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Datasheet for the decision of 18 January 2023

Case Number: T 2835/19 - 3.3.08

Application Number: 16189216.1

Publication Number: 3170904

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
Compositions and methods for nucleic acid sequencing

Patent Proprietor:
Pacific Biosciences Of California, Inc.

Opponent:
Oxford Nanopore Technologies PLC

Headword:
Methods for nucleic acid sequencing II/PACIFIC BIOSCIENCES

Relevant legal provisions:
EPC Art. 100(c), 123(2), 76(1)

Keyword:
Main request, auxiliary requests 1 to 3 and 5 to 8 - added subject-matter (yes)

Decisions cited:
G 0002/10, T 1219/19

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Case Number: T 2835/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 18 January 2023

Appellant: (Patent Proprietor)	Pacific Biosciences Of California, Inc. 1305 O'Brien Drive Menlo Park, CA 94025 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	Oxford Nanopore Technologies PLC Gosling Building Edmund Halley Road Oxford Science Park Oxford OX4 4DQ (GB)
Representative:	Patent Boutique LLP 10A Printing House Yard Hackney Road London E2 7PR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 August 2019 revoking European patent No. 3170904 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	R. Morawetz
	A. Bacchin

Summary of Facts and Submissions

I. European patent EP 3 170 904 ("the patent") is based on European patent application No. 16 189 216.1 ("the application"), which was filed as a divisional application in respect of earlier (parent) European patent application No. 15 191 903.2 ("the parent application"). The latter had been filed as a divisional application in respect of earlier (grandparent) European patent application No. 09 724 672.2, published as WO 2009/120372 ("the grandparent application"). The patent is entitled "Compositions and methods for nucleic acid sequencing".

II. One opposition to the granted patent was filed. The patent was opposed under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and (c) EPC.

III. The opposition division revoked the patent. The opposition division's decision is based on the sets of claims of a main request (patent as granted), auxiliary requests 1 to 3, submitted by letter dated 11 October 2018, and auxiliary requests 4 to 7, submitted by letter dated 24 June 2019. The opposition division held *inter alia* that the subject-matter of claim 1 of the main request and of auxiliary requests 1 to 3, 5 and 6 infringed Articles 123(2) and 76(1) EPC. Claim 1 of auxiliary request 7 was held to comply with Articles 123(2) and 76(1) EPC but to lack clarity (Article 84 EPC). Auxiliary request 4 was not admitted into the proceedings.

IV. The patent proprietor (appellant) filed notice of appeal against the opposition division's decision.

V. With the statement setting out the grounds of appeal, the appellant maintained the patent as granted as its main request and submitted sets of claims of auxiliary requests 1 to 8. Auxiliary requests 1 to 7 were identical to auxiliary requests 1 to 7 considered in the decision under appeal while auxiliary request 8 was newly filed.

VI. Claim 1 of the main request (patent as granted) reads as follows:

"1. A method for carrying out nucleic acid sequence analysis, said method comprising:
a. Providing a double stranded nucleic acid having two complementary strands;
b. Fragmenting said double stranded nucleic acid into double stranded nucleic acid fragments;
c. Connecting the two complementary strands of the double stranded nucleic acid fragments prepared in step (b) with a linking oligonucleotide, wherein the 3' end of one complementary strand is linked to the 5' end of the other complementary strand via the linking oligonucleotide in each double stranded nucleic acid fragment, whereby the linking oligonucleotide provides a single stranded portion of the resulting linked nucleic acid fragments;
d. Determining the consensus sequence of each double stranded nucleic acid fragment from the sequences of the two complementary strands by single-molecule sequencing of the linked nucleic acid fragments."

Claim 1 of each of auxiliary requests 1 to 3 is identical to claim 1 of the main request.

Claim 1 of auxiliary request 5 differs from claim 1 of the main request in that step (d) is amended to indicate that the consensus sequence is determined "*by single-molecule, real-time sequencing of the linked nucleic acid fragments obtained in step (c)*" (amendments with respect to claim 1 of the main request are shown by underlining).

Claim 1 of auxiliary request 6 differs from claim 1 of the main request in that step (d) is amended to indicate that the consensus sequence is determined "*by performing a single-molecule, real-time sequencing process ~~of~~ using the linked nucleic acid fragments obtained in step (c) as templates*" (amendments with respect to claim 1 of the main request are shown by underlining and strike-through).

Claim 1 of auxiliary request 7 differs from claim 1 of the main request in that step (d) is amended to indicate that the consensus sequence is determined "*by template-directed single-molecule, real-time sequencing of the linked nucleic acid fragments obtained in step (c)*" (amendments with respect to claim 1 of the main request are shown by underlining).

Claim 1 of auxiliary request 8 differs from claim 1 of the main request in that step (c) is amended by the insertion of the feature "Configuring the double stranded nucleic acid fragments prepared in step (b) as templates for sequencing by ..." and in that step (d) is amended to indicate that the consensus sequence is determined "*by performing a template-directed single-molecule, real-time sequencing process ~~of~~ using the*

linked nucleic acid fragments *obtained in step (c)*"
(amendments with respect to claim 1 of the main request are shown by underlining and strike-through).

VII. The opponent (respondent) filed a reply to the appeal.

VIII. The board scheduled oral proceedings in accordance with the parties' requests and subsequently issued a communication under Article 15(1) RPBA.

IX. Oral proceedings before the board took place as scheduled. During the oral proceedings, the appellant stated that regarding the ground for opposition under Article 100(c) EPC with respect to claim 1 of the main request, it would be relying solely on the submissions made during the oral proceedings that same day in case T 1219/19. The appellant later withdrew auxiliary request 4. At the end of the oral proceedings the Chairwoman announced the board's decision.

