Appellant's claims to recite the judicial exception of an abstract idea, including the mental process of receiving data, generating a mechanism hypotheses, and then calculating activity measures and weight values to generate a score, we must inquire whether the claim as a whole integrates the abstract ideas into a practical application under step 2A, prong 2 of the 2019 Guidelines. (*See* 2019 Guidelines, 84 Fed. Reg. at 54–55.)

We agree with the Examiner that Appellant's claims do not describe any specific computational steps or any specific structures for a computer to carry out the abstract ideas. (*See* Ans. 23.) Appellant argues that the claimed method solves the need for improved computing systems and methods of analyzing system-wide biological data, but fails to point to any improved computer technology that was developed to carry out the claimed

methods. (*See* Appeal Br. 25–28, Reply Br. 14, 24.) We are not persuaded by this argument because Appellant's Specification provides that the methods can be carried out on "a conventional standalone computer." (Spec. ¶ 108.) As the Examiner finds, Appellant's claimed methods are not about an improvement in computing technology, but rather an improvement in the analysis of biological data. (*See* Ans. 21.)

According to Appellant, the claim element "generating, with the at least one processor, a score for the scorable network model" creates a network model to understand disease mechanisms and the underlying effect of harmful agents, and can thus directly effect a particular treatment or prophylaxis for a disease or medical condition as provided in the 2019 Guidelines. (*See* Appeal Br. 29–30; Reply Br. 25–29.) We are not persuaded by Appellant's argument because the claimed methods do not recite any treatments or prophylaxis. (*See* 2019 Guidelines, 84 Fed. Reg. at 55; *see* Ans. 20.) Whereas claims that recite actually treatments or prophylaxis, such as immunization or administration of a drug, have been held to be patent eligible, Appellant's claims recite no similar treatment or prophylaxis. *See Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1066–68 (Fed. Cir. 2011); *Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1135 (Fed. Cir. 2018).

Because Appellant's claims do not integrate the judicial exception into a practical application, we continue to evaluate patent eligibility by considering whether the claim provides an inventive concept that amounts to significantly more than the exception itself, under step 2B of the 2019 Guidelines. (*See* 2019 Guidelines, 84 Fed. Reg. at 56.) Appellant argues that the claimed methods more accurately predict the changes of entities

underlying biological mechanisms. (*See* Appeal Br. 28–30.) We disagree because the claimed method simply appends understood, routine, conventional activities previously known to the industry, specified at a high level of generality to the judicial exception of the mental activity of receiving data, generating a set of hypotheses, and scoring the hypotheses. Claim 1 recites only generic computer components, "processors," that are used for implementing the abstract idea. Furthermore, for the reasons discussed in the analysis of the Examiner's rejection of claim 1 as being obvious under 35 U.S.C. § 103(a), we are not persuaded the claimed methods provide any inventive concept beyond what was known in the art and the abstract ideas recited in the claims.

Accordingly, we are not persuaded that the Examiner erred in rejecting Appellant's pending claims as being directed to ineligible subject matter under 35 U.S.C. § 101.

Conclusion

Upon consideration of the record and for the reasons given, we affirm the Examiner's rejection.

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1, 4–23, 26–28	112, first paragraph			1, 4–23, 26–28
1, 4–23, 26–28	101		1, 4–23, 26–28	
1, 4–13, 15–21, 23, 28	103	Ladd, Toyoshiba, Strimmer	1, 4–13, 15–21, 23, 28	

14	103	Ladd, Toyoshiba, Strimmer, Löfroth	14	
14, 26, 27	103	Ladd, Toyoshiba, Strimmer, Sexton	14, 26, 27	
22	103	Ladd, Toyoshiba, Strimmer, Friedman	22	
Overall Outcome			1, 4–23, 26–28	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136.

AFFIRMED