X. The following documents are referred to in this decision:

D13 Shendure J. and Hanlee J., Nature Biotechnology 26 (10), 2008, 1135 to 1145

D18 Clarke J. et al., Nature Nanotechnology 4, 2009, 265 to 270

XI. The appellant's arguments, in so far as they are relevant to the decision, are summarised below.

Main request (patent as granted)
Added subject-matter (Article 100(c) in conjunction with Articles 123(2) and 76(1) EPC) - claim 1

The processes for sequencing in terms of concrete steps to be taken to reproduce the template sequence described in the grandparent application were polymerase-mediated sequencing-by-synthesis processes.

In addition, though, the grandparent application disclosed template constructs and their utility (see paragraphs [0053] and [0054]). These paragraphs, when read together, provided a stand-alone direct and unambiguous disclosure of the utility of the template configurations according to the invention in any single-molecule sequencing process, without further qualification, and not just in the more limited context of the polymerase-dependent SMRT™ sequencing technology.

Thus, paragraph [0053] of the grandparent application disclosed that one of the advantages of the invention, in so far as it related to the templates of the invention, was that it enabled "*single molecular consensus sequence determination*" because the template included both sense and antisense strands and these were sequenced in the same single-molecule sequencing process. This was further explained in paragraph [0053] (see page 13, lines 5 to 7).

The understanding that "*single molecular consensus sequence determination*" meant single-molecule sequencing was confirmed by Example 2 of the

grandparent application (see paragraph [0142]), which provided an example of single molecular consensus sequence determination, namely single-molecule sequencing at the same level of generality as paragraph [0053] of the grandparent application.

Paragraph [0054] of the grandparent application gave an example of how the template configurations of the invention could be used in the context of a single-molecule sequencing process (see page 13, lines 16 to 20).

In summary, paragraph [0053] of the grandparent application described the utility of the template of the invention, namely that it could be used to achieve consensus sequence determination in a single-molecule sequencing process, and paragraph [0054] of the grandparent application extended this utility to any single-molecule sequencing process by describing a process that took advantage of the template.

Therefore, what was disclosed when paragraphs [0053] and [0054] of the grandparent application were read together was that the template of the invention could be used to generate a consensus sequence in a single-molecule sequencing process. This disclosure provided the basis for a claim drafted to the use of a template construct of the invention for determining the consensus sequence using a single-molecule sequencing process by the method described at the end of paragraph [0053] of the grandparent application. Claim 1, a method claim, was merely a re-drafted version of such a use claim.

Contrary to the respondent's submissions, the processes mentioned in paragraph [0054] of the grandparent

application in relation to a registration sequence ("*e.g. the same molecule, or identical molecules in a template population*") were single-molecule sequencing processes because a registration sequence had no use in ensemble sequencing. In so far as paragraph [0054] referred to a "*template population*", it referred to parallel single-molecule sequencing. The argument that everything from paragraph [0052] of the grandparent application onwards related to bioinformatics and not to sequencing processes was contradicted by paragraph [0054], which described a sequencing process.

It was irrelevant that paragraph [0054] of the grandparent application did not provide any technical information regarding which single-molecule sequencing processes could be used because it was stated that the templates of the invention could be used in any single-molecule sequencing process. What was disclosed was a genus of single-molecule sequencing processes, not a species.

Paragraph [0054] of the grandparent application made it clear (see "*e.g., is primed*" on page 13, line 23) that it was optional, not essential, to use a sequencing process that involved priming, i.e. a polymerase-mediated sequencing-by-synthesis process.

The use of the term "single-molecule sequencing" in claim 1 therefore met the requirements of Articles 123(2) and 76(1) EPC.

Auxiliary requests 1 to 3
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The subject-matter of claim 1 of auxiliary requests 1

to 3 did not add matter for the same reasons as given for claim 1 of the main request.

Auxiliary request 5
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

A verbatim basis for the claimed process was found in paragraph [0048] of the grandparent application. The skilled person would directly and unambiguously derive from paragraph [0048] that they would benefit most from the templates of the invention by employing them in "*single molecule, real-time sequencing processes*", which were otherwise not further defined.

The "*single molecule, real-time sequencing processes*" disclosed in paragraph [0048] of the grandparent application were a subset of the template-directed processes mentioned at the beginning of paragraph [0048].

The references to "*nanopore*" and document D18 in paragraph [0046] of the grandparent application made it clear that the templates of the invention had utility in nanopore sequencing. From the disclosure in paragraph [0046], the skilled person would therefore understand that nanopore sequencing processes were encompassed by the "*single molecule, real-time sequencing*" processes in paragraph [0048] of the grandparent application.

By stating "*e.g., is primed*", paragraph [0054] of the grandparent application contradicted the assertion that the application only disclosed polymerase-mediated sequencing-by-synthesis processes (see page 13, line 23). In addition, by stating "*By way of*

example" (see page 23, line 20), paragraph [0083] of the grandparent application provided evidence that the application disclosed more than sequencing-by-synthesis processes.

At the priority date, nanopore sequencing was known by the skilled person to be a single-molecule, real-time sequencing process (see document D13, Box 3). It was therefore encompassed by the language "*single molecule, real-time sequencing processes*" in paragraph [0048] of the grandparent application anyway.

The disclosure in paragraph [0048] of the grandparent application was therefore not limited to "*single molecule, real-time sequencing processes*" that were also sequencing-by-synthesis processes, and claim 1 complied with Articles 123(2) and 76(1) EPC.

Auxiliary request 6
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The language of claim 1 was closer to the language of paragraph [0048] of the grandparent application.

Auxiliary request 7
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

Claim 1 of auxiliary request 7 had exactly the same wording as paragraph [0048] of the grandparent application. Template-directed processes were processes that exploited the template configurations of the invention. They were template-directed to the extent that the template made it possible to provide

duplicative or replicate data.

Auxiliary request 8
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

Claim 1 made reference to a template-directed "*single-molecule, real-time sequencing process*" in accordance with the disclosure in paragraph [0048] of the grandparent application.

XII. The respondent's arguments, in so far as they are relevant to the decision, are summarised below.

Main request (patent as granted)
Added subject-matter (Article 100(c) in conjunction with Articles 123(2) and 76(1) EPC) - claim 1

There was no teaching anywhere in the grandparent application of a generic group of sequencing processes that might be used and which could be equated with the expression "a single-molecule sequencing process" as used in claim 1. Every single method described in the grandparent application related to sequencing-by-synthesis processes (see paragraphs [0037] to [0047]).

In discussing paragraph [0053] of the grandparent application, the appellant had ignored its context, in particular paragraph [0052], which was important in understanding paragraph [0053]. Paragraph [0053] related to handling data, not to how those data were obtained.

The term "*single molecular consensus sequence determination*" described an alleged technical benefit of the constructs of the disclosure, not a sequencing

process. Paragraph [0053] of the grandparent application did not equate the term "*single molecular consensus sequence determination*" with sequencing both the sense and antisense strands "in the same single-molecule sequencing process". Paragraph [0053] taught nothing about the sequencing process – it merely discussed a feature provided by the structure of the templates.

There was nothing in the grandparent application as filed that encouraged the skilled person to infer from the term "*single molecular consensus sequence determination*" that this feature of the template configurations of obtaining duplicative or replicate data was applicable only to the field of single-molecule sequencing and not to the ensemble sequencing processes that were also discussed in the earlier application as filed. There was no reason, therefore, to interpret paragraph [0053] as providing a disclosure of a broad concept of single-molecule sequencing.

From paragraph [0142] of the grandparent application it did not follow that "*single molecular consensus sequence determination*" as referred to in paragraph [0053] was "single-molecule sequencing" by definition. Example 2 used a sequencing-by-synthesis process, i.e. SMRT™, to assess how accurate the consensus determination was. It therefore confirmed that paragraph [0053] was about data handling, not single-molecule sequencing.

The sentence in paragraph [0054] of the grandparent application relied on by the appellant (see page 13, lines 16 to 20) referred to "*a single template molecule*", not to a single molecule; it did not describe the sequencing process and was not limited to

single-molecule sequencing processes. Reference to "*a single template molecule*" in this sentence meant that a single species of template molecule was used in one integrated process to obtain sense and antisense sequence reads. It was immediately apparent to the skilled reader that the teaching of paragraph [0054] related to both ensemble methods and the single-molecule sequencing methods disclosed in the application. Therefore, it did not make sense to interpret "*a single template molecule*" in this sentence as referring to just one molecule and thus to single-molecule sequencing. The purpose of the registration sequence was spelled out in paragraph [0054] and was not that alleged by the appellant, namely aligning multiple copies in parallel single-molecule sequencing, which was not mentioned in the application at all. There was no disclosure in the grandparent application that Figure 3A related exclusively to single-molecule sequencing.

Even if the skilled person understood paragraph [0054] of the grandparent application as referring to single-molecule sequencing, the paragraph taught nothing about how that sequencing should be carried out, i.e. the steps to be taken. How the process was to be carried out was described in paragraphs [0037] to [0047] of the grandparent application as filed. These were all sequencing-by-synthesis processes, whether they were single-molecule sequencing processes or ensemble sequencing processes. The only single-molecule sequencing processes that were described in the grandparent application were sequencing-by-synthesis methods, and there was nothing in paragraph [0054] that changed that.

Paragraph [0054] of the grandparent application (see

page 13, line 23) was not enough to change the impression that the skilled person got from reading the whole grandparent application. Therefore, asserting that "*e.g., is primed*" should be construed as disclosing any single-molecule sequencing process was not credible.

Since all single-molecule sequencing methods disclosed in the grandparent application were sequencing-by-synthesis methods, the lack of reference to sequencing-by-synthesis in claim 1 added matter.

Auxiliary requests 1 to 3
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

Claim 1 of auxiliary requests 1 to 3 added matter for the same reasons as given for claim 1 of the main request.

Auxiliary request 5
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The sequencing process in claim 1 was more generic than what was disclosed in paragraph [0048] of the grandparent application.

The reference in paragraph [0048] to "*template directed processes described herein*" indicated that the sentence referred to sequencing processes described in the grandparent application.

The skilled person would understand that, in so far as the invention related to methods, paragraphs [0037] to [0047] of the grandparent application under the heading

"DETAILED DESCRIPTION OF THE INVENTION" described sequencing processes in which the (later-described) templates of the invention were to be used.

The skilled person reading paragraph [0048] of the grandparent application would turn to this section and to the examples to learn what the "*template directed processes described herein*" and the "*preferred single molecule, real-time sequencing processes*" used to illustrate the invention were. The only single-molecule sequencing processes described in the grandparent application were SMRT™ sequencing and any similar process encompassed by the teaching of paragraphs [0042] to [0045] of the grandparent application. SMRT™ was also used in Examples 2 to 4 of the grandparent application. These were all sequencing-by-synthesis processes.

Paragraph [0046] of the grandparent application did not disclose nanopore sequencing. Nanopore was mentioned in the context of SMRT processes for detection only. Document D18 provided means for detecting analogs.

The phrase in paragraph [0048] of the grandparent application therefore did not redefine the sequencing processes or provide a new generic class of sequencing processes that were "*single molecule, real-time sequencing processes*" but not sequencing-by-synthesis processes.

The disclosure of "*e.g., is primed*" in paragraph [0054] of the grandparent application did not change the teaching of the application in paragraphs [0037] to [0047] of the grandparent application. It did not follow from the disclosure of "*By way of example,*" in paragraph [0083] of the grandparent application that

not all processes described were sequencing-by-synthesis processes because paragraph [0037] of the grandparent application also disclosed sequencing-by-synthesis processes that were ligase-mediated, not polymerase-mediated.

There was no direct and unambiguous disclosure of sequencing methods that were not sequencing-by-synthesis single-molecule, real-time sequencing processes in the grandparent application. Since claim 1 was not limited to processes that were sequencing-by-synthesis processes, it added matter.

Auxiliary request 6
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The amendments to claim 1 in auxiliary request 6 did not limit the claimed subject-matter to sequencing-by-synthesis processes.

Auxiliary request 7
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The opposition division's finding that auxiliary request 7 complied with Articles 123(2) and 76(1) EPC was incorrect as the opposition division had taken a purely linguistic approach. Paragraph [0048] of the grandparent application did not disclose a generic class of sequencing processes that were "*single molecule, real-time sequencing processes*".

The appellant also agreed that the feature "*template-directed*" did not limit the claimed subject-matter to sequencing-by-synthesis processes. The amendments

therefore did not solve the added-matter problem.

Auxiliary request 8
Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

The amendments made did not solve the added-matter problem because they did not limit the claimed subject-matter to sequencing-by-synthesis processes.

XIII. The appellant (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained as granted (main request) or, alternatively, that the patent be maintained as amended on the basis of one of auxiliary requests 1 to 3. As a further alternative, it requested that the patent be maintained as amended on the basis of one of auxiliary requests 5 to 7. As a further alternative, it requested that auxiliary request 8 be admitted into the proceedings and the patent be maintained as amended on that basis. In the context of all of the above requests, it requested that the case be remitted to the opposition division for consideration of the grounds under Article 100(a) EPC, as to lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) EPC if the requirements of Articles 76(1) and 123(2) EPC were held to be satisfied in respect of any of the claim requests.

The respondent (opponent) requested that the appeal be dismissed, that auxiliary request 8 not be admitted into the appeal proceedings and that the case be remitted to the opposition division for further prosecution in the event that the appeal was allowed in relation to any claim request.

Reasons for the Decision

Main request (patent as granted) - claim 1

The claimed invention - claim construction

1. The claim is directed to a method for carrying out nucleic acid sequence analysis, said method comprising the step of determining the consensus sequence of each double-stranded nucleic acid fragment from the sequences of the two complementary strands by "*single-molecule sequencing*" of the linked nucleic acid fragment.

2. It was common ground that the expression "*single-molecule sequencing*" did not imply any particular sequencing process and in particular did not limit the claimed subject-matter to sequencing-by-synthesis processes. The board sees no reason to deviate from this understanding.

Added subject-matter (Article 100(c) in conjunction with Articles 123(2) and 76(1) EPC) - claim 1

3. The opposition division held that the application, the parent application and the grandparent application did not provide a basis for a generic process of "*single-molecule sequencing*" as recited in step (d) of claim 1 and that claim 1 therefore infringed Articles 123(2) and 76(1) EPC.

4. If a divisional application is amended, it must meet the requirements of both Article 123(2) EPC and Article 76(1) EPC. It is established jurisprudence that the standard for assessing compliance with the

requirements of Articles 123(2) EPC and 76(1) EPC is the same (see G 1/05, OJ EPO 2008, 271, Reasons 5.1), namely the standard set out in decision G 2/10 (OJ EPO 2012, 376, Reasons 4.3), also known as the "gold standard". Amendments are only permitted within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the (earlier) application as filed. After the amendment, the skilled person may not be presented with new technical information (ibid., Reasons 4.5.1).

5. It is common ground that the descriptions of the divisional application as filed, the parent application as filed and the grandparent application as published are identical (including the paragraph numbering), with the exception that the claims of the grandparent application are incorporated as items into the descriptions of the parent application as filed and the divisional application as filed. Since in the case in hand the test for whether the claimed subject-matter extends beyond the content of the divisional application (Article 123(2) EPC) and the test for whether the claimed subject-matter extends beyond the content of the parent or the grandparent application (Article 76(1) EPC) are based on the consideration of identical passages in all three applications, the tests can be combined. For ease of reference, the divisional application, the parent application and the grandparent application are referred to in the following simply as "the application" and, unless indicated otherwise, reference is made in this decision to the page and paragraph numbering of the grandparent application (published as WO 2009/120372).

6. Under the heading "DETAILED DESCRIPTION OF THE INVENTION", Chapter I of the application describes what are known in the art as sequencing-by-synthesis methods: To identify the nucleotide sequence of the template, a polymerase or ligase is used to generate a complementary strand, and individual bases, or groups of bases, are identified as they are incorporated into an elongating strand that is complementary to the template (see paragraph [0037]). These methods are further illustrated by reference to Sanger sequencing methods, which use populations of template molecules (see paragraph [0038]; also referred to as ensemble sequencing processes in this decision, in line with the respondent's submissions). The methods are further illustrated by reference to single-molecule real-time sequencing methods, such as the SMRT™ sequencing method and the like, which are sequencing-by-synthesis methods in which the incorporation of differently labelled nucleotides is observed in real time as they are added in a polymerase-mediated primer extension reaction (see paragraphs [0042] to [0045]). In agreement with the respondent's submissions, the board considers that Chapter I of the application describes the processes that are intended to be used to implement the sequencing methods of the invention.

7. In Chapter II, entitled "Contiguous Double Stranded Templates", the application sets out the structure of partially and completely contiguous templates with double-stranded segments, their general construction, preparation and advantages in terms of sequence data handling "[f]*ollowing sequence determination*" (see in particular paragraphs [0052], [0053] and [0054]).

8. The appellant did not dispute that the application describes processes for single-molecule sequencing in terms of concrete steps to be taken to reproduce the template sequences, which involve a polymerase-mediated sequencing-by-synthesis process, or that the application did not verbatim disclose performing "*a single-molecule sequencing process*" on a nucleic acid sequencing template.

9. However, it submitted that in paragraphs [0053] and [0054] the application provided a stand-alone disclosure of the utility of the template configurations of the invention in any single-molecule sequencing process, in terms which were not limited to sequencing-by-synthesis processes, thus providing a basis for claim 1.

10. The appellant's line of reasoning hinges on the propositions that (i) paragraph [0053] of the application discloses that one of the advantages of the invention, in so far as it relates to the templates of the invention, is that it enables "*single molecular consensus sequence determination*" because the template includes both sense and antisense strands and these are sequenced in the same single-molecule sequencing process, and that (ii) paragraph [0054] of the earlier application extends this teaching to any single-molecule sequencing process (see section XI. above).

11. The passage in paragraph [0053] of the application relied on by the appellant as disclosing single-molecule sequencing reads as follows:

"*The templates of the invention provide numerous advantages over simple linear template sequences, and even other circular template sequences (...). In*

particular, as with circular templates, the template configurations of the invention allow for single molecular consensus sequence determination, where sequencing a given template provides duplicative or replicate data of the sequence information obtained, and thereby improves accuracy over linear templates by providing multiple reads for a given template sequence or sequence portion, that can be used to derive consensus sequence data from a given template sequence and/or for specific base locations within such sequence" (emphasis added by the board).

12. It is apparent that this passage neither specifically mentions single-molecule sequencing nor equates the expression "*single molecular consensus sequence determination*" with sequencing a template in a single-molecule sequencing process. Indeed, paragraph [0053] of the application is silent on the process used for "*sequencing a given template*" and provides no technical information regarding any of the steps involved in sequencing the template, i.e. it does not explicitly disclose a single-molecule sequencing process.

13. The appellant's argument that paragraph [0053] of the application discloses that one of the advantages of the invention, in so far as it relates to the templates of the invention, is that it enables "*single molecular consensus sequence determination*" because the template includes both sense and antisense strands and these are sequenced in the same single-molecule sequencing process is thus understood by the board to mean that paragraph [0053] implicitly discloses a single-molecule sequencing process.

14. It is established jurisprudence that the term "implicit disclosure" relates solely to matter that any person

skilled in the art, using common general knowledge, would consider as necessarily implied by the application as a whole, as a clear and unambiguous consequence of what is explicitly mentioned (see also the Case Law of the Boards of Appeal, 10th edition 2022 ("CLBA"), section II.E.1.3.3).

15. Paragraph [0053] of the application defines "*single molecular consensus sequence determination*" as "*where sequencing a given template provides duplicative or replicate data (...) by providing multiple reads for a given template sequence or sequence portion, that can be used to derive consensus sequence data from a given template sequence ...*" (see page 12, fifth line from the bottom to the last line).

16. The skilled person reading paragraph [0053] of the application understands that obtaining duplicative data is a feature of the template configuration, not the mode of sequencing, since the template's partially contiguous structure allows both strands of the template to be sequenced, providing "*duplicative or replicate data*". This understanding is further supported by paragraph [0053], which sets out that "*the templates of the invention, by virtue of their inclusion of double stranded segments, provide consensus sequence determination through the sequencing of both the sense and antisense strand of such sequences (in both the partially and completely contiguous configurations)*" (see page 13, lines 4 to 7).

17. The board concludes from the above that the skilled person reading paragraph [0053] would understand that the expression "*single molecular consensus sequence determination*" describes a benefit of the templates for

deriving a consensus sequence but not a sequencing process. The skilled person would furthermore understand this benefit to be the result of the templates' structure, not of the particular process for sequencing the template. Moreover, there is nothing in paragraph [0053] to indicate that the feature of obtaining "*duplicative or replicate data*" is only achieved in a single-molecule sequencing process and would not also be achieved in any other sequencing process, e.g. sequencing processes that use populations of identical template molecules.

18. Contrary to the appellant's submission, the expression "*single molecular consensus sequence determination*" in the context of paragraph [0053] therefore does not necessarily imply to the skilled reader that the sense and antisense strands of the template are sequenced in the same single-molecule sequencing process.

19. Nor does consideration of Example 2 support the appellant's assertion that "single molecular consensus sequence determination" means single-molecule sequencing. The reasons are as follows. Example 2 does not equate the term "*single molecular consensus sequencing*" with single-molecule sequencing, and while Example 2 uses SMRT™ sequencing, which is a single-molecule sequencing process, it is evident that the expression "*single molecular consensus sequencing*" as used in Example 2 relates not to the sequencing process itself but to the subsequent determination of a consensus sequence from multiple sequence reads (see paragraphs [0142] and [0143] of the application). Contrary to the appellant's submission, Example 2 therefore also fails to provide an example of single molecular consensus sequence determination which is single-molecule sequencing. Instead it supports the

understanding that the expression "*single molecular consensus sequencing*" relates not to the sequencing process as such but to the sequence data analysis, following sequence determination.

20. The passage in paragraph [0054] relied on by the appellant as providing a basis for single-molecule sequencing processes in general reads as follows:

"*By way of example, with respect to a partially contiguous template shown in Figure 2A, obtaining the entire sequence, e.g., that of segments 202, 204 and 206 provides a measure of consensus sequence determination by virtue of having sequenced both the sense strand, e.g., segment 202, and the antisense strand, e.g., segment 204. In addition to providing sense and antisense sequence reads from a single template molecule that can be sequenced in one integrated process, the presence of linking segment 206 also provides an opportunity to provide a registration sequence that permits the identification of when one segment, e.g., 202, is completed and the other begins, e.g., 204. Such registration sequences provide a basis for alignment sequence data from multiple sequence reads from the same template sequences, e.g., the same molecule, or identical molecules in a template population. The progress of sequencing processes is schematically illustrated in Figure 3A. In particular, as shown, a sequencing process that begins, e.g., is primed, at the open end of the partially contiguous template, proceeds along the first or sense strand, providing the nucleotide sequence (A) of that strand, as represented in the schematic sequence readout provided.*" (emphasis added by the board; see paragraph [0054], page 13, lines 13 to 26).

21. While this passage mentions that "*a single template molecule ... can be sequenced in one integrated process*", it is silent about the steps of the "*integrated process*" and does not explicitly disclose that this process is a single-molecule sequencing process.

22. It is evident that the skilled person would not necessarily interpret the reference to "*from a single template molecule*" (see point 20. above) as referring to just one molecule in view of the following sentence in paragraph [0054], which discloses that the "*same template sequences*" can be "*the same molecule, or identical molecules in a template population*" (see point 20. above).

23. The skilled person would understand this reference to "*the same molecule, or identical molecules in a template population*" to relate to single-molecule sequencing or ensemble sequencing processes that use populations of identical template molecules. In this context, the board notes that the reference to the "*registration sequence*" in paragraph [0054] does not alter this understanding. Paragraph [0054] explains that the purpose of the registration sequence is applicable to single-molecule sequencing and ensemble sequencing processes. On the other hand, the application does not disclose using the registration sequence when aligning multiple copies in parallel single-molecule sequencing, which was cited by the appellant to refute the disclosure of ensemble sequencing.

24. The reference to "*from a single template molecule*" therefore does not implicitly limit the "*integrated process*" disclosed in paragraph [0054] (see point 20.

above) to single-molecule sequencing processes.

25. Furthermore, assuming that the skilled person understands paragraph [0054] of the application to be referring to single-molecule sequencing as one option, it remains a fact that paragraph [0054] is silent on the technical details of the sequencing process. However, contrary to the appellant's assertion, the consequence of this lack of teaching is not that paragraph [0054] discloses a genus of single-molecule sequencing processes.

26. Instead, the consequence is that the skilled person reading paragraph [0054] with the common general knowledge in mind and in the context of the application as a whole (see point 4. above) turns to the remainder of the application for guidance on how to perform the sequencing process mentioned in paragraph [0054]. As set out in point 6. above, the sequencing processes that are described in the application are all sequencing-by-synthesis methods, be it ensemble or single-molecule sequencing processes. The appellant has not argued that the skilled person would arrive at a different conclusion on the basis of their common general knowledge.

27. Contrary to the appellant's submissions, therefore, paragraph [0054] of the application does not disclose that the templates of the invention can be used in single-molecule sequencing processes in general.

28. This conclusion is not changed by the appellant's further argument that paragraph [0054] of the application made it clear that it was optional to use a sequencing process that involved priming, i.e. a polymerase-mediated sequencing-by-synthesis process,

meaning that the technical teaching of the application as filed was not limited to polymerase-mediated sequencing-by-synthesis methods.

29. Even if the skilled person were to interpret paragraph [0054] of the application as disclosing that priming is optional, this does not mean that there is any disclosure of a single-molecule sequencing process that would not be a sequencing-by-synthesis process.

30. It remains a fact that paragraph [0054] of the application is silent on the technical details of the sequencing process, and the mention of "*e.g., is primed*" does not change that. The skilled person reading paragraph [0054] of the application would still turn to Chapter I for guidance, and as set out above (see point 26.) the processes disclosed in that paragraph are all sequencing-by-synthesis processes.

31. In summary, the board concludes from the above considerations that paragraphs [0053] and [0054] of the application provide no basis for a generic process of "single-molecule sequencing" as recited in claim 1.

32. The board also concurs with the respondent that there is no teaching anywhere in the application of a generic group of sequencing processes that could be equated with the expression "a single-molecule sequencing process" as used in claim 1. The only single-molecule sequencing processes described in the application are sequencing-by-synthesis processes (see point 6. above). Omission of the limitation to sequencing-by-synthesis processes therefore presents the skilled person with new technical information.

33. Claim 1 does not meet the requirements of Articles 123(2) and 76(1) EPC. Article 100(c) EPC therefore prejudices the maintenance of the patent as granted.

Auxiliary requests 1 to 3

Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

34. Claim 1 of each of auxiliary requests 1 to 3 is identical to claim 1 of the main request. Auxiliary requests 1 to 3 therefore do not comply with Articles 123(2) and 76(1) EPC for the same reasons as set out above for claim 1 of the main request.

Auxiliary request 5

Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

35. Claim 1 of auxiliary request 5 defines in step (d) that the consensus sequence is determined "*by single-molecule, real-time sequencing*".

36. The appellant's main line of reasoning was that paragraph [0048] of the application provided a literal basis for the claimed process and that the skilled person would directly and unambiguously derive from paragraph [0048] that they would benefit most from the templates of the invention by employing them in "*single molecule, real-time sequencing processes*", which were otherwise not further defined.

37. As set out above (see point 4.), for the assessment of whether the claim complies with Articles 123(2) and 76(1) EPC, it needs to be determined whether the amendments made provide the skilled person with

additional technical information not contained in the application documents.

38. In the case in hand, the decisive factor for determining the technical information conveyed by the disclosure in paragraph [0048] of the application is what the skilled person reading the phrase "*preferred single molecule, real-time sequencing processes*" in context would understand as being directly and unambiguously disclosed, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application documents as filed.

39. The relevant passage of paragraph [0048] of the application is set out below.

"*The present invention provides novel template configurations and methods for exploiting these compositions in template directed sequencing processes. While these compositions and methods have utility across all of the various template directed processes described herein, for ease of discussion, they are being primarily discussed in terms of preferred single molecule, real-time sequencing processes, in which they provide myriad benefits. In particular, the present invention is generally directed to nucleic acid sequences that employ improved template sequences to improve the accuracy of sequencing processes.*"

40. Paragraph [0048] of the application is concerned not with sequencing processes but with the templates of the invention and their use. Thus, it sets out that they "*have utility across all of the various template directed processes described herein*" but that "*for ease of discussion, they are being primarily discussed in*

terms of preferred single molecule, real-time sequencing processes".

41. From reading the phrase "*preferred single molecule, real-time sequencing processes*" in context, it is directly and unambiguously derivable for the skilled person that these sequencing processes are a preferred subset of the "*template directed processes described herein*" mentioned in paragraph [0048] of the application. This is not disputed by the appellant.

42. Since paragraph [0048] of the application does not describe any sequencing process in terms of steps to be taken to sequence a template of the invention, the skilled person would understand the reference "*described herein*" to refer to sequencing processes that are described elsewhere in the application.

43. In agreement with the respondent's submissions, the board considers that, in so far as the invention relates to methods, the skilled person understands paragraphs [0037] to [0047] of the application under the heading "DETAILED DESCRIPTION OF THE INVENTION" as describing sequencing processes in which the (later-described) templates of the invention are to be used while the use of the templates of the invention is exemplified in the examples.

44. To understand what the "*template directed processes described herein*" and the "*preferred single molecule, real-time sequencing processes*" used for discussing the compositions and methods of the invention are, the skilled person would therefore turn to said parts of the application as they provide information on these sequencing processes.

45. The disclosure regarding "*single molecule, real-time sequencing processes*" is set out in paragraphs [0042] to [0047] of the application and concerns processes like the SMRT™ sequencing method (schematically illustrated in Figure 1) and similar single-molecule, real-time sequencing methods. In these processes, an individual immobilised nucleic acid synthesis complex comprising a polymerase enzyme, a template and a primer is provided. The reaction mixture surrounding the complex contains the four different nucleotides (A, G, T and C), each labelled with a spectrally distinguishable fluorescent label attached through its terminal phosphate group. Nucleotides that are complementary to the template sequence are incorporated through a polymerase-mediated primer extension reaction and, on the basis of the fluorescent label associated with the nucleotide, the identity of each incorporated base is detected in real time as it is added by the polymerase. Accordingly, the single-molecule, real-time sequencing processes described in paragraphs [0042] to [0047] of the application are sequencing-by-synthesis methods (see also point 6. above). The SMRT™ methods are also used in Examples 2 to 4 of the application.

46. The appellant's line of reasoning that paragraph [0046] of the application also disclosed that the templates of the invention have utility in nanopore sequencing is not found persuasive.

47. Nanopore sequencing is a single-molecule, real-time sequencing process in which an exonuclease enzyme cleaves individual nucleotide molecules from a nucleic acid as it is driven through a nanopore (either a biological membrane protein such as alpha-hemolysin or a synthetic pore) and the nucleotides are identified in order of release (see e.g. document D13, Box 3 and

document D18, abstract).

48. The relevant passage of paragraph [0046] of the application relied on by the appellant as disclosing nanopore sequencing is set out below.

"*Although described in terms of the specific SMRT™ sequencing process, it will be appreciated that in accordance with the sequencing compositions of the invention, the nucleotides or nucleotide analogs may be detectable by any of a variety of different mechanisms (...). Likewise, non-optical labels may be employed, such as highly charged moieties, magnetic particles or the like, that may be detected by electrochemical systems, e.g., ChemFET sensors, nanopore sensors (see, e.g., Clarke et al., Nature Nanotechnology, Published online: 22 February 2009|doi:10.1038/nnano.2009.12* [document D18 in these appeal proceedings]*), and the like.*"

49. Evidently, paragraph [0046] of the application does not disclose a nanopore sequencing process; it does not even mention nanopore sequencing. Instead this paragraph sets out alternative means for detecting nucleotides or nucleotide analogs, and in this context it mentions the possibility of detecting non-optical labels by "*nanopore sensors*". However, detecting the nucleotides concerns only one step of the single-molecule, real-time sequencing processes described in paragraphs [0042] to [0047] (see point 45. above).

50. Mentioning document D18, referred to in paragraph [0046] as a reference for "*nanopore sensors*" (see point48. above), does not bring any teaching of document D18 with respect to nanopore sequencing within the disclosure of paragraph [0046] of the application

either.

51. From the references to "*nanopore sensors*" and document D18 in paragraph [0046] of the application, the skilled person would therefore not directly and unambiguously derive that templates of the invention have utility in nanopore sequencing.

52. The board concludes from the above considerations that the skilled person reading the phrase "*preferred single molecule, real-time sequencing processes*" in context would directly and unambiguously understand that paragraph [0048] of the application does not extend the teaching of sequencing processes beyond those discussed elsewhere in the application and does not disclose the use of a generically defined group of "*single-molecule, real-time sequencing processes*". Instead they would understand that the sequencing processes in relation to which the template configurations and methods of the invention are being discussed (see paragraph [0048] and point 39. above) are those described in paragraphs [0042] to [0047] of the application and used in the examples of the application and are single-molecule, real-time sequencing-by-synthesis processes (see point 45. above).

53. The appellant's main line of reasoning (see point 36. above) therefore fails.

54. As a further line of reasoning the appellant submitted that the application did not only disclose sequencing-by-synthesis processes, or at least not only polymerase-mediated sequencing-by-synthesis processes (see point XI. above, "Auxiliary request 5", fifth paragraph).

55. This line of reasoning cannot succeed, regardless of whether or not it is true that the application does not only disclose (polymerase-mediated) sequencing-by-synthesis processes. It has been established above (see points 45. and 52.) that the skilled person would construe the phrase "*preferred single molecule, real-time sequencing processes*" in paragraph [0048] of the application as relating to the "*single molecule, real-time sequencing processes*" described in paragraphs [0042] to [0047] of the application and those used in the examples; these are sequencing-by-synthesis processes.

56. The appellant's additional line of reasoning, which is based on the submission that at the priority date nanopore sequencing was known by the skilled person to be a single-molecule, real-time sequencing process, is not found persuasive either.

57. While the skilled person reads the application with the common general knowledge in mind, it has been established (see point 52. above) that paragraph [0048] of the application does not extend the teaching of sequencing processes beyond those discussed elsewhere in the application and does not disclose using a generically defined group of "*single molecule, real-time sequencing processes*". The skilled person's common general knowledge regarding nanopore sequencing therefore has no bearing on the meaning of the phrase "*preferred single molecule, real-time sequencing processes*" as understood in the context of paragraph [0048] of the application. In particular, it does not expand the meaning of this phrase to also encompass nanopore sequencing processes and hence methods which are not sequencing-by-synthesis methods.

58. The fact that the consensus sequence in step (d) of claim 1 is determined "*by single molecule, real-time sequencing*" which is not limited to a sequencing-by-synthesis process therefore provides the skilled person with technical information not disclosed in the application.

59. Claim 1 of auxiliary request 5 does not comply with Articles 123(2) and 76(1) EPC.

Auxiliary request 6

Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

60. The amendment in claim 1 (see section VI. above) does not limit the claimed subject-matter to single-molecule, real-time sequencing processes that are sequencing-by-synthesis methods; the objection set out above for claim 1 of auxiliary request 5 applies, *mutatis mutandis*. Claim 1 of auxiliary request 6 therefore does not comply with Articles 123(2) and 76(1) EPC.

Auxiliary request 7

Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

61. Claim 1 of auxiliary request 7 defines in step (d) that the consensus sequence is determined "*by template-directed single-molecule, real-time sequencing*".

62. The opposition division considered that paragraph [0048] of the application provided a literal basis for using the template configurations in template-directed single-molecule real-time sequencing processes and that claim 1 therefore complied with

Articles 123(2) and 76(1) EPC.

63. However as set out in point 52. above, it is the board's view that the skilled person would construe the phrase "*preferred single molecule, real-time sequencing processes*" in paragraph [0048] of the application as relating to sequencing processes that are described in the application, not as a generic disclosure of "*single molecule, real-time sequencing processes*".

64. The appellant did not assert that the expression "*template-directed*" implied that the claimed processes were limited to sequencing-by-synthesis methods. On the contrary, the appellant argued that "*template-directed*" processes were processes that exploited the template configurations of the invention and are "*template-directed*" to the extent that the template makes it possible to provide duplicative or replicate data.

65. The amendment in claim 1 of auxiliary request 7 therefore does not limit the claimed subject-matter to single-molecule, real-time sequencing processes that are sequencing-by-synthesis methods; the objection set out above for claim 1 of auxiliary request 5 applies, *mutatis mutandis*.

66. Claim 1 of auxiliary request 7 does not comply with Articles 123(2) and 76(1) EPC.

Auxiliary request 8

67. The respondent submitted that auxiliary request 8 should be held inadmissible pursuant to Article 12(4) RPBA 2007, applicable to this appeal case pursuant to Articles 24 and 25(2) RPBA as in force since 1 January 2020. In view of the board's conclusion

on the issue of added subject-matter (see points 68. et seq.), there is no need for the board to give reasons for having decided to take the claim request into account under Article 12(4) RPBA 2007 and to consider it in substance.

Added subject-matter (Articles 123(2) and 76(1) EPC) - claim 1

68. The amendment in claim 1 (see section VI. above) does not limit the claimed subject-matter to single-molecule, real-time sequencing processes that are sequencing-by-synthesis methods (see also point 64. above); the objection set out above for claim 1 of auxiliary request 5 applies, *mutatis mutandis*. Claim 1 of auxiliary request 8 therefore does not comply with Articles 123(2) and 76(1) EPC.

Remittal

69. Since none of the claim requests was found to meet the requirements of Articles 76(1) and 123(2) EPC, the board did not need to address the appellant's conditional request for remittal of the case to the opposition division for consideration of the grounds under Article 100(a) EPC, as to lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